

# UNCLASSIFIED

<b>AD NUMBER</b>
ADB247840
<b>NEW LIMITATION CHANGE</b>
<b>TO</b> Approved for public release, distribution unlimited
<b>FROM</b> Distribution authorized to U.S. Gov't. agencies only; Proprietary Info; Nov 98 Other requests shall be referred to USAMRMC, Fort Detrick, MD 21702-5012
<b>AUTHORITY</b>
U.S. Army Medical Research and Materiel Command ltr., dtd January 28, 2000.

THIS PAGE IS UNCLASSIFIED

AD \_\_\_\_\_

GRANT NUMBER DAMD17-95-1-5002

TITLE: Database of Autotransplants for Breast Cancer

PRINCIPAL INVESTIGATOR: Mary M. Horowitz, M.D.

CONTRACTING ORGANIZATION: Medical College of Wisconsin  
Milwaukee, Wisconsin 53226

REPORT DATE: November 1998

TYPE OF REPORT: Final

PREPARED FOR: Commander  
U.S. Army Medical Research and Materiel Command  
Fort Detrick, Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Distribution authorized to U.S. Government agencies only (proprietary information, Nov 98). Other requests for this document shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

DTIC QUALITY INSPECTED 4

19990930 045

## NOTICE

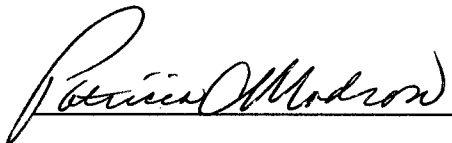
USING GOVERNMENT DRAWINGS, SPECIFICATIONS, OR OTHER DATA INCLUDED IN THIS DOCUMENT FOR ANY PURPOSE OTHER THAN GOVERNMENT PROCUREMENT DOES NOT IN ANY WAY OBLIGATE THE U.S. GOVERNMENT. THE FACT THAT THE GOVERNMENT FORMULATED OR SUPPLIED THE DRAWINGS, SPECIFICATIONS, OR OTHER DATA DOES NOT LICENSE THE HOLDER OR ANY OTHER PERSON OR CORPORATION; OR CONVEY ANY RIGHTS OR PERMISSION TO MANUFACTURE, USE, OR SELL ANY PATENTED INVENTION THAT MAY RELATE TO THEM.

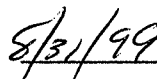
### LIMITED RIGHTS LEGEND

Award Number: DAMD17-95-1-5002  
Organization: Medical College of Wisconsin  
Location of Limited Rights Data (Pages):

Those portions of the technical data contained in this report marked as limited rights data shall not, without the written permission of the above contractor, be (a) released or disclosed outside the government, (b) used by the Government for manufacture or, in the case of computer software documentation, for preparing the same or similar computer software, or (c) used by a party other than the Government, except that the Government may release or disclose technical data to persons outside the Government, or permit the use of technical data by such persons, if (i) such release, disclosure, or use is necessary for emergency repair or overhaul or (ii) is a release or disclosure of technical data (other than detailed manufacturing or process data) to, or use of such data by, a foreign government that is in the interest of the Government and is required for evaluational or informational purposes, provided in either case that such release, disclosure or use is made subject to a prohibition that the person to whom the data is released or disclosed may not further use, release or disclose such data, and the contractor or subcontractor or subcontractor asserting the restriction is notified of such release, disclosure or use. This legend, together with the indications of the portions of this data which are subject to such limitations, shall be included on any reproduction hereof which includes any part of the portions subject to such limitations.

THIS TECHNICAL REPORT HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION.

  
\_\_\_\_\_

  
\_\_\_\_\_

# REPORT DOCUMENTATION PAGE

*Form Approved*  
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY <i>(Leave blank)</i>	2. REPORT DATE November 1998	3. REPORT TYPE AND DATES COVERED Final (1 Nov 94 - 31 Oct 98)	
4. TITLE AND SUBTITLE Database of Autotransplants for Breast Cancer		5. FUNDING NUMBERS DAMD17-95-1-5002	
6. AUTHOR(S) Mary M. Horowitz, M.D.		7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Medical College of Wisconsin Milwaukee, Wisconsin 53226	
8. PERFORMING ORGANIZATION REPORT NUMBER		9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012	
10. SPONSORING / MONITORING AGENCY REPORT NUMBER		11. SUPPLEMENTARY NOTES	
12a. DISTRIBUTION / AVAILABILITY STATEMENT Distribution authorized to U.S. Government agencies only (proprietary information, Nov 98). Other requests for this document shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, Maryland 21702-5012.		12b. DISTRIBUTION CODE	
13. ABSTRACT <i>(Maximum 200 words)</i>  The Autologous Blood and Marrow Transplant Registry (ABMTR) is a voluntary organization of 260 autotransplant centers that contribute clinical data on consecutive autotransplant recipients to a Statistical Center at the Medical College of Wisconsin. The ABMTR's database includes information for more than 16,500 women receiving autotransplants for breast cancer. According to data reported to the ABMTR, breast cancer is the most common indication for blood and marrow transplantation (allogeneic or autologous) in North America. This contract facilitated numerous enhancements to the ABMTR's clinical database, statistical support services and informational programs. These include collection of socioeconomic and clinical data on women receiving autotransplants for breast cancer and institutional data on centers doing transplants, streamlining data entry and management, development of appropriate statistical techniques for analyzing posttransplant data, and expansion of programs to provide access to collected data for patients, physicians and others involved in caring for women with breast cancer.			
14. SUBJECT TERMS Breast Cancer, Autologous Transplants, Bone Marrow Transplant, Periperal Blood Stem Cells, High Dose Therapy, Survival Analysis		15. NUMBER OF PAGES 621	
16. PRICE CODE		17. SECURITY CLASSIFICATION OF REPORT Unclassified	
18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified		19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	
20. LIMITATION OF ABSTRACT Limited			



FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

\_\_\_\_\_ Where copyrighted material is quoted, permission has been obtained to use such material.

*MA* Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

*MA* Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

\_\_\_\_\_ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

\_\_\_\_\_ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

\_\_\_\_\_ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

\_\_\_\_\_ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

\_\_\_\_\_ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

*MA* 11/30/98  
\_\_\_\_\_  
PI - Signature Date

## TABLE OF CONTENTS

Grant Number: DAMD17-95-1-5002

### FINAL REPORT

Database of Autotransplants for Breast Cancer

Front Cover .....	1
SF298 Report Documentation Page .....	2
Foreword .....	3
Table of Contents .....	4
Introduction .....	5
Body .....	5-17
Conclusions .....	17

#### Appendices

Appendix 1	ABMTR Report Forms
Appendix 2	ABMTR Participating Centers and ABMTR Breast Cancer Working Committee
Appendix 3	1998 Data Management Sessions
Appendix 4	Publications/Analyses in Progress
Appendix 5	Statisticians' Manual
Appendix 6	ABMTR Newsletters, including 1998 IBMTR/ABMTR Summary Slides
Appendix 7	World Wide Web Pages
Appendix 8	Presentations on Breast Cancer
Appendix 9	Letter of Support

## INTRODUCTION

Use of high-dose therapy with autologous blood or bone marrow hematopoietic support (autotransplants) to treat breast cancer continues to increase. According to data reported to the Autologous Blood and Marrow Transplant Registry (ABMTR), breast cancer was the most common indication for allogeneic or autologous blood or marrow transplantation in 1997-8. The ABMTR maintains a large database of clinical information on persons receiving autotransplants. This database provides important information relevant to breast cancer treatment. The purpose of the work funded in this contract was 1.) to enhance the existing ABMTR database so that important unresolved issues in use of autotransplants to treat breast cancer could be addressed and accurate information on autotransplants could be provided to women with breast cancer; and, 2.) to develop and make available appropriate biostatistical models for analyzing this database. Considerable progress was made during the four years of this contract including development of revised data collection forms, development of software for distributed data entry, computerization of log-in and error reporting processes, migration to state of the art computer hardware, completion of a survey of transplant center characteristics, evaluation of statistical models for analyzing transplant data, analysis of autotransplant results in persons with breast cancer, direct provision of data to patients and clinicians, presentation of data to national societies and organizations involved in planning breast cancer research, and implementation of a World Wide Web site with information related to autotransplants for breast cancer. Work began and continues (now without DAMD funding) in several other areas, including migration to a new database software system and implementation of a revised audit program. Accomplishments in each of the Technical Objectives outlined in our contract proposal is outlined below. Since this comprises the final report for DAMD17-95-1-5002, work in all four years is reviewed with focus on work in the fourth and final year.

## PROGRESS IN ACHIEVING TECHNICAL OBJECTIVES

### 1.0 *Develop and enhance an observational database for autotransplants in breast cancer, including demographic, clinical, treatment, financial, and outcome data.*

#### 1.1 Data collection

ABMTR centers are required to register all consecutive autotransplants with the ABMTR Statistical Center. Registration data include age, sex, race, disease stage and duration, graft type, graft treatment, conditioning regimen, graft treatment, and posttransplant disease status, survival and second cancers. Registration data allow analysis of trends in transplant use and outcome and identification of patients for specific studies. Comprehensive data are collected on a subset of these cases using the ABMTR Report Forms developed during Year 1 of this contract (Appendix 1). Report Forms were reviewed and underwent minor revisions in the fourth year of this contract, based on feedback from Statistical Center data management staff and participating centers. Data collection for 1994-1998 is summarized in Table 1.1.

Table 1.1 Accrual of autotransplants to the ABMTR database, 1994-1998.

Dates	Registration data		Report data	
	All diseases	Breast cancer	All diseases	Breast cancer
7/94 - 6/95	4,804	1,857	1,594	637
7/95 - 6/96	5,414	2,256	1,955	958
7/96 - 6/97	5,611	2,461	2,923	1,044
7/97 - 6/98	5,940	2,514	2,691	1,213
TOTAL	21,769	9,088	9,163	3,852

Two hundred sixty centers now participate in the ABMTR Research Program (Appendix 2). The ABMTR database now has registration data for a total of 16,723 recipients of autotransplants for breast cancer and comprehensive data for 5,479. The database is longitudinal; centers are requested to provide follow-up on survivors yearly.

As noted, data collection instruments (Report Forms) underwent major revisions during the first year of this contract (Appendix 1). Report Form enhancements included enhancements include collection of the following: 1.) income, occupation, educational level, and place of residence of autotransplant recipients; 2.) source and mode of payment for transplant procedure (insurer, fixed fee versus fee for service); 3.) inpatient versus outpatient setting for high-dose treatment; 4.) total number of hospital days in the first 100 days posttransplant; 5.) reason for using bone marrow versus peripheral blood stem cells for hematopoietic support; 6.) additional details regarding prior treatment for breast cancer; 7.) graft procurement procedures. In the final contract year, forms were reviewed and revised to improve clarity and collect additional data items, including *her2/neu* status of breast cancer tumors. Revisions are undergoing final review by Information Systems personnel who must program these changes into the database. Revised forms are expected to be in use by early 1999. The result of these enhancements and continued accrual of patients is a database with greater capabilities to address multiple issues relevant to breast cancer treatment. These data are increasingly used for timely clinical studies (see Section 4.0 below).

In the fourth contract year, Registration Forms were reviewed and are undergoing major revision so that more data can be collected on all patients and more sophisticated programs used to select patients for comprehensive reporting. A near final draft of the new Registration Form (Transplant Essential Data Form) is included in Appendix 1.

## 1.2 Uniform reporting of data

During the second year of this contract, work began on a revised Data Manual to accompany the new Report Forms. The revised Manual was distributed for review during the third contract year. Substantial modifications were requested by users. Work on a revised version was delayed by loss of personnel (Sandra Murphy, M.S., formerly the statistician for the Breast Cancer Working Committee, and Dr. Phil Rowlings) and subsequent training of new personnel. Work now continues under the supervision of Dr. Doug Rizzo and Diane Knutson with plans for distribution at the next IBMTR/ABMTR Participants' Meeting in March 1999.

Continuing the program of education for data managers in participating centers, the ABMTR conducted a two-day training session in January 1998, in conjunction with the ABMTR Annual Meeting in Keystone, Colorado (see Meeting Program and Evaluation Summary in Appendix 3). One hundred forty-two persons attended; 53 of these received travel grants to partially offset expenses of attending (see list of grantees in Appendix 3). This was the fourth data manager training session supported by DAMD funds. The DAMD travel grants, which were given preferentially to first time attendees, allowed many persons to attend who would not otherwise be able to participate. Participants indicated a high level of satisfaction with topics covered and training provided. In response to requests for additional sessions, a two-day training session was conducted by IBMTR/ABMTR Statistical Center personnel in November 1998 in Milwaukee (see Meeting Program and Evaluation Summary in Appendix 3). Forty-three data managers attended. Based on the positive feedback from participants, we now plan to hold two data manager training sessions per year to increase the opportunity for attendance. DAMD funding was critical in establishing this program of data manager training, both by allowing first-time attendance by data managers (many of whom now return annually) and by supporting personnel who have planned, conducted and refined the training program (specifically, D Knutson, A Kummerow, J Stone, L Lehrmann, B McGary, S Nell, J Rebro, D Rizzo, P Rowlings, SC Murphy).

## 1.3 Data review and entry

Forty of 260 ABMTR teams now submit Registration data on disk rather than paper. Statistical Center personnel continue to work on conversion programs to accommodate multiple data formats. Barbara Liu has primary responsibility for this task. During the second year of the contract, we computerized the log-in procedure for paper Report Forms to allow electronic comparison with data previously supplied on Registration. This provided verification of key fields; all discrepancies are resolved with the reporting center. During the third contract year, these programs were further developed and log-in procedures were streamlined. Thus, despite handling larger numbers of reports and verifying key fields, the lag time between Report Form receipt and log-in decreased from six to 1-2 months during this contract. Additionally, in the third and fourth year of the contract, we continued our work with StemCell Technologies to develop software for distributed data entry. Barbara McGary and Barbara Liu have primary responsibility for this collaboration. Patricia Vespalec and Ying Hu are involved in testing new StemSoft

programs. In December of 1997 a new version of BMTbase Registration was released which incorporated all new codes defined for our February 1998 registration period. This software, which includes the capability to generate disks for the ABMTR registration, was made available to all reporting centers free of charge and training in its use was provided at the Keystone meeting in January 1998. After working collaboratively with StemCell Technologies personnel to refine their programs, we recently received a copy of the soon to be released new version of BMTbase Reports for entering and submitting ABMTR Report Forms. The biggest advantage of this version over earlier versions is extensive data validation checking that occurs as data re entered at the reporting center. We worked with the software developers to include the data consistency checks normally done at the Statistical Center, particularly checking that event dates are reasonable chronologically. Catching incorrectly entered data at the time of entry by transplant center personnel, when it can be corrected quickly, means fewer errors to report back to the centers. Software (BMTransfer) to directly convert data entered on StemSoft software to a computerized format appropriate for incorporation in the IBMTR/ABMTR database was developed in cooperation with StemCell and was tested at the Statistical Center in the third and fourth contract years. This system is now operational. Sixty-five Centers are currently using the StemCell BMTbase Reports to enter report forms at their site and submit them to the registry. Twenty of these teams routinely submit these reports on disk; the remaining 45 are expected to do so within the next year.

During the fourth contract year, a computer program was developed by Barbara Liu to detect omissions, inconsistencies and out of range values as Report Forms are entered in the database at the Statistical Center and to automatically generate an error report to centers. Previously, the error report was generated manually by data entry personnel (Sharon Nell and Jane Rebro). The new system greatly increases the efficiency of this process and allows missing data to be provided and ambiguous data to be clarified quickly so that the database is as complete and accurate as possible. Centers are not reimbursed for their Report Forms until they respond to the error report providing an incentive for prompt resolution of problems.

#### 1.4 Data validation

An Audit Schema was developed and approved in 1995. Audits revealed a high level of accuracy for reported data and no evidence of selective reporting but there was dissatisfaction with the audit procedures expressed by auditors, audited centers and Statistical Center personnel. These included appropriate selection of auditors to avoid conflicts of interest, adequate instruction of auditors, adequate instruction for audited centers to prepare for audits, selection and numbers of reports and data fields audited, and format and timeliness of audit reports. Audit procedures were extensively reviewed at the 1997 Annual Meeting. Guidelines for auditors and for evaluation of audit reports were developed in the third contract year. Computer programs to select teams and cases for auditing were revised in the fourth contract year. Sessions on the audit program were included in the 1997 and 1998 Data Manager Education sessions. An Audit Coordinator was hired and trained in the fourth contract year (no DOD funds used). The new audit program is now being implemented with 50 centers scheduled for audit in the current

IBMTR/ABMTR fiscal year (7/98-6/99).

### 1.5 Computer capabilities

Our efforts to allow electronic data submission are outlined in Section 1.2 above. During the past two contract years, the inadequacy of Scientific Information Retrieval (SIR), which has been the Statistical Center's database platform since 1980, to meet the challenges of collecting and managing an ever increasing volume of data became increasingly apparent as we attempted to implement functionalities to improve the efficiency of data handling. SIR had not kept pace with developments in database technology over the past 3-5 years. Limitations included a character-based rather than graphical user interface, lack of screen painters or report painters, the requirement to develop screens and entry-time validation in a non-standard command language, no mechanism for defining multi-step transactions or automatic maintenance of relationships between tables, and no mechanism to access SIR databases directly from third party analysis or applications development software, preventing us from using powerful tools available from other vendors. Declining availability of technical support and software upgrades were additional problems. Consequently, a review of currently available database software was done during the third contract year to assess new platforms by B McGary, B Liu, JP Klein, MJ Zhang and MM Horowitz. An outline of needed functionalities was also done. This included a careful analysis of data flow patterns, reimbursement tracking and communications between the Statistical Center and participating transplant centers as well as extensive error and validity checking. A preliminary plan for conversion of the IBMTR/ABMTR database from the current SIR to Oracle was developed. Work on this project was begun in the third contract year and continued in the fourth contract year. A consultant was hired to assist in the evaluation of database platforms and applications development software, to work with our staff to define the system requirements and begin the programming work. The decision was made to store the research data in an ORACLE database on a UNIX file server. UNIX was selected for this purpose over a PC server because of the more robust security and maturity of the operating system functions for backup and other utilities and because of power & speed possible. PCs were chosen as the client machine for the data entry /maintenance/reporting application because of the familiarity of the Windows environment and true compatibility between various applications by using Windows standards. VisualBasic was selected as the programming tool for building the application on the PC for use by our data entry and administrative staff. Reports and data extracts produced by the VisualBasic application can be clipped and pasted to any word processing document or spread sheet. SAS was defined as the analysis tool for use by the statistical staff. The ORACLE database can be accessed directly through a utility provided by SAS from the statisticians UNIX workstation or PC. After a developing a detailed design document and database specification, programming began. IBMTR/ABMTR personnel worked with the consultant to assist with the development and to provide continuity for future maintenance after the consultant completed the implementation of the first phase, which was to program the underlying database structure for both the Registration and Research database and to move the Registration database to ORACLE. The initial plan was to use our existing HP UNIX machine to

house our ORACLE database, but their limitations and the expense of HP upgrading made us seek a better alternative. We subsequently purchased two much more powerful SUN UNIX file servers as well as five SUN workstations for statistical analysis and modeling. The performance advantages of the new machines seemed to outweigh any delay involved by not being able to install ORACLE immediately. VisualBasic programming work continued on the PC platform using Microsoft ACCESS on the PC for the preliminary database for testing. Database communication with ACCESS was through ODBC, the same communication gateway that was to be used with ORACLE. The delay for the delivery of the new machines, the installation and configuration of the operating system and network took much longer than scheduled. We were not able to install ORACLE on the SUN server until September of this year. Phase I of this project includes an integrated PC application to register new transplants, log in Report Forms whether they come to us on paper or disk, and allow entry of update information requested twice a year. All incoming data is compared to existing data and discrepancies are logged for reporting to the transplant teams. Features of this system that go beyond our current capabilities include:

1. Maintenance of information about the reporting centers as part of the database for statistical analysis and administrative functions;
2. Logging modifications to data, maintaining a history of changes to the data with *when, why* and *by whom* information;
3. Allowing attachment of notes to any data item as well as a general note page for each patient to store pertinent information not covered directly by the questions on the forms;
4. Stored information about data that violate validation rules as part of the database. Error/missing data reports are generated from these error flags. Error flags are cleared when the reporting center provides a correction;
5. A dynamic code table allows additional codes for new treatments; diagnosis codes or outcome categories to be added easily without changes or recompilation of the application code.

Testing is now underway on all features of the Phase I project. B Liu, B McGary, F Loberiza, P Vespalec, J Stone, S Nell, J Rebro, P Vespalec and Y Hu are all involved in this project. Communication from the PC application to the ORACLE database has been established. Substantial amounts of data have been converted from the SIR databases and loaded to ORACLE. Problems that occur during the testing process are logged to a database, prioritized and tracked through resolution. The Phase II component of the IBMTR/ABMTR database system is also underway to carry the basic features of the Phase I project to the much more complex structure to house all the data elements contained in our comprehensive Report Forms and to provide statistical access to the ORACLE database from SAS. We have contracted with a new department at the medical college (The Informatics Resource Center) for assistance with this phase. They provide expertise with SAS/ORACLE communication as well as data warehousing strategies to provide the statisticians a view of the data that is consistent, where data is only available after meeting the required validation standards. The status of this component so far is that a replica of the 12 tables now holding the information collected on our CORE form,



the Report Form data that is common to all diseases and all types of grafts, has been constructed in ORACLE on the SUN system. A substantial sample of data from the current SIR research data has been extracted and loaded to the ORACLE replica. The link between SAS and the ORACLE database has been established.

These database enhancements, made possible through funds provided by the DAMD, the National Cancer Institute and the Medical College of Wisconsin, are a major advance in our ability to handle large volumes of data, use advanced statistical techniques and provide information to the medical and general community.

**2.0 *Identify institutional characteristics of centers performing autotransplants for breast cancer in the United States and Canada, including academic affiliation, patient volume, physician training, staff/patient ratio.***

The institutional survey designed in Year 1 was completed in Year 2. Analysis of responses was done in collaboration with the American Society for Blood and Marrow Transplantation which also conducted a survey of U.S. transplant centers focusing on monitoring high-dose chemotherapy administration (see reprint in Appendix 4). Additional analyses of these data have been incorporated into completed and ongoing studies of autotransplants in breast cancer (see Section 4.0).

**3.0 *Evaluate and develop statistical models and software for effectively analyzing transplant data.***

Statistical Center faculty, particularly Drs. JP Klein and Dr. MJ Zhang, often working in collaboration with other Medical College of Wisconsin (MCW) and non-MCW faculty as well as with Biostatistics graduate students, were successful in exploring diverse aspects of statistical analysis of transplantation data, with publication of novel approaches in peer-reviewed journals. They have also made these and other useful statistical approaches available by posting SAS macros on the World Wide Web. A summary of their work follows. Reprints of publications are included in Appendix 4.

**3.1 Proportional hazards regression with random groups effects.** Frailty models are used in survival analysis to model unobserved heterogeneity or to model group effects (e.g. center effects). The model for group effects assumes that, conditional on a random effect, individuals within a group follow a standard proportional hazards model multiplied by the random effect. Common models for the random effect are the gamma distribution, the inverse Gaussian distribution, and the positive stable model. SAS macros were developed to fit these three models. The macros are available at the Division of Biostatistics Website ([www.biostat.mcw.edu](http://www.biostat.mcw.edu)).

**3.2 Accelerated failure time models with random effects.** To date, all models for random effects are based on a multiplicative model for the effect of frailty on the conditional hazard rate. Drs. John Klein and Mei-Jie Zhang at the ABMTR Statistical Center have studied an alternative model in which an accelerated failure time model is assumed, conditional on the frailty. The common frailty in a group either adds or subtracts a

common amount from each group member's log survival times. Assuming a Gaussian distribution for the frailty and for the log survival times, this leads to a multivariate normal model for the life lengths within a group. Maximum likelihood estimates of the model parameters are obtained for this model and the properties of the model are studied. A paper discussing this approach will appear in *Biometrics* (Appendix 4.1)

3.2 Joint modeling of the number of transfusions and time to death. Drs. Klein and Hee-Chang Park (Changwon National University, South Korea) have looked at models for the number of transfusions a patient receives after transplant. The models look at joint models for numbers of transfusions and death times. Weibull models are assumed for the event times and Poisson models are assumed for the counts. The counts and event times are assumed to be independent given random effects which affect either the event time and/or the counts. In a paper under review for *Biometrics*, a common random effect is assumed and maximum likelihood estimates of the model parameters is assumed. This model allows one to study the effects of covariates on the counts and event times, to estimate the expected number of transfusions a patient may have at a given time, and to study the effects of the number on transfusions on survival. Alternative models to the common random effects model have been studied. These include models where the random effects are different for the counts and the event time, but these random effects are themselves correlated. These models are important for studying hematopoietic recovery after high-dose therapy. (Appendix 4.2)

3.3 Comparison of statistical tests for center effects. Drs. Klein, Zhang and Per Andersen (University of Copenhagen) have completed a Monte Carlo study of methods for testing for the presence of a center effect following a Cox regression analysis. The study compared an approach which treats center effects as fixed versus an approach which treats center effects as random. Random effects were tested using a score test. The study found that the random effects test worked quite well for small to moderate samples when either the random effects or fixed effects model held true. For the fixed effects model, larger sample sizes were required. When the sample size was small (<10 per center), the fixed effects model falsely rejected the hypothesis of a center effect when there was an effect. This study has important implications for analysis of multi-center trials. The results are to appear in *Statistics in Medicine* (Appendix 4.3). A SAS macro to perform the random effects score test has been developed and is available on our Website.

3.4 Models for excess and relative mortality. Drs. Klein and Zhang have studied techniques for comparing the mortality rates of transplant patients with standard published mortality rates. As opposed to existing techniques, these models allow for the incorporation of risk factors for transplant. Two models are considered. The first is the model for relative mortality. In this model the arbitrary baseline hazard rate in the Cox model is replaced by the known population hazard rate. The second is a model for excess mortality. Here a modification of the additive hazards model is used. Both models allow for point and interval estimates of the time after transplant when a transplant recipient with a given set of risk factors has a mortality rate which has returned to that in the reference population. This is important in studying long-term survivors of cancer treatment. The model for relative mortality is to appear in *Statistics in Medicine*.

(Appendix 4.4)

3.5 Confidence regions for the times when two survival curves are different. Drs. Klein and Zhang have developed procedures to determine a confidence region for the times at which two treatments are different. The regions are based on either an assumed proportional hazards analysis or on an additive hazards regression model. Both models allow for the adjustment of fixed covariates. This is important when comparing treatments with different time patterns of adverse events. A paper discussing these methods is to appear in the *Journal of Planning and Inference* (Appendix 4.5). A second paper in this area has developed confidence bands, based on a proportional hazards model, for the difference in two survival curves. For this problem, the large sample distribution of the estimated covariate adjusted survival difference is quite intractable, so a novel method of simulating the correct confidence band is presented. The paper discussing this approach is under review (Appendix 4.6)

3.6 Multistate modeling in survival analysis. Dr. Klein has studied techniques for modeling the recovery process after a transplant as a dynamic function of intermediate events occurring after transplantation. The model can be used to provide a prediction of a patient's ultimate prognosis at any point in time given the patient's history up to that time. With Dr. Qain (Ohio State University) a number of semi-parametric models and analyses have been developed. This material has appeared in the *Proceedings of the ASA Conference*. With a Ph.D. student from the University of Wisconsin, Dr. Klein is examining modifications of these models which allow for the incorporation of random effects (Appendix 4.7).

3.7 General statistical analysis. Dr. Klein has authored a book chapter for the volume, *Clinical Bone Marrow and Stem Cell Transplantation: Reference Textbook* which surveys statistical procedures commonly used in transplantation. He has also written an article for the *Encyclopedia of Statistics* on "Survival Distributions and their Characteristics." Dr. Zhang has contributed two short articles to the *Encyclopedia of Biostatistics* on techniques for grouped survival data. Dr. Klein, with Prof. Richard Johnson of the University of Wisconsin has authored an article for the *Handbook of Biostatistics* on regression techniques for censored (survival) data. (See Appendix 4.8-4.10 for Technical Reports describing the subjected matter included in these textbook chapters)

4.0 ***Provide access to data and biostatistical support for clinical studies related to autotransplants in breast cancer.***

During the four years of this contract, the ABMTR Working Committee initiated several studies of the use and outcome of autotransplants for breast cancer. A summary of studies completed and in progress follows. Reprints are found in Appendix 4.

4.1 Overview of autotransplants for breast cancer. (Study chair: K. Antman, Columbia University, New York City; Study statistician: S.C. Murphy, ABMTR). This study described the increasing use of high-dose chemotherapy with autologous hematopoietic

stem cell support to treat high-risk breast cancer and analyzed outcome in 5,886 women. It documented a decrease in 100-day mortality from 22% in 1989 to 5% in 1995 ( $p < 0.0001$ ). Three-year PFS and survival probabilities (95% confidence intervals) were 65 (59-71)% and 74 (68-80)%, respectively, for stage 2 disease, and 60 (53-67)% and 70 (63-77)% for stage 3 disease. In stage 4 breast cancer, three-year probabilities of PFS and survival were 7 (4-10)% and 16 (12-20)%, respectively, for women with no response to conventional dose chemotherapy; 13 (9-17)% and 29 (25-33)% for those with partial response; and 32 (27-37)% and 46 (42-50)% for those with complete response. This study was published in the *Journal of Clinical Oncology* (Appendix 4.11).

4.2 Prognostic factors in autotransplants for metastatic breast cancer. (Study chairs: K. Antman, Columbia University, New York City, P Rowlings, ABMTR; Study statistician: S.C. Murphy, ABMTR). We analyzed data for 1,188 consecutive women receiving autotransplants for metastatic breast cancer in North America. Transplants were performed in 63 institutions between 1989 and 1995. The 2-year probability of survival was  $42 \pm 3\%$  and progression-free survival,  $18 \pm 2\%$ . Multivariate analyses identify older age, Karnofsky performance score  $< 90\%$ , absence of estrogen receptors, metastases developing  $< 18$  months after adjuvant therapy, resistance to chemotherapy pretransplant, and more than two sites of disease or liver or central nervous system involvement as predictors of poor outcome. There is no significant difference in outcome among the most frequently used conditioning regimens. A manuscript is in press in the *Journal of the American Medical Association* (Appendix 4.12).

4.3 Comparison of autotransplants with conventional chemotherapy for metastatic breast cancer. (Study chairs: D. Berry, CALGB, Duke University; J.D. Rizzo, ABMTR; Study statistician: D. Berry, CALGB and W Perez, ABMTR Statistical Center). To date only one small ( $n=90$  women) randomized trial has compared outcome of conventional therapy with autotransplants for metastatic breast cancer. This showed a modest survival advantage for autotransplants in women with newly diagnosed metastatic breast cancer. The validity and generalizability of this results has been questioned. We are using the data set described in 4.1 above to study this issue in a large group of women by comparing autotransplants with conventional therapy of women treated on protocols of the Cancer and Leukemia Group B (CALGB). Statistical techniques and the detailed patient-level data available for these patients were used to adjust for differences in patient- and disease-related characteristics between the cohorts. Results indicate that outcome of women having complete or partial response to conventional dose chemotherapy is similar whether subsequent treatment includes conventional or high-dose chemotherapy. An abstract describing these results has been submitted for presentation at the 1999 American Society of Clinical Oncology meetings (Appendix 4.13) and a manuscript is in preparation.

4.4 Prognostic factors in autotransplants for Stage II/III Breast Cancer. (Study chair: E. Reed, University of Nebraska, Omaha; Study statistician: W Perez, ABMTR). In 1990, only 15% of autotransplants for breast cancer were in women with Stage II/III disease; in 1995 45% were for early stage disease. The ABMTR is studying outcome of autotransplants for 689 women with Stage II/III breast cancer to determine outcome and

identify prognostic factors. Median age was 43 (range, 28-66) years. Median number of involved axillary nodes was 12 (range, 0-46). More than 90% of women received an anthracycline-based chemotherapy regimen prior to high-dose therapy. The most commonly used conditioning regimens were cyclophosphamide and thiotepa (CT, 40%) and CT plus carboplatin (20%). A preliminary analysis of this data set was presented at the meeting of the American Society for Clinical Oncology in May 1997, Denver. At that time the median follow-up of this cohort was <2 years. The follow-up has been updated; median follow-up is now three years. Three-year probability of survival is 72% (95% confidence interval, 67-76%). Univariate and multivariate analyses of these data are provided in Appendix 4.14.

4.5 Autotransplants in men with breast cancer. (*Study chair: P. McCarthy, Roswell Park Cancer Institute, Buffalo; Study statistician: JD Rizzo, ABMTR*). Breast cancer is rare in men. Consequently, there are few data regarding results of autotransplant for men with breast cancer. We studied 13 men receiving autotransplants for breast cancer and reported to the Autologous Blood & Marrow Transplant Registry (ABMTR) by 10 centers. Six men had Stage 2 breast cancer, four had Stage 3, and three had metastatic breast cancer. There were no unexpected regimen-related toxicities. Of ten men receiving autotransplants as adjuvant therapy, three relapsed three, five and 50 months posttransplant and died 16, 19 and 67 months posttransplant. Seven of ten are disease-free with median follow-up of 23 months (range, 6-50 months). Of three men treated for metastatic breast cancer, one had progressive disease and two recurrent disease at six, seven and 16 months posttransplant. Results appear similar to those reported for women receiving autotransplants for breast cancer. A manuscript describing these results has been submitted for publication (Appendix 4.15).

4.6 Assessment of variation in costs of autotransplants for breast cancer among institutions. (*Study chair: C. Bennett, Northwestern University, Chicago; Study statistician: T. Waters, Northwestern University, Chicago and J Stone, ABMTR Statistical Center*). Preliminary data on more than 800 patients transplanted in four centers were analyzed. These data suggest that costs of autotransplants for breast cancer are significantly less than costs for transplants for hematologic malignancies. these data were presented at the 1998 American Society of Hematology meetings (Appendix 4.16). A manuscript is in preparation.

4.7 Determination of second cancer risk after autotransplants for breast cancer. (*Study chairs: M.M. Horowitz and JD Rizzo, ABMTR Statistical Center; Study statisticians: R. Curtis, National Cancer Institute and J Stone, ABMTR Statistical Center*) Increased surveillance for second cancers was part of several efforts at supplemental data collection under this contract. Centers registering second cancers are now asked to supply diagnostic information on Supplemental New Malignancy Forms (Appendix 1). We have identified 19 second primary breast cancers and 50 cancers of other types (18 leukemia/myelodysplasias, 6 cancers of the female genital tract, 6 skin cancers, 4 lung cancers, 3 thyroid cancers and 13 other cancers) thus far. Comparison of second cancer risk in women receiving autotransplants for breast cancer versus an age-, sex- and race-matched general population is in progress.

All of these studies were enhanced by the improved data collection, entry and management funded by this contract and by the greater level of detail now available on transplant recipients. Awareness of the resources of data and statistical expertise available through the Statistical Center is steadily increasing as are proposals to use the database for clinical research. To clearly delineate the procedures for proposing and conducting studies, Statistical Center staff developed a Statistician's Manual for studies using Registry data and statistical personnel (Appendix 5). This document helps focus study proposals, ensure that data handling and analysis are of high quality and ensure that the expertise of Registry Working Committees (Appendix 2) is fully utilized. Excerpts from these documents are now also available on our Website ([www.ibmtr.org](http://www.ibmtr.org)).

**5.0 *Disseminate information regarding autotransplants for breast cancer to patients, physicians and others involved in care of women with breast cancer.***

The ABMTR database is a unique resource of information regarding use and outcome of transplants, containing data not readily available in the medical literature. Summary statistics on the use and outcome of autotransplants for breast cancer were included in the November 1997 issue of the ABMTR Newsletter (Appendix 6), which is widely distributed to transplant and oncology centers. These data are also available on-line at the IBMTR/ABMTR homepage on the World Wide Web (address: [www.ibmtr.org](http://www.ibmtr.org); Appendix 7). In the fourth contract year we completely redesigned our Website to provide users with better understanding of the IBMTR/ABMTR's mission and organization and with better access to IBMTR/ABMTR data. Dr. M Horowitz, J Eder, L Lehrmann, S Nell and M Nugent spent considerable effort on this project. Answers to frequently asked questions and instructions for requesting additional information or proposing specific studies are given. There is also a link to a site, developed during the third and fourth contract years, with information regarding transplants for specific diseases, including breast cancer (see below). Report Forms may now be downloaded from the Website, which is anticipated to save the Statistical Center money in printing and mailing costs. Plans were developed for collecting data electronically and for Working Committee "chat rooms" although these functionalities will not be implemented until 1999.

There were many presentations of ABMTR data related to use and/or outcome of autotransplants for breast cancer during the four years of this contract year. Those presented at national and international meetings are listed in Appendix 8). Materials were provided for many other local presentations. Appendix 8 includes hard copy of a typical set of slides provided for such presentations. Additionally, the ABMTR, through its Information Resource program (partially funded by this contract) provides information regarding use and outcome of autotransplants for breast cancer physicians, patients and health-related agencies or companies. About 350 such requests were answered in the fourth contract year. Data provided in response to these requests often included survival and other outcome data not readily available in the medical literature. The importance of this resource to patients is reflected in a letter recently received from Mr. Clarence Mayer, husband of a woman with breast cancer, and included, with his permission in Appendix 9. Individuals may now request such information through our Website.

In addition to [www.ibmtr.org](http://www.ibmtr.org), in collaboration with the National Marrow Donor Program and the American Society of Blood and Marrow Transplantation, the ABMTR developed a World Wide

Web site with comprehensive information on the role of transplantation in treating various cancers. The site includes general transplant information, disease-specific information, and an "Ask the Expert" page where users may post questions which are triaged to appropriate persons for response. A comprehensive review of the role of high-dose chemotherapy in treating breast cancer was among the first topics to be made available. The Website was opened to the public in December 1997 at the following address: <http://www.bmtinfo.org>. Hard copies of pages relevant to breast cancer are enclosed in Appendix 7. Information is provided at basic (the average lay person) and technical (general physician or sophisticated lay person) levels, with an extensive bibliography aimed at transplant physicians that will be updated periodically, and with links to other relevant Web sites providing information on transplantation and cancer.

## **CONCLUSIONS**

We are grateful for the support provided by the DAMD which has facilitated numerous enhancements to the ABMTR database and Statistical Center. This support enabled us to elevate the quality of information available for scientific studies and for health care providers and consumers. It also allowed us to make this information more available through peer-reviewed papers, educational materials and the World Wide Web.

FINAL REPORT - DAMD17-95-1-5002

Database of Autotransplants for Breast Cancer

Bibliography of all publications and meeting abstracts: see Appendix 4

List of Personnel Receiving Pay from this Effort

Bodine, Beverly A.

Eder, Jean M.

Hogg, Susan J.

Horowitz, Mary M.

Hu, Ying

Klein, John P.

Knutson, Diane J.

Kummerow, Angela S.

Lehrmann, Lisa J.

Liu, Barbara

Loberiza, Fausto R.

McGary, Barbara M.

Murphy, Sandra C.

Nell, Sharon

Nugent, Melodee L.

Pelz, Corey J.

Pérez, Waleska S.

Rebro, Jane R.

Rizzo, J. Douglas

Rowlings, Philip A.

Schneider, Linda M.

Stone, Judith Veum

Trzcinko, Deanne

Waldoch, D'Etta

Vespalec, Patricia A.

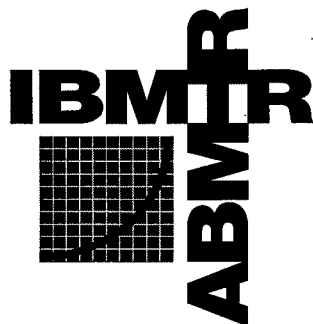
Zhang, Mei-Jie

Consultants

Antman, Karen H.

Hillner, Bruce E.





# APPENDICES

Grant No. DAMD17-95-1-5002

## FINAL REPORT

### “Database of Autotransplants for Breast Cancer”

- |                   |   |
|-------------------|---|
| <b>Appendix 1</b> | ABMTR Report Forms  |
| <b>Appendix 2</b> | ABMTR Participating Centers and ABMTR Breast Cancer Working Committee |
| <b>Appendix 3</b> | 1998 Data Management Sessions   |
| <b>Appendix 4</b> | Publications/Analyses in progress                                     |
| <b>Appendix 5</b> | Statisticians' Manual   |
| <b>Appendix 6</b> | ABMTR Newsletters, including 1998 IBMTR/ABMTR Summary Slides          |
| <b>Appendix 7</b> | World Wide Web Pages  |
| <b>Appendix 8</b> | Presentations on Breast Cancer  |
| <b>Appendix 9</b> | Letter of Support   |

Submitted to: U.S. Army Medical Research and Material Command  
December 22, 1998

---

Statistical Center  
Autologous Blood & Marrow Transplant Registry  
Medical College of Wisconsin  
8701 Watertown Plank Road • P.O. Box 26509  
Milwaukee, WI 53226 USA



**DAY 100 CORE FORM**

TEAM

IUBMID   
*(Institutional Unique Blood or Marrow Transplant Identification Number)*

Date of transplant for which this form is being completed:     
Month Day Year

**FOR REGISTRY USE ONLY:**

I.D.  -  -

Date received:

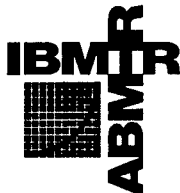
Log: \_\_\_\_\_ PC: \_\_\_\_\_

Registry (circle one): **IBMTR** **ABMTR**

Date of report:     
Month Day Year

*(Use same date on Graft Insert & Disease Insert for this transplant.)*

**Series 095 Reporting Forms**



**Statistical Center**

**Medical College of Wisconsin**  
P.O. Box 26509, 8701 Watertown Plank Road  
Milwaukee, WI 53226  
Telephone: 414-456-8325 Fax: 414-456-6530

Day 100 post transplant:     
Month Day Year

Date of last actual contact with patient to determine medical status for this report:     
*(See Q.6 on CORE Voucher for help determining date of last contact.)*

*(If patient died prior to Day 100 with no further infusions, enter date of death and check here .)*

**Demographics**

**\* If this is a report of a second (or subsequent) transplant check here , complete Disease Insert and go to Q.20**

1. Institutional protocol number (if applicable):

2. Was patient enrolled in cooperative group (eg. CALGB, CCG, EBMT, ECOG, EORTC, MRC, NAMTG, NSABP, POG, SWOG, etc.) study at any time or reported to the NMDP or EBMT? *(include transplant and non-transplant studies)*

- 1  Yes
- 0  No
- 8  Unknown

Study 1: 3. Group \_\_\_\_\_ 4. Study No. \_\_\_\_\_ 5. Patient No. \_\_\_\_\_

Study 2: 6. Group \_\_\_\_\_ 7. Study No. \_\_\_\_\_ 8. Patient No. \_\_\_\_\_

Study 3: 9. Group \_\_\_\_\_ 10. Study No. \_\_\_\_\_ 11. Patient No. \_\_\_\_\_

12. Sex: 1  Male 2  Female

14. Date of birth:     
Month Day Year

13. Race: *(If patient's parents are from two separate groups of the following, check both)*

**Caucasian/White**

- 11  European or Western Russia
- 12  Middle East or North Coast of Africa
- 10  White, not otherwise specified

**Black**

- 21  African American
- 22  African Black (both parents born in Africa)
- 23  Caribbean Black
- 24  South or Central American Black
- 20  Black, not otherwise specified

**Asian/Pacific Islander**

- 31  Asian Indian
- 32  Filipino
- 33  Hawaiian (Polynesian)
- 34  Japanese
- 35  Korean
- 36  Northern Chinese
- 37  Southeast Asian/Southern Chinese
- 30  Oriental, not otherwise specified

**Hispanic**

- 41  Caribbean Hispanic
- 42  Mexican or Southwestern USA Hispanic
- 43  South or Central American Hispanic
- 40  Hispanic, not otherwise specified

**Native American**

- 51  Native Alaskan/Eskimo/Aleut
- 52  American Indian
- 50  Native American, not otherwise specified

**Other**

- 90  Other, specify: \_\_\_\_\_
- 88  Unknown

TEAM

IUBMID

### Disease

15. What was the primary disease for which transplant was performed?  
(Appropriate Insert must be submitted with this form)

10  Acute myelogenous leukemia (AML or ANLL)

- 11  M1, myeloblastic
- 12  M2, myelocytic
- 13  M3, promyelocytic (APML, APL)
- 14  M4, myelomonocytic
- 15  M5, monocytic
- 16  M6, erythroblastic
- 17  M7, megakaryoblastic
- 18  Granulocytic sarcoma
- 19  Other, specify: \_\_\_\_\_
- 10  AML or ANLL unclassified

Complete Insert I and continue with Q.17 on Page 5

20  Acute lymphoblastic leukemia (ALL)

- 21  Mature B-cell (L3)
- 22  T-cell
- 23  Null cell (early Pre-B)
- 24  cALLa (includes Pre-B)
- 26  B-lineage
- 29  Other, specify: \_\_\_\_\_
- 20  ALL, unclassified

Complete Insert II and continue with Q.17 on Page 5

40  Chronic myelogenous leukemia (CML)

- 41  Ph<sup>1</sup> +; BCR/ABL+
- 42  Ph<sup>1</sup> +; BCR/ABL -
- 43  Ph<sup>1</sup> +; BCR/ABL unknown
- 44  Ph<sup>1</sup> -; BCR/ABL +
- 45  Ph<sup>1</sup> -; BCR/ABL -
- 46  Ph<sup>1</sup> -; BCR/ABL unknown
- 47  Ph<sup>1</sup> unknown; BCR/ABL +
- 48  Ph<sup>1</sup> unknown; BCR/ABL -
- 49  Other, specify: \_\_\_\_\_
- 40  Ph<sup>1</sup> unknown; BCR/ABL unknown

Complete Insert III and continue with Q.17 on Page 5

170  Multiple myeloma/Plasma cell disorder

- 171  Multiple myeloma  
Complete Insert VII and continue with Q.17 on Page 5
- 172  Plasma cell leukemia  
Complete Insert VII and continue with Q.17 on Page 5
- 173  Waldenstrom macroglobulinemia
- 174  Amyloidosis
- 175  Solitary plasmacytoma
- 179  Other, specify: \_\_\_\_\_
- 170  Plasma cell disorders, unclassified

Continue with Q.16 on Page 5

30  Other leukemia

- 34  Chronic lymphocytic leukemia (CLL)
- 35  Hairy cell leukemia
- 37  Prolymphocytic leukemia (PLL)  
Complete Insert IV and continue with Q.17 on Page 5
- 36  Juvenile CML (no evidence of Philadelphia chromosome or BCR/ABL)  
Complete Insert V and continue with Q.17 on Page 5
- 38  M0, stem cell
- 31  Acute undifferentiated leukemia
- 32  Biphenotypic, bilineage or hybrid leukemia
- 33  Acute mast cell leukemia
- 39  Other, specify: \_\_\_\_\_
- 30  Other leukemia, unclassified

Complete Insert I and continue with Q.17 on Page 5

50  Myelodysplastic/myeloproliferative disorders (MDS)

(Please classify all preleukemias)

(If patient has transformed to AML, also complete Insert I and indicate AML as the primary disease)

- 51  Refractory anemia (RA)
- 52  Refractory anemia with excess blasts (RAEB)
- 53  Refractory anemia with excess blasts in transformation (RAEBT)
- 54  Chronic myelomonocytic leukemia (CMML)
- 55  Acquired idiopathic sideroblastic anemia (RARS)
- 56  Paroxysmal nocturnal hemoglobinuria (PNH)
- 57  Polycythemia vera
- 58  Essential or primary thrombocythemia
- 59  Myelofibrosis with myeloid metaplasia
- 60  Other myelofibrosis or myelosclerosis
- 69  Other myelodysplasia or myeloproliferative disorder, specify: \_\_\_\_\_
- 50  MDS, unclassified

Complete Insert V and continue with Q.17 on Page 5

TEAM

IUBMID

200  Other malignancies—

100  Non-Hodgkin lymphoma (If low grade lymphoma—101, 121, 102, 103—transformed before conditioning, use code 128)—

- 101  Small cell lymphocytic
- 121  Small lymphocytic plasmacytoid (Lymphoplasmacytoid lymphoma)
- 102  Follicular, predominantly small cleaved cell (Grade I follicle center lymphoma)
- 103  Follicular, mixed, small cleaved and large cell (Grade II follicle center lymphoma)
- 104  Follicular, predominantly large cell (Grade III follicle center lymphoma)
- 105  Diffuse, small cleaved cell (Follicle center lymphoma, diffuse)
- 106  Diffuse, mixed, small and large cell
- 107  Diffuse, large cell
- 108  Large cell, immunoblastic (B-cell only)
- 125  Primary mediastinal large B-cell lymphoma
- 109  Lymphoblastic (Precursor B-lymphoblastic lymphoma/leukemia)
- 127  Precursor T-lymphoblastic lymphoma/leukemia
- 110  Small noncleaved cell, unclassified
- 111  Small noncleaved cell, Burkitt
- 112  Small noncleaved cell, non-Burkitt
- 113  Mycosis fungoides/Sezary syndrome
- 114  Histiocytic
- 115  Mantle cell
- 116  Composite, specify: \_\_\_\_\_
- 117  Large cell anaplastic lymphoma, Ki1 positive
- 118  Primary CNS lymphoma
- 122  Mucosal Associated Lymphoid Tissue type (Extranodal marginal zone B-cell lymphoma)
- 123  Nodal marginal zone B-cell lymphoma
- 124  Splenic marginal zone B-cell lymphoma
- 126  Large granular lymphocytic leukemia
- 128  Transformed low grade lymphoma
- 131  Angioimmunoblastic T-cell lymphoma
- 132  Angiocentric lymphoma
- 133  Intestinal T-cell lymphoma
- 134  Adult T-cell lymphoma/leukemia (HTLV1 associated)
- 139  Other peripheral T-cell lymphoma, specify: \_\_\_\_\_
- 130  Peripheral T-cell lymphomas, unclassified
- 119  Other non-Hodgkin lymphoma, specify: \_\_\_\_\_
- 100  Non-Hodgkin lymphoma, unclassified

Complete Insert VI and continue with Q.17 on Page 5

150  Hodgkin lymphoma—

- 151  Lymphocyte predominant
- 152  Nodular sclerosis
- 153  Mixed cellularity
- 154  Lymphocyte depleted
- 159  Other Hodgkin lymphoma, specify: \_\_\_\_\_
- 150  Hodgkin lymphoma, unclassified

Complete Insert VI and continue with Q.17 on Page 5

250  Breast cancer  
Complete Insert VIII and continue with Q.17 on Page 5

- 201  Head & neck
  - 202  Lung, small cell
  - 203  Lung, non-small cell
  - 239  Lung, other
  - 204  Mediastinal neoplasm, specify: \_\_\_\_\_
  - 205  GI tract
  - 206  Pancreatic
  - 207  Hepatobiliary
  - 208  Kidney & urinary tract
  - 209  Prostate
  - 210  Testicular
  - 225  Germ cell tumor
  - 211  External genitalia
  - 216  Sarcoma unspecified
  - 217  Soft tissue sarcoma
  - 218  Bone sarcoma (excluding Ewing sarcoma)
  - 219  Melanoma
  - 220  Central nervous system tumor
- Complete Insert XVIII and continue with Q.17 on Page 5
- 221  Wilm tumor
  - 222  Neuroblastoma
- Complete Insert XVII and continue with Q.17 on Page 5
- 223  Retinoblastoma
  - 224  Ewing sarcoma
  - 226  Medulloblastoma
  - 227  PNET
  - 231  Thymoma
  - 269  Other malignancy, specify: \_\_\_\_\_
  - 200  Other malignancies, unclassified

Continue with Q.16 on Page 5

300  Severe aplastic anemia—

- 301  Idiopathic
- 302  Secondary to hepatitis
- 303  Secondary to toxin/other drug
- 304  Amegakaryocytosis (not congenital)
- 305  Schwachmann-Diamond
- 306  Acquired Pure Red Cell Aplasia
- 309  Other SAA, specify: \_\_\_\_\_

Complete Insert IX and continue with Q.17 on Page 5

310  Inherited abnormalities of erythrocyte differentiation or function (If patient has developed leukemia, also complete Insert for appropriate leukemia diagnosis)—

- 311  Fanconi anemia
  - 312  Diamond-Blackfan anemia (pure red cell aplasia)
  - 319  Other, specify: \_\_\_\_\_
- Complete Insert IX and continue with Q.17 on Page 5
- 355  Sickle Thalassemia major
  - 356  Sickle cell anemia
  - 359  Other hemoglobinopathy, specify: \_\_\_\_\_
  - 350  Thalassemia major & oth hemoglobinop., unclass.
  - 310  Inherited abnorm. of erythrocyte diff, unclass.

Complete Insert XI and continue with Q.17 on Page 5

TEAM     IUBMID

400  SCID and other disorders of the immune system

- 401  ADA deficiency  
severe combined immunodeficiency (SCID)
- 402  Absence of T and B cells SCID
- 403  Absence of T, normal B cell SCID
- 404  Omenn syndrome
- 405  Reticular dysgenesis
- 406  Bare lymphocyte syndrome
- 419  SCID other, specify: \_\_\_\_\_
- 451  Ataxia telangiectasia
- 452  HIV infection
- 454  DiGeorge anomaly
- 455  Chronic granulomatous disease
- 456  Chediak-Higashi syndrome  
*Complete Insert XIX and continue with Q.17 on Page 5*
- 457  Common variable immunodeficiency
- 458  X-linked lymphoproliferative syndrome
- 459  Leukocyte adhesion deficiencies, incl. GP180,  
CD-18, LFA and WBC adhesion deficiencies
- 460  Kostmann agranulocytosis  
(congenital neutropenia)
- 461  Neutrophil actin deficiency
- 462  Cartilage-hair hypoplasia
- 464  CD40 ligand deficiency
- 470  Combined immunodeficiency disease (CID),  
unspecified
- 474  CID other, specify: \_\_\_\_\_
- 479  Other immunodeficiencies, specify: \_\_\_\_\_  
*Complete Insert XII and continue with Q.17 on Page 5*
- 453  Wiskott Aldrich syndrome  
*Complete Insert XIII and continue with Q.17 on Page 5*

500  Inherited abnormalities of platelets

- 501  Amegakaryocytosis/congenital thrombocy-  
topenia
- 502  Glanzmann thrombasthenia
- 509  Other inherited abnorm. of platelets,  
specify: \_\_\_\_\_
- 500  Inherited abnorm. of plate. unclassified  
*Continue with Q.16 on Page 5*

600  Autoimmune diseases

- 601  Myasthenia gravis
- 602  Multiple sclerosis
- 603  Rheumatoid arthritis
- 604  Psoriatic arthritis/psoriasis
- 605  Systemic lupus erythematosus (SLE)
- 606  Polymyositis-dermatomyositis
- 607  Scleroderma
- 608  Sjogren syndrome
- 609  Polyarteritis nodosa
- 610  Wegener granulomatosis
- 611  Other vasculitis, specify: \_\_\_\_\_
- 612  Inflammatory bowel disease
- 629  Other autoimmune disease, specify: \_\_\_\_\_
- 600  Autoimmune disease unclassified  
*Continue with Q.16 on Page 5*

520  Inherited disorders of metabolism

- 521  Osteopetrosis (malignant infantile osteopetrosis)  
*Complete Insert XV and continue with Q.17 on Page 5*
- 522  Lesch-Nyhan (HGPRT deficiency)
- 523  Neuronal ceroid lipofuscinosis (Batten disease)
- Mucopolysaccharidosis
- 531  Hurler syndrome (IH)
- 532  Scheie syndrome (IS)
- 533  Hunter syndrome (II)
- 534  Sanfilippo (III)
- 535  Morquio (IV)
- 536  Maroteaux-Lamy (VI)
- 537   $\beta$ -glucuronidase deficiency (VII)
- 538  Mucopolysaccharidosis (V)
- 539  Other mucopolysaccharidosis, specify: \_\_\_\_\_
- 530  Mucopolysaccharidosis, unclassified
- Mucolipidoses
- 541  Gaucher disease
- 542  Metachromatic leukodystrophy (MLD)
- 543  Adrenoleukodystrophy (ALD)
- 544  Krabbe disease (globoid leukodystrophy)
- 545  Neimann-Pick disease
- 546  I-cell disease
- 547  Wolman disease
- 548  Glucose storage disease
- 549  Lysosomal storage disease
- 559  Other mucolipidoses, specify: \_\_\_\_\_
- 540  Mucolipidoses, unclassified
- Polysaccharide hydrolase abnormalities
- 561  Aspartyl glucosaminuria
- 562  Fucosidosis
- 563  Mannosidosis
- 569  Other polysaccharide hydrolase abnorm., spec.: \_\_\_\_\_
- 560  Polysaccharide hydrolase abnorm., unclassified
- 529  Other inherited metabolic disorders, specify: \_\_\_\_\_
- 520  Inherited disorders of metabolism, unclassified  
*Complete Insert XIV and continue with Q.17 on Page 5*

570  Histiocytic disorders

- 571  Familial erythrophagocytic  
lymphohistiocytosis (FEL, Familial hemoph-  
agocytic lymphohistiocytosis)
- 572  Histiocytosis-X
- 573  Hemophagocytosis
- 574  Malignant histiocytosis
- 579  Other histiocytic disorder, specify: \_\_\_\_\_
- 570  Histiocytic disorder, unclassified  
*Continue with Q.16 on Page 5*

900  Other

Specify: \_\_\_\_\_  
*Continue with Q.16 on Page 5*

TEAM

IUBMID

### Clinical Status of Patient Prior to Conditioning

16. Date of diagnosis of primary disease:          
Month Day Year

*Complete only if a disease-specific  
 Insert is not required.*

17. **Allografts only:** Patient's blood type:

- |                                   |                                   |   |
|-----------------------------------|-----------------------------------|---|
| 1 <input type="checkbox"/> A Rh+  | 5 <input type="checkbox"/> A Rh-  | 9 <input type="checkbox"/> A Rh unknown   |
| 2 <input type="checkbox"/> B Rh+  | 6 <input type="checkbox"/> B Rh-  | 10 <input type="checkbox"/> B Rh unknown  |
| 3 <input type="checkbox"/> AB Rh+ | 7 <input type="checkbox"/> AB Rh- | 11 <input type="checkbox"/> AB Rh unknown |
| 4 <input type="checkbox"/> O Rh+  | 8 <input type="checkbox"/> O Rh-  | 12 <input type="checkbox"/> O Rh unknown  |
|                                   |                                   | 88 <input type="checkbox"/> Unknown       |

18. Has patient ever been pregnant?

- 1  Yes —   **19. Number of pregnancies (Gravida):**
- 0  No
- 8  Unknown
- 7  Not applicable (patient is male, or a female child)

20. Did patient receive blood transfusions at any time prior to conditioning?

- 1  Yes —   **21. Give number (best estimate) of donor exposures:**
- |                                    |                                  |                                    |
|------------------------------------|----------------------------------|------------------------------------|
| 0 <input type="checkbox"/> No      | 1 <input type="checkbox"/> 1-5   | 5 <input type="checkbox"/> 31-40   |
| 8 <input type="checkbox"/> Unknown | 2 <input type="checkbox"/> 6-10  | 6 <input type="checkbox"/> 41-50   |
|                                    | 3 <input type="checkbox"/> 11-20 | 7 <input type="checkbox"/> > 50    |
|                                    | 4 <input type="checkbox"/> 21-30 | 8 <input type="checkbox"/> Unknown |

22. What was the functional status of patient prior to conditioning?

*If the patient is 16 years of age or older, complete the Karnofsky Scale.  
 If patient is younger than 16 years of age, complete the Lansky Scale.  
 Rate activity of patient immediately prior to initiation of conditioning.*

#### Karnofsky Scale (age ≥16 yrs)

Select the phrase in the Karnofsky Scale which best describes the activity status of the patient:

**Able to carry on normal activity; no special care is needed.**

- 100  Normal; no complaints; no evidence of disease  
 90  Able to carry on normal activity  
 80  Normal activity with effort

**Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed.**

- 70  Cares for self; unable to carry on normal activity or to do active work  
 60  Requires occasional assistance but is able to care for most needs  
 50  Requires considerable assistance and frequent medical care

**Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.**

- 40  Disabled; requires special care and assistance  
 30  Severely disabled; hospitalization indicated, although death not imminent  
 20  Very sick; hospitalization necessary  
 10  Moribund; fatal process progressing rapidly

#### Lansky Scale (age <16 yrs)

Select the phrase in the Lansky Play-Performance Scale which best describes the activity status of the patient:

**Normal range.**

- 100  Fully active  
 90  Minor restriction in physically strenuous play  
 80  Restricted in strenuous play, tires more easily, otherwise active

**Mild to moderate restriction.**

- 70  Both greater restrictions of, and less time spent in, active play  
 60  Ambulatory up to 50% of time, limited active play with assistance/supervision  
 50  Considerable assistance required for any active play; fully able to engage in quiet play

**Moderate to severe restriction.**

- 40  Able to initiate quiet activities  
 30  Needs considerable assistance for quiet activity  
 20  Limited to very passive activity initiated by others (i.e., TV)  
 10  Completely disabled, not even passive play

TEAM

IUBMID

23. Was there clinically significant coexisting disease or organ impairment prior to conditioning?  
(Report liver disease in Q.63-69)

- 1  Yes  
0  No

What were the diagnoses?

Yes No

24. 1  0  Significant hemorrhage (e.g. CNS or GI), specify site(s): \_\_\_\_\_

Cardiovascular

25. 1  0  Coronary artery disease

26. 1  0  Hypertension

27. 1  0  Other cardiac disease, specify: \_\_\_\_\_

Endocrine

28. 1  0  Diabetes mellitus

29. 1  0  Thyroid disease

20. 1  0  Other endocrine disease, specify: \_\_\_\_\_

CNS

31. 1  0  Seizure disorder

32. 1  0  Other CNS disease, specify: \_\_\_\_\_

Pulmonary

33. 1  0  Asthma

34. 1  0  Other pulmonary disease, specify: \_\_\_\_\_

35. 1  0  Genitourinary disease, specify: \_\_\_\_\_

36. 1  0  Gastrointestinal disease, specify: \_\_\_\_\_

37. 1  0  Hematologic disease, specify: \_\_\_\_\_

Chromosomal

38. 1  0  Fanconi anemia

39. 1  0  Down syndrome

40. 1  0  Other chromosomal disorders, specify: \_\_\_\_\_

41. 1  0  History of other malignancy, specify: \_\_\_\_\_

42. 1  0  Neonatal GVHD

Autoimmune disease

43. 1  0  Rheumatoid arthritis

44. 1  0  Systemic lupus erythematosus

45. 1  0  Multiple sclerosis

46. 1  0  Polyarteritis nodosa

47. 1  0  Psoriasis

48. 1  0  Other autoimmune disease, specify: \_\_\_\_\_

49. 1  0  Other, specify: \_\_\_\_\_

TEAM     IUBMID

**Organ Function Values Just Prior to Conditioning**

Liver function:

		<u>Specify Units</u>	<u>Date tested:</u> Month Day Year	<u>Not Tested</u>
AST (SGOT)				
50.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> U/L 2 <input type="checkbox"/> $\mu$ kat/L	51. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>
52.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>	Upper limit of normal		
ALT (SGPT)				
53.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> U/L 2 <input type="checkbox"/> $\mu$ kat/L	54. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>
55.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>	Upper limit of normal		
Total serum bilirubin				
56.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/>	1 <input type="checkbox"/> mg/dL 2 <input type="checkbox"/> $\mu$ mol/L	58. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>
59.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/>	Upper limit of normal		
LDH				
60.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> U/L 2 <input type="checkbox"/> $\mu$ kat/L	61. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>
62.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>	Upper limit of normal		

63. Did patient have known clinical liver disease (eg. viral hepatitis) at any time prior to conditioning?

1  Yes  
0  No

Specify:

	<u>Yes</u>	<u>No</u>	<u>Unknown</u>	
64.	1 <input type="checkbox"/> 0 <input type="checkbox"/> 8 <input type="checkbox"/>			Hepatitis B
65.	1 <input type="checkbox"/> 0 <input type="checkbox"/> 8 <input type="checkbox"/>			Hepatitis A
66.	1 <input type="checkbox"/> 0 <input type="checkbox"/> 8 <input type="checkbox"/>			Hepatitis C
67.	1 <input type="checkbox"/> 0 <input type="checkbox"/> 8 <input type="checkbox"/>			Drug toxicity
68.	1 <input type="checkbox"/> 0 <input type="checkbox"/> 8 <input type="checkbox"/>			Other, specify: _____
69.	Date of onset: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>			<input type="checkbox"/> Date Unknown
				Month Day Year

Serum creatinine just prior to conditioning:

		<u>Specify Units</u>	<u>Date tested:</u> Month Day Year	<u>Not Tested</u>
70.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> mg/dL 2 <input type="checkbox"/> mmol/L 3 <input type="checkbox"/> $\mu$ mol/L	72. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>

**Hematologic Findings Just Prior to Conditioning**

Date of CBC:        
Month Day Year

Actual CBC results

	<u>Specify Units</u>	<u>Transfused</u>	<u>Not Tested</u>
WBC: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/>	1 <input type="checkbox"/> $\times 10^9/L$ 2 <input type="checkbox"/> $\times 10^6/L$	<input type="checkbox"/>	<input type="checkbox"/>
Neutrophils: <input type="text"/> <input type="text"/> %		<input type="checkbox"/>	<input type="checkbox"/>
Lymphocytes: <input type="text"/> <input type="text"/> %		<input type="checkbox"/>	<input type="checkbox"/>
Hemoglobin: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> g/dL 2 <input type="checkbox"/> g/L 3 <input type="checkbox"/> mmol/L	<input type="checkbox"/>	<input type="checkbox"/>
Hematocrit: <input type="text"/> <input type="text"/> %		<input type="checkbox"/>	<input type="checkbox"/>
Platelets: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> $\times 10^9/L$ 2 <input type="checkbox"/> $\times 10^6/L$	<input type="checkbox"/>	<input type="checkbox"/>



TEAM

IUBMID

73. Patient smokes cigarettes, or has in the past:

1  Yes

0  No

8  Unknown

74. Average number of packs per day:     8  Unknown

75. Number of years:   8  Unknown

76. Was clinically important infection(s) present or being treated within one week prior to conditioning?

Note: Report later infections on page 30 of this report.

1  Yes

0  No

Select site and organism from lists shown on the next page and place number in the appropriate spaces. If more than one site or organism were involved, list one site of infection and organism on the first line, second site and/or organism on second line.

*If more than two infections of any category, check here  and copy page to provide information on 3rd or subsequent infection (do not report in Q.106-110).*

Site

Organism

77.  Bacterial

Typical

First

78.

79. \_\_\_\_\_

Second

80.

81. \_\_\_\_\_

Atypical

First

83.

84.

Second

85.

86.

87. Other atypical bacterium, specify: \_\_\_\_\_

88.  Fungal

First

89.

90.

Second

91.

92.

93. Other fungus, specify: \_\_\_\_\_

94.  Viral

First

95.

96.

Second

97.

98.

99. Other virus, specify: \_\_\_\_\_

100.  Parasitic

First

101.

102.

Second

103.

104.

105. Other parasite, specify: \_\_\_\_\_

106.  Other infections

First

107.

108.

Second

109.

110.

TEAM

IUBMID

### Codes for Common Sites of Infection

- |  |  |
|--|--|
| 1 Blood/buffy coat   | 40 <u>Genito-Urinary Tract unspecified</u>                     |
| 2 Disseminated – generalized, isolated at 3 or more distinct sites | 41 Kidneys, renal pelvis, ureters and bladder                  |
| 3 <u>Central Nervous System unspecified</u>                        | 42 Prostate  |
| 4 Brain  | 43 Testes  |
| 5 Spinal cord  | 44 Fallopian tubes, uterus, cervix                             |
| 6 Meninges and CSF   | 45 Vagina  |
| 10 <u>Gastrointestinal Tract unspecified</u>                       | 50 <u>Skin unspecified</u>                                     |
| 11 Lips  | 51 Genital area  |
| 12 Tongue, oral cavity and oro-pharynx                             | 52 Cellulitis  |
| 13 Esophagus   | 53 Herpes Zoster   |
| 14 Stomach   | 54 Rash, pustules or abscesses not typical of any of the above |
| 15 Gallbladder and biliary tree (not hepatitis), pancreas          | 60 <u>Central venous catheter unspecified</u>                  |
| 16 Small intestine   | 61 Catheter insertion or exit site                             |
| 17 Large intestine   | 62 Catheter tip  |
| 18 Feces/stool   | 70 Eyes  |
| 19 Peritoneum  | 75 Ear   |
| 20 Liver   | 81 Joints  |
| 30 <u>Respiratory unspecified</u>                                  | 82 Bone marrow   |
| 31 Upper airway and nasopharynx                                    | 83 Bone cortex (osteomyelitis)                                 |
| 32 Laryngitis/larynx   | 84 Muscle (excluding cardiac)                                  |
| 33 Lower respiratory tract (lung)                                  | 85 Cardiac (endocardium, myocardium, pericardium)              |
| 34 Pleural cavity, pleural fluid                                   | 86 Lymph nodes   |
| 35 Sinuses   | 87 Spleen  |

### Codes for Commonly Reported Organisms

- |   |  |
|---|--|
| <b>1. Bacteria</b> (Indicate code for atypical bacteria; list bacterium for non-atypical bacteria in <b>Q.79, 81.</b> ) | <b>3. Viral Infections</b>   |
| 100 Atypical bacteria, not otherwise specified  | 301 Herpes Simplex (HSV1, HSV2)  |
| 101 Coxiella  | 302 Herpes Zoster (Chicken pox, Varicella)   |
| 102 Legionella  | 303 Cytomegalovirus (CMV)  |
| 103 Leptospira  | 304 Adenovirus   |
| 104 Listeria  | 305 Enterovirus (Coxsackie, Echo, Polio)   |
| 105 Mycoplasma  | 306 Hepatitis A (HAV)  |
| 106 Nocardia  | 307 Hepatitis B (HBV, Australian antigen)  |
| 107 Rickettsia  | 308 Hepatitis C (HCV)  |
| 110 Tuberculosis, NOS (AFB, acid fast bacillus, Koch bacillus)  | 309 HIV-1 (HTLV-III)   |
| 111 Typical tuberculosis (TB, Tuberculosis)   | 310 Influenza  |
| 112 Mycobacteria (avium, bovis, intracellulare)   | 311 Measles (Rubeola)  |
| 113 Chlamydia   | 312 Mumps  |
| 119 Other atypical bacteria, <i>specify in Q.87</i>   | 313 Papovavirus  |
| <b>2. Fungal Infections</b>   | 314 Respiratory syncytial virus (RSV)  |
| 200 Candida, not otherwise specified  | 315 Rubella (German Measles)   |
| 201 Candida albicans  | 316 Parainfluenza  |
| 202 Candida krusei  | 317 Human herpesvirus-6 (HHV-6)  |
| 203 Candida parapsilosis  | 318 Epstein-Barr virus (EBV)   |
| 204 Candida tropicalis  | 319 Polyomavirus   |
| 205 Torulopsis glabrata (a subspecies of candida)   | 320 Rotavirus  |
| 209 Other Candida, <i>specify in Q.93</i>   | 321 Rhinovirus   |
| 210 Aspergillus, not otherwise specified  | 329 Other viral, <i>specify in Q.99</i>  |
| 211 Aspergillus flavus  | <b>4. Parasite Infections</b>  |
| 212 Aspergillus fumigatus   | 401 Pneumocystis (PCP)   |
| 213 Aspergillus niger   | 402 Toxoplasma   |
| 219 Other Aspergillus, <i>specify in Q.93</i>   | 403 Giardia  |
| 220 Cryptococcus species  | 404 Cryptosporidium  |
| 230 Fusarium species  | 409 Other parasite (amebiasis, echinococcal cyst, trichomonas – either vaginal or gingivitis), <i>specify in Q.105</i> |
| 240 Mucormycosis (zygomycetes, rhizopus)  | <b>5. Other Infections</b>   |
| 250 Yeast, not otherwise specified  | 501 Suspected atypical bacterial infection   |
| 259 Other fungus, <i>specify in Q.93</i>  | 502 Suspected bacterial infection  |
|   | 503 Suspected fungal infection   |
|   | 504 Suspected viral infection  |
|   | 505 Suspected parasite infection   |
|   | 509 No organism identified   |

TEAM

IUBMID

112. Did patient have a history of clinically important fungal infection at any time prior to conditioning for transplant?

- 1  Yes
- 0  No

Specify:

113. Date of onset:     
Month Day Year

114. Select organism from list on previous page:      
F

Other fungus, specify: \_\_\_\_\_

115. Select site(s) from list on previous page:   116.

### Tests for Serological Evidence of Prior Viral Exposure/Infection

Recipient:	Positive	Negative	Inconclusive	Not Tested
117. HTLV1 antibody	1 <input type="checkbox"/>	0 <input type="checkbox"/>	3 <input type="checkbox"/>	7 <input type="checkbox"/>
118. Toxoplasma antibody	1 <input type="checkbox"/>	0 <input type="checkbox"/>	3 <input type="checkbox"/>	7 <input type="checkbox"/>
119. Cytomegalovirus antibody	1 <input type="checkbox"/>	0 <input type="checkbox"/>	3 <input type="checkbox"/>	7 <input type="checkbox"/>
120. Epstein-Barr antibody	1 <input type="checkbox"/>	0 <input type="checkbox"/>	3 <input type="checkbox"/>	7 <input type="checkbox"/>
121. Hepatitis B surface and/or core antibody	1 <input type="checkbox"/>	0 <input type="checkbox"/>	3 <input type="checkbox"/>	7 <input type="checkbox"/>
122. Hepatitis B surface antigen	1 <input type="checkbox"/>	0 <input type="checkbox"/>	3 <input type="checkbox"/>	7 <input type="checkbox"/>
123. Hepatitis C antibody	1 <input type="checkbox"/>	0 <input type="checkbox"/>	3 <input type="checkbox"/>	7 <input type="checkbox"/>
124. Hepatitis A antibody	1 <input type="checkbox"/>	0 <input type="checkbox"/>	3 <input type="checkbox"/>	7 <input type="checkbox"/>
125. Human Immunodeficiency Virus (HIV) antibody	1 <input type="checkbox"/>	0 <input type="checkbox"/>	3 <input type="checkbox"/>	7 <input type="checkbox"/>

6  Not able to release information for HIV

### High-Dose Therapy (Pretransplant Conditioning)

126. Does protocol for high-dose therapy (conditioning) require some or all agents be given as an inpatient?

Protocol requires:

- 0  All agents given as outpatient
- 2  Some, but not all agents given as inpatient
- 3  All agents given as inpatient
- 7  No high dose therapy given

127. Was patient treated in an isolation room during the peri-transplant period?

- 1  Yes
- 0  No

Please specify:

	Yes	No	
128.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Conventional private room
129.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Laminar air flow room
130.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	HEPA filtered room
131.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Positive pressure
132.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

133. Date pretransplant conditioning (radiation or drugs) was begun:     
Month Day Year

134. Height at initiation of pretransplant conditioning:    cm    inches

135. Actual weight at initiation of pretransplant conditioning:    kg    pounds

TEAM

IUBMID

136. Was irradiation performed as part of the pretransplant conditioning regimen? 1  Yes 0  No Go to Q.182

137. Source of x-ray therapy:

1  Linear accelerator

2  <sup>60</sup>Co

7  Other, specify: \_\_\_\_\_

138. Maximum energy:    MV (million volts)

139. Calculated mid-line dose-rate during irradiation:   .  cGy (rad)/min

**What was the radiation field?**

140. Total Body Radiation

1  Yes

0  No

141. Total dose:     cGy

Prescription point:

Yes No

142. 1  0  Midline umbilicus

143. 1  0  Other, specify: \_\_\_\_\_

Patient orientation:

Yes No

144. 1  0  AP/PA

145. 1  0  Other, specify: \_\_\_\_\_

Method of dose verification:

Yes No

146. 1  0  Phantom

147. 1  0  Diodes on patient

148. 1  0  Other, specify: \_\_\_\_\_

149. Starting date:         
Month Day Year

150. Was radiation fractionated?

1  Yes

0  No

8  Unknown

151. Dose per fraction:     cGy

152. Number of days:

153. Total number of fractions:

154. Was shielding used?

1  Yes

0  No

8  Unknown

Yes No

155. 1  0  Lungs

156. 1  0  Eyes

157. 1  0  Liver

158. 1  0  Kidney

159. 1  0  Other, specify: \_\_\_\_\_

Radiation field data continued on next page

TEAM

IUBMID

Radiation field data continued from previous page

**160. Total lymphoid or nodal regions**      1  Yes    0  No

**161.** Total dose:  cGy      **162.** Start date:     
Month    Day    Year

**163.** Was radiation fractionated?  
1  Yes  
0  No  
8  Unknown

**164.** Dose per fraction:  cGy

**165.** Number of days:

**166.** Total number of fractions:

**167. Thoraco-abdominal region**      1  Yes    0  No

**168.** Total dose:  cGy      **169.** Start date:     
Month    Day    Year

**170.** Was radiation fractionated?  
1  Yes  
0  No  
8  Unknown

**171.** Dose per fraction:  cGy

**172.** Number of days:

**173.** Total number of fractions:  **Go to Q.182**

**182.** Was (additional) radiation given to other sites?

1  Yes  
0  No

**183.** Was CNS irradiation performed?  
1  Yes  
0  No

**184.** Dose:  cGy      **185.** Start date:     
Month    Day    Year

**186.** Was gonadal irradiation performed?  
1  Yes  
0  No

**187.** Dose:  cGy      **188.** Start date:     
Month    Day    Year

**189.** Was splenic irradiation performed?  
1  Yes  
0  No

**190.** Dose:  cGy      **191.** Start date:     
Month    Day    Year

**191.<sup>2</sup>** Radiation to site of residual tumor?  
1  Yes  
0  No

**191.<sup>3</sup>** Specify site: \_\_\_\_\_

**191.<sup>4</sup>** Dose:  cGy      **191.<sup>5</sup>** Start date:     
Month    Day    Year

**192.** Other?  
1  Yes  
0  No

**192.<sup>2</sup>** Specify site: \_\_\_\_\_

**193.** Dose:  cGy      **194.** Start date:     
Month    Day    Year

TEAM

IUBMID

195. Were drugs given for pretransplant conditioning? 1  Yes 0  No Go to Q.361

196. Date started:													
		Month	Day	Year									
		Drug Given		Total dose (in mg) pre-marrow infusion (not daily dose)	Number of doses	Continuous infusion ≥24hrs		Number of days					
		Yes	No			Yes	No						
197.	ALG, ALS, ATG, ATS	1 <input type="checkbox"/>	0 <input type="checkbox"/>	198. <input type="text"/>	199. <input type="text"/>	200. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	201. <input type="text"/>					
202.	Anthracycline	1 <input type="checkbox"/> 0 <input type="checkbox"/>											
203.	Daunomycin	1 <input type="checkbox"/>	0 <input type="checkbox"/>	204. <input type="text"/>	205. <input type="text"/>	206. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	207. <input type="text"/>					
208.	Doxorubicin (Adriamycin)	1 <input type="checkbox"/>	0 <input type="checkbox"/>	209. <input type="text"/>	210. <input type="text"/>	211. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	212. <input type="text"/>					
213.	Idarubicin	1 <input type="checkbox"/>	0 <input type="checkbox"/>	214. <input type="text"/>	215. <input type="text"/>	216. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	217. <input type="text"/>					
218.	Rubidazole	1 <input type="checkbox"/>	0 <input type="checkbox"/>	219. <input type="text"/>	220. <input type="text"/>	221. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	222. <input type="text"/>					
223.	Other anthracycline, specify: _____	1 <input type="checkbox"/>	0 <input type="checkbox"/>	224. <input type="text"/>	225. <input type="text"/>	226. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	227. <input type="text"/>					
228.	Bleomycin	1 <input type="checkbox"/>	0 <input type="checkbox"/>	229. <input type="text"/>	230. <input type="text"/>	231. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	232. <input type="text"/>					
233.	Busulfan (myleran)	1 <input type="checkbox"/>	0 <input type="checkbox"/>	234. <input type="text"/>	235. <input type="text"/>	236. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	237. <input type="text"/>					
238.	Carboplatin	1 <input type="checkbox"/>	0 <input type="checkbox"/>	239. <input type="text"/>	240. <input type="text"/>	241. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	242. <input type="text"/>					
243.	Cisplatin	1 <input type="checkbox"/>	0 <input type="checkbox"/>	244. <input type="text"/>	245. <input type="text"/>	246. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	247. <input type="text"/>					
248.	Corticosteroids (excluding anti-nausea medication)	1 <input type="checkbox"/> 0 <input type="checkbox"/>											
249.	Methylprednisolone (Solumedrol)	1 <input type="checkbox"/>	0 <input type="checkbox"/>										
		250. <input type="checkbox"/> Oral <input type="checkbox"/> IV		251. <input type="text"/>	252. <input type="text"/>	253. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	254. <input type="text"/>					
255.	Prednisone	1 <input type="checkbox"/>	0 <input type="checkbox"/>	256. <input type="text"/>	257. <input type="text"/>	258. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	259. <input type="text"/>					
260.	Dexamethasone	1 <input type="checkbox"/>	0 <input type="checkbox"/>	261. <input type="text"/>	262. <input type="text"/>	263. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	264. <input type="text"/>					
265.	Other corticosteroids, specify: _____	1 <input type="checkbox"/>	0 <input type="checkbox"/>	266. <input type="text"/>	267. <input type="text"/>	268. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	269. <input type="text"/>					
270.	Cyclophosphamide	1 <input type="checkbox"/>	0 <input type="checkbox"/>	271. <input type="text"/>	272. <input type="text"/>	273. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	274. <input type="text"/>					
275.	Cytarabine (Ara-C)	1 <input type="checkbox"/>	0 <input type="checkbox"/>	276. <input type="text"/>	277. <input type="text"/>	278. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	279. <input type="text"/>					
280.	Etoposide (VP16)	1 <input type="checkbox"/>	0 <input type="checkbox"/>	281. <input type="text"/>	282. <input type="text"/>	283. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	284. <input type="text"/>					
284. <sup>2</sup>	Fludarabine	1 <input type="checkbox"/>	0 <input type="checkbox"/>	284. <sup>3</sup> <input type="text"/>	284. <sup>4</sup> <input type="text"/>	284. <sup>5</sup> 1 <input type="checkbox"/>	0 <input type="checkbox"/>	284. <sup>6</sup> <input type="text"/>					
285.	Ifosfamide	1 <input type="checkbox"/>	0 <input type="checkbox"/>	286. <input type="text"/>	287. <input type="text"/>	288. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	289. <input type="text"/>					

Continued on next page

TEAM

IUBMID

Continued from previous page

	Drug Given		Total dose (in mg) pre-marrow infusion (not daily dose)	Number of doses	Continuous infusion >24hrs		Number of days
	Yes	No			Yes	No	
290. Intrathecal chemotherapy	<input type="checkbox"/> <input type="checkbox"/>						
291. Cytarabine	<input type="checkbox"/>	<input type="checkbox"/>	292. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	293. <input type="checkbox"/> <input type="checkbox"/>			294. <input type="checkbox"/>
295. Methotrexate	<input type="checkbox"/>	<input type="checkbox"/>	296. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	297. <input type="checkbox"/> <input type="checkbox"/>			298. <input type="checkbox"/>
299. Other, specify:	<input type="checkbox"/>	<input type="checkbox"/>	300. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	301. <input type="checkbox"/> <input type="checkbox"/>			302. <input type="checkbox"/>
303. Melphalan (L-PAM)	<input type="checkbox"/>	<input type="checkbox"/>					
304. <input type="checkbox"/> Oral <input type="checkbox"/> IV			305. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	306. <input type="checkbox"/> <input type="checkbox"/>	307. <input type="checkbox"/> <input type="checkbox"/>		308. <input type="checkbox"/>
309. Mitoxantrone	<input type="checkbox"/>	<input type="checkbox"/>	310. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	311. <input type="checkbox"/> <input type="checkbox"/>	312. <input type="checkbox"/> <input type="checkbox"/>		313. <input type="checkbox"/>
314. Monoclonal antibody	<input type="checkbox"/> <input type="checkbox"/>						
315. Radionuclide-tagged Mab, specify:	<input type="checkbox"/>	<input type="checkbox"/>	316. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	317. <input type="checkbox"/> <input type="checkbox"/>	318. <input type="checkbox"/> <input type="checkbox"/>		319. <input type="checkbox"/>
320. Campath	<input type="checkbox"/>	<input type="checkbox"/>	321. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	322. <input type="checkbox"/> <input type="checkbox"/>	323. <input type="checkbox"/> <input type="checkbox"/>		324. <input type="checkbox"/>
325. Other Mab, specify:	<input type="checkbox"/>	<input type="checkbox"/>	326. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	327. <input type="checkbox"/> <input type="checkbox"/>	328. <input type="checkbox"/> <input type="checkbox"/>		329. <input type="checkbox"/>
330. Nitrosourea	<input type="checkbox"/> <input type="checkbox"/>						
331. BCNU	<input type="checkbox"/>	<input type="checkbox"/>	332. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	333. <input type="checkbox"/> <input type="checkbox"/>	334. <input type="checkbox"/> <input type="checkbox"/>		335. <input type="checkbox"/>
336. CCNU	<input type="checkbox"/>	<input type="checkbox"/>	337. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	338. <input type="checkbox"/> <input type="checkbox"/>	339. <input type="checkbox"/> <input type="checkbox"/>		340. <input type="checkbox"/>
341. Other nitrosourea, specify:	<input type="checkbox"/>	<input type="checkbox"/>	342. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	343. <input type="checkbox"/> <input type="checkbox"/>	344. <input type="checkbox"/> <input type="checkbox"/>		345. <input type="checkbox"/>
345. <sup>2</sup> Paclitaxel (Taxol)	<input type="checkbox"/>	<input type="checkbox"/>	345. <sup>3</sup> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	345. <sup>4</sup> <input type="checkbox"/> <input type="checkbox"/>	345. <sup>5</sup> <input type="checkbox"/> <input type="checkbox"/>		355. <sup>6</sup> <input type="checkbox"/>
346. Teniposide (VM26)	<input type="checkbox"/>	<input type="checkbox"/>	347. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	348. <input type="checkbox"/> <input type="checkbox"/>	349. <input type="checkbox"/> <input type="checkbox"/>		350. <input type="checkbox"/>
351. Thiotepa	<input type="checkbox"/>	<input type="checkbox"/>	352. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	353. <input type="checkbox"/> <input type="checkbox"/>	354. <input type="checkbox"/> <input type="checkbox"/>		355. <input type="checkbox"/>
356. Other, specify:	<input type="checkbox"/>	<input type="checkbox"/>	357. <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	358. <input type="checkbox"/> <input type="checkbox"/>	359. <input type="checkbox"/> <input type="checkbox"/>		360. <input type="checkbox"/>

TEAM

IUBMID

361. Was this the first transplant for this recipient?

- 1  Yes
- 0  No

362. Is a second transplant planned as part of treatment protocol?

- 1  Yes
- 0  No

Go to Q.384

**Previous Transplants**

363. Number of previous transplants recipient has had:

*(if more than 1 previous transplant, photocopy this page and answer Q.364-383 for each previous transplant)*

364. Date of previous transplant:     
Month Day Year

364.<sup>2</sup> Was previous transplant performed at a different institution?

- 1  Yes
- 0  No

Name: \_\_\_\_\_  
 City: \_\_\_\_\_ State: \_\_\_\_\_  
 Country: \_\_\_\_\_

365. Graft type of previous transplant:

- 1  Autologous

Yes No  
 366. 1  0  Bone marrow  
 367. 1  0  Peripheral blood  
 368. 1  0  Other, specify: \_\_\_\_\_  
 369. Was this transplant reported to the ABMTR?  
 1  Yes  
 0  No  
 8  Unknown

- 2  Allogeneic, unrelated donor

370. Same donor as current transplant? 1  Yes 0  No

Yes No  
 371. 1  0  Bone marrow  
 372. 1  0  Peripheral blood  
 373. 1  0  Cord Blood  
 374. 1  0  Fetal tissue  
 375. 1  0  Other, specify: \_\_\_\_\_

- 3  Allogeneic, related donor

376. Was this transplant reported to the IBMTR?  
 1  Yes  
 0  No  
 8  Unknown

383. Reason for re-transplant:

- 1  No engraftment
- 2  Partial engraftment
- 3  Graft failure/rejection
- 4  Persistent malignancy
- 5  Recurrent malignancy
- 6  Planned second transplant, per protocol

Date of rejection/failure:     
Month Day Year

Date of relapse:     
Month Day Year

8  Secondary malignancy (specify disease from lists on pg 2-4):

90  Other, specify: \_\_\_\_\_

*Please complete disease-specific insert for secondary malignancy and continue as well with disease insert for disease of first transplant.*



TEAM

IUBMID

384. What type of graft did patient receive for the current transplant?

1  Autologous

385. From where were stem cells obtained?

1  Bone marrow  Complete INSERT AUTOBM

2  Blood  Complete INSERT AUTOPB

3  Bone marrow & Blood  Complete INSERTS AUTOBM & AUTOPB

2  Allogeneic

**Yes No**

1  0  Bone marrow  If yes, complete INSERT ALLOBM

1  0  Peripheral blood  If yes, complete INSERT ALLOPB

3  Syngeneic

1  0  Umbilical cord blood  If yes, complete INSERT ALLOCB

1  0  Fetal tissue  If yes, complete INSERT ALLOBM

1  0  Other  If yes, complete INSERT ALLOBM

specify: \_\_\_\_\_

TEAM

IUBMID

### Posttransplant Information

387. Did patient die prior to day 100 after this transplant?  
1  Yes – Answers on pages 19-37 should reflect clinical status immediately prior to death, if no further infusions  
0  No – Answers on pages 19-37 should reflect clinical status on day of actual contact for this follow-up examination (approximately 100 days posttransplant), if no further infusions

388. Did patient receive a subsequent blood or marrow infusion after the transplant for which this report is being completed? (other than peripheral blood leukocytes or T-lymphocytes from original allogeneic donor)

- 1  Yes  
0  No

#### Subsequent transplant

Answers on pages 19-37 of this report should reflect clinical status immediately prior to start of conditioning for subsequent infusion.

**A separate report covering the subsequent transplant must be submitted unless the subsequent transplant is autologous for treatment of graft failure posttransplant.**

389. Date of subsequent infusion:  /  /   
Month Day Year

390. Reason for subsequent infusion:

1  No engraftment

2  Partial engraftment

3  Late graft failure

**Autologous re-infusions for these reasons do not require separate report completion**

4  Persistent malignancy

5  Relapse

6  Planned second transplant, per protocol

8  Secondary malignancy

**Complete new malignancy Q.864-878**

90  Other, specify: \_\_\_\_\_

391. Type of graft:

1  Allogeneic, related

2  Allogeneic, unrelated

3  Autologous

Donor:

1  Same donor

2  Different donor

3  Not applicable, initial transplant was autologous

Source of cells:

392. 1  Fresh

2  Cryopreserved

393. Check all that apply:

**Yes No**

1  0  Bone marrow

1  0  Peripheral blood

1  0  Cord blood

1  0  Fetal tissue

1  0  Other, specify: \_\_\_\_\_

TEAM

IUBMID

395. Has patient received an infusion of peripheral blood leukocytes or T-lymphocytes from the original donor?

- 1  Yes  
0  No

396. Date first infusion given:    /   /     
Month Day Year

397. Patient weight within 2 weeks of first infusion:   kg    pounds

398. Total number of infusions:

399. Total dose of mononuclear cells given:    .  x 10 (supply exponent)

400. Were cells manipulated prior to infusion?  
1  Yes  
0  No

401. Indicate method:

Yes	No
1 <input type="checkbox"/>	0 <input type="checkbox"/>
1 <input type="checkbox"/>	0 <input type="checkbox"/>
1 <input type="checkbox"/>	0 <input type="checkbox"/>
1 <input type="checkbox"/>	0 <input type="checkbox"/>

1  0  Other, specify: \_\_\_\_\_

402. Indication for the infusion(s) of donor cells:

1  Prophylaxis against B-cell lymphoproliferative disorder (or viral infection)  
2  Prophylaxis against relapse

3  Treatment of relapse  
4  Treatment of B-cell lymphoproliferative disorder  
5  Treatment of viral infection, specify: \_\_\_\_\_  
6  Graft failure  
7  Other, specify: \_\_\_\_\_

*If answers 3-7 were selected, then answers on pages 19-37 should reflect clinical status immediately prior to infusion. This is considered a transplant and a separate report covering this infusion and post-infusion events must be submitted.*

TEAM

IUBMID

### Hematopoietic Reconstitution Posttransplant

403. Has patient received hematopoietic growth factors or cytokines post conditioning? 1  Yes 0  No Go to Q.481

				Date Started			Date Stopped			Still Receiving	Indication Code		
		Yes	No	Month	Day	Year	Month	Day	Year				
<b>1st course:</b>													
G-CSF	404.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	405.				406.				<input type="checkbox"/>	
GM-CSF	407.	2 <input type="checkbox"/>	0 <input type="checkbox"/>	408.				409.				<input type="checkbox"/>	
Erythropoietin	409. <sup>2</sup>	3 <input type="checkbox"/>	0 <input type="checkbox"/>	409. <sup>3</sup>				409. <sup>4</sup>				<input type="checkbox"/>	
Thrombopoietin	409. <sup>5</sup>	4 <input type="checkbox"/>	0 <input type="checkbox"/>	409. <sup>6</sup>				409. <sup>7</sup>				<input type="checkbox"/>	
Interleukin-2	409. <sup>8</sup>	5 <input type="checkbox"/>	0 <input type="checkbox"/>	409. <sup>9</sup>				409. <sup>10</sup>				<input type="checkbox"/>	
Interleukin-3	410.	6 <input type="checkbox"/>	0 <input type="checkbox"/>	411.				412.				<input type="checkbox"/>	
Interleukin-6	413.	7 <input type="checkbox"/>	0 <input type="checkbox"/>	414.				415.				<input type="checkbox"/>	
PIXY-321	416.	8 <input type="checkbox"/>	0 <input type="checkbox"/>	417.				418.				<input type="checkbox"/>	
Stem Cell Factor (SCF)	419.	9 <input type="checkbox"/>	0 <input type="checkbox"/>	420.				421.				<input type="checkbox"/>	
Interferon-alpha	421. <sup>2</sup>	10 <input type="checkbox"/>	0 <input type="checkbox"/>	421. <sup>3</sup>				421. <sup>4</sup>				<input type="checkbox"/>	
Interferon-gamma	421. <sup>5</sup>	11 <input type="checkbox"/>	0 <input type="checkbox"/>	421. <sup>6</sup>				421. <sup>7</sup>				<input type="checkbox"/>	
Blinded growth factor trial, specify agent(s) being studied:	422.	89 <input type="checkbox"/>	0 <input type="checkbox"/>	423.				424.				<input type="checkbox"/>	
Other, specify:	425.	90 <input type="checkbox"/>	0 <input type="checkbox"/>	426.	<input type="text"/>	<input type="text"/>	<input type="text"/>	427.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="text"/>
<b>2nd course:</b>													
G-CSF	428.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	429.				430.				<input type="checkbox"/>	431.
GM-CSF	432.	2 <input type="checkbox"/>	0 <input type="checkbox"/>	433.				434.				<input type="checkbox"/>	435.
Erythropoietin	436.	3 <input type="checkbox"/>	0 <input type="checkbox"/>	437.				438.				<input type="checkbox"/>	439.
Thrombopoietin	440.	4 <input type="checkbox"/>	0 <input type="checkbox"/>	441.				442.				<input type="checkbox"/>	443.
Interleukin-2	444.	5 <input type="checkbox"/>	0 <input type="checkbox"/>	445.				446.				<input type="checkbox"/>	447.
Interleukin-3	448.	6 <input type="checkbox"/>	0 <input type="checkbox"/>	449.				450.				<input type="checkbox"/>	451.
Interleukin-6	452.	7 <input type="checkbox"/>	0 <input type="checkbox"/>	453.				454.				<input type="checkbox"/>	455.
PIXY-321	456.	8 <input type="checkbox"/>	0 <input type="checkbox"/>	457.				458.				<input type="checkbox"/>	459.
Stem Cell Factor (SCF)	460.	9 <input type="checkbox"/>	0 <input type="checkbox"/>	461.				462.				<input type="checkbox"/>	463.
Interferon-alpha	464.	10 <input type="checkbox"/>	0 <input type="checkbox"/>	465.				466.				<input type="checkbox"/>	467.
Interferon-gamma	468.	11 <input type="checkbox"/>	0 <input type="checkbox"/>	469.				470.				<input type="checkbox"/>	471.
Blinded growth factor trial, specify agent(s) being studied:	472.	89 <input type="checkbox"/>	0 <input type="checkbox"/>	473.				474.				<input type="checkbox"/>	475.
Other, specify:	476.	90 <input type="checkbox"/>	0 <input type="checkbox"/>	477.	<input type="text"/>	<input type="text"/>	<input type="text"/>	478.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	479.

**Coding for Indication of Therapy**

0. Planned therapy per protocol to promote engraftment	4. Intervention for delay/decline in red blood cell counts
1. Intervention for delay/decline in Absolute Neutrophil Count (ANC)	5. Anti-leukemic or tumor agent to <u>prevent</u> relapse
2. Intervention for delay/decline in platelets	6. Anti-leukemic or tumor agent to <u>treat</u> relapse
3. Intervention for delay/decline in both ANC and platelets	7. Other indication

Continued on next page

TEAM

IUBMID

Continued from previous page

480. Did patient receive other courses of growth factors or cytokines posttransplant?

1  Yes

0  No

8  Unknown

Photocopy Q.428-479 and answer for each additional course given.

## Granulopoiesis

481. Is (was) there evidence of hematopoietic recovery following the initial hematopoietic cell infusion? (check only one)

1  Yes,

ANC  $\geq$  500/mm<sup>3</sup> achieved and sustained for 3 consecutive days

482. Date ANC  $\geq$  500/mm<sup>3</sup> (First of 3 consecutive days):      
Month Day

483. Was ANC  $\geq$  1000/mm<sup>3</sup> achieved and sustained for 3 consecutive days?

1  Yes

0  No

8  Unknown

484. Date achieved (first of 3 consecutive days):

Month Day Year  Date unknown

Go to Q.512

2  Yes,

ANC  $\geq$  500/mm<sup>3</sup> for 3 consecutive days with subsequent decline in ANC to  $<$ 500/mm<sup>3</sup> for greater than 3 days

485. Date ANC  $\geq$  500/mm<sup>3</sup> (First of 3 consecutive days):       
Month Day Year

486. Was ANC  $\geq$  1000/mm<sup>3</sup> achieved and sustained for 3 consecutive days?

1  Yes

0  No

8  Unknown

487. Date achieved (first of 3 consecutive days):

Month Day Year  Date unknown

488. Date of decline in ANC to  $<$  500/mm<sup>3</sup> for greater than 3 days (First of 3 days that ANC declined):      
Month Day Year

489. Did patient recover and maintain ANC  $\geq$  500/mm<sup>3</sup> following the decline?

1  Yes

0  No

490. Date of ANC recovery:      
Month Day Year

Go to Q.491

3  No, ANC  $\geq$  500/mm<sup>3</sup> was not achieved and there was no evidence of recurrent disease in the bone marrow

Go to Q.491

4  No, ANC  $\geq$  500/mm<sup>3</sup> was not achieved and there was documented persistent disease in the bone marrow posttransplant

Go to Q.491

7  ANC never dropped below 500/mm<sup>3</sup>

Go to Q.512

TEAM

IUBMID

Suspected etiology of failure to achieve ANC  $\geq$  500/mm<sup>3</sup> or of a decline in ANC:

491. Persistent disease or relapse:

- 1  Yes  
0  No  
8  Unknown

492. Graft versus host disease:

- 1  Yes  
0  No  
8  Unknown

493. Immune-mediated rejection:

- 1  Yes  
0  No  
8  Unknown

494. Non-viral infection:

- 1  Yes  
0  No  
8  Unknown

495. Suspected viral infection:

- 1  Yes  
0  No  
8  Unknown

Virus suspected:

- |      | Yes                        | No                         |                                  |
|------|----------------------------|----------------------------|----------------------------------|
| 496. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Cytomegalovirus (CMV)            |
| 497. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Human Herpes Virus Type 6 (HHV6) |
| 498. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Herpes Simplex Virus (HSV)       |
| 499. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Varicella                        |
| 500. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other, specify: _____            |

501. Documented viral infection:

- 1  Yes  
0  No  
8  Unknown

Virus involved:

- |      | Yes                        | No                         |                                  |
|------|----------------------------|----------------------------|----------------------------------|
| 502. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Cytomegalovirus (CMV)            |
| 503. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Human Herpes Virus Type 6 (HHV6) |
| 504. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Herpes Simplex Virus (HSV)       |
| 505. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Varicella                        |
| 506. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other, specify: _____            |

507. Drugs:

- 1  Yes  
0  No  
8  Unknown

Specify:

- |      | Yes                        | No                         |  |
|------|----------------------------|----------------------------|--|
| 508. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Ganciclovir                                    |
| 509. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Bactrim, Septra, Trimethoprim-sulfamethoxazole |
| 510. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other, specify: _____                          |

511. Etiology undetermined:

- 1  Yes  
0  No

TEAM

IUBMID

### Megakaryopoiesis

The following questions relate to initial platelet recovery. All dates should reflect no transfusions in previous 7 days, and the first of 3 consecutive laboratory results.

512. Was a platelet count of  $\geq 20 \times 10^9/L$  achieved?

- 1  Yes
- 0  No
- 7  Never dropped below 20
- 8  Unknown

Go to Q.518

513. Date platelets  $\geq 20 \times 10^9/L$ :

- Date estimated
- Date unknown

Month Day Year

514. Was a platelet count of  $\geq 50 \times 10^9/L$  achieved?

- 1  Yes
- 0  No
- 7  Never dropped below 50
- 8  Unknown

Go to Q.518

515. Date platelets  $\geq 50 \times 10^9/L$ :

- Date estimated
- Date unknown

Month Day Year

516. Was a platelet count of  $\geq 100 \times 10^9/L$  achieved?

- 1  Yes
- 0  No
- 8  Unknown

517. Date platelets  $\geq 100 \times 10^9/L$ :

- Date estimated
- Date unknown

Month Day Year

518. Was patient ever platelet transfusion independent?

- 1  Yes
- 0  No
- 8  Unknown
- 7  Not applicable (never dependent)

519. Date of last (most recent) platelet transfusion\*:

- Date unknown

Month Day Year

\* If patient was platelet transfusion independent for  $\geq 14$  days but subsequently experienced a decline in platelet count and required platelet transfusions, record date of last platelet transfusion before decline in counts. If patient has not required platelet transfusions since initial date of recovery, record date of last platelet transfusion.

520. Did patient receive platelet transfusions within 7 days of last contact/death?

- 1  Yes
- 0  No
- 8  Unknown

### Erythropoiesis

521. Was patient ever red blood cell (RBC) transfusions independent?

- 1  Yes
- 0  No

522. Date of last (most recent) RBC transfusion\*:

- Date unknown

Month Day Year

\* If patient was RBC transfusion independent for  $\geq 1$  month but subsequently experienced a decline in RBC count and required RBC transfusions, record date of last RBC transfusion before decline in counts. If patient has not required RBC transfusions since initial date of recovery, record date of last RBC transfusion.

523. Did patient receive RBC transfusions within 1 month of last contact/death?

- 1  Yes
- 0  No
- 8  Unknown

TEAM    IUBMID

**Current Hematologic Findings**

Date of most recent CBC:        
Month Day Year

**Actual CBC results**

		<u>Specify Units</u>	<u>Transfused</u>	<u>Not Tested</u>
WBC:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> x10 <sup>9</sup> /L 2 <input type="checkbox"/> x10 <sup>6</sup> /L	<input type="checkbox"/>	<input type="checkbox"/>
Neutrophils:	<input type="text"/> <input type="text"/> %			<input type="checkbox"/>
Lymphocytes:	<input type="text"/> <input type="text"/> %			<input type="checkbox"/>
Hemoglobin:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> g/dL 2 <input type="checkbox"/> g/L 3 <input type="checkbox"/> mmol/L	<input type="checkbox"/>	<input type="checkbox"/>
Hematocrit:	<input type="text"/> <input type="text"/> %		<input type="checkbox"/>	<input type="checkbox"/>
Platelets:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> x10 <sup>9</sup> /L 2 <input type="checkbox"/> x10 <sup>6</sup> /L	<input type="checkbox"/>	<input type="checkbox"/>

**Acute Graft-vs-Host Disease (GVHD)**

524. Was specific therapy used posttransplant to prevent or induce acute GVHD, or promote engraftment (other than growth factors reported in Q.403)?

- 1  Yes  
 0  No  
 8  Unknown

For each agent listed below indicate whether or not it was used to prevent or induce acute GVHD:

	<u>Yes</u>	<u>No</u>	
525.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Methotrexate
526.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cyclosporine
527.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	FK 506 (Tacrolimus)
528.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Corticosteroids
529.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	ALS, ALG, ATS, ATG
530.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Azathioprine
531.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cyclophosphamide
532.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	In vivo anti T-lymphocyte monoclonal antibody _____
538.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	In vivo immunotoxin, specify: _____
539.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Blinded randomized trial; specify agent being studied: _____
540.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

	<u>Yes</u>	<u>No</u>	
533.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Anti IL-2
534.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Anti CD 25
535.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Campath
536.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	OKT3
537.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

Allografts:  
Go to Q.541

Autografts:  
Go to Q.680



TEAM

IUBMID

541. Did acute GVHD occur?

- 1  Yes
- 2  Acute GVHD persists from prior transplant/infusion
- 0  No
- 8  Unknown

Go to Q.593

542. Maximum overall grade: 1  I 2  II 3  III 4  IV

What was diagnosis based on?

543. Histologic evidence: 1  Yes 0  No

548. Clinical evidence: 1  Yes 0  No

Sites:

	Yes	No
544. Skin	1 <input type="checkbox"/>	0 <input type="checkbox"/>
545. Gut	1 <input type="checkbox"/>	0 <input type="checkbox"/>
546. Liver	1 <input type="checkbox"/>	0 <input type="checkbox"/>
547. Other, specify:	1 <input type="checkbox"/>	0 <input type="checkbox"/>

549. Date of onset:            
Month Day Year

550. Was acute GVHD still present at time of this report?  
1  Yes  
0  No  
2  Progressed to chronic GVHD  
8  Unknown

List the maximum severity of organ involvement attributed to acute GVHD:

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
551. Skin:	1 <input type="checkbox"/> No rash	2 <input type="checkbox"/> Maculopapular rash, <25% of body surface	3 <input type="checkbox"/> Maculopapular rash, 25-50% of body surface	4 <input type="checkbox"/> Generalized erythroderma	5 <input type="checkbox"/> Generalized erythroderma with bullae formation and desquamation
552. Intestinal tract (use ml/day for adult patients and ml/m <sup>2</sup> /day for pediatric patients):	0 <input type="checkbox"/> No diarrhea 1 <input type="checkbox"/> Diarrhea <500 ml/day or <280 ml/m <sup>2</sup> /day	2 <input type="checkbox"/> Diarrhea >500 but <1000 ml/day or 280-555 ml/m <sup>2</sup> /day	3 <input type="checkbox"/> Diarrhea >1000 but <1500 ml/day or 556-833 ml/m <sup>2</sup> /day	4 <input type="checkbox"/> Diarrhea >1500 ml/day or >833 ml/m <sup>2</sup> /day	5 <input type="checkbox"/> Severe abdominal pain, with or without ileus
553. Liver:	1 <input type="checkbox"/> Bilirubin <2.0 mg/dL or <35 μmol/L	2 <input type="checkbox"/> Bilirubin 2.0-3.0 mg/dL or 35-52 μmol/L	3 <input type="checkbox"/> Bilirubin 3.1-6.0 mg/dL or 53-103 μmol/L	4 <input type="checkbox"/> Bilirubin 6.1-15.0 mg/dL or 104-256 μmol/L	5 <input type="checkbox"/> Bilirubin >15.0 mg/dL or >256 μmol/L
554. Other organ involvement? 1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No	Yes No 555. 1 <input type="checkbox"/> 0 <input type="checkbox"/> Upper GI tract 556. 1 <input type="checkbox"/> 0 <input type="checkbox"/> Lung 557. 1 <input type="checkbox"/> 0 <input type="checkbox"/> Other, specify: _____				

TEAM

IUBMID

558. Was specific therapy used to treat acute GVHD? 1  Yes 0  No Go to Q.593

For each agent listed below indicate whether or not it was used to treat acute GVHD:

	No, drug not given	Drug continued at prophylactic dose	Yes, drug started	Yes, dose increased		Still taking?	
	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>		Yes <input type="checkbox"/>	No <input type="checkbox"/>
559. Methotrexate	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	560.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
561. Cyclosporine	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	562.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
563. FK 506 (Tacrolimus)	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	564.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
565. Systemic Corticosteroids	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	566.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
567. Topical Corticosteroids	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	568.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
569. ALS, ALG, ATS, ATG	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	570.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
571. Azathioprine	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	572.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
573. Cyclophosphamide	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	574.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
575. Thalidomide	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	576.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
In vivo anti-T-lymphocyte monoclonal antibody:							
577. Anti IL-2	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	578.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
579. Anti CD 25	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	580.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
581. Campath	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	582.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
583. OKT3	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	584.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
585. Other,	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	586.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify: _____							
587. In vivo immunotoxin,	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	588.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify: _____							
589. Blinded randomized trial;	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	590.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify agent being studied: _____							
591. Other,	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	592.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify: _____							

TEAM

IUBMID

### Chronic Graft-vs-Host Disease (GVHD)

593. Has patient developed clinical chronic GVHD?

1  Yes  
 0  No  
 8  Unknown

Go to  
Q.680

594. Date of onset:     Date unknown  
Month Day Year

595. Progressed from acute GVHD?  
 1  Yes  
 0  No

596. Karnofsky/Lansky score (see page 5) at diagnosis of chronic GVHD:

597. Platelet count at diagnosis of chronic GVHD:       x 10<sup>9</sup>/L

598. Total serum bilirubin at diagnosis of chronic GVHD:

599. Units for bilirubin:  
 1  mg/dL 2  μmol/L

What was diagnosis based on?

600. Histologic evidence:  
 1  Yes  
 0  No

Sites:

	Yes	No	
601.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Skin
602.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Gut
603.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Liver
604.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Buccal mucosa/lip
605.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Conjunctiva
606.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Lung
607.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Muscle
608.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

609. Clinical evidence:  
 1  Yes  
 0  No

610. Maximum grade of chronic GVHD:  
 1  Limited (*Localized skin involvement and/or hepatic dysfunction due to chronic GVHD*)  
 2  Extensive (*Generalized skin involvement; or localized skin involvement and/or hepatic dysfunction due to chronic GVHD, plus:*  
*-Liver histology showing chronic aggressive hepatitis, bridging necrosis or cirrhosis; or,*  
*-Involvement of eye: Schirmer's test with < 5 mm wetting; or,*  
*-Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy; or,*  
*-Involvement of any other target organ)*

611. Overall severity:            1  Mild            2  Moderate            3  Severe

Continued on next page

TEAM

IUBMID

Continued from previous page

Indicate organ involvement with chronic GVHD from list below:

		Absent	Mild	Moderate	Severe	Present, but unknown whether Severity Involved	
Skin/Hair:	612.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Subclinical (biopsy findings only)
	613.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Rash
	614.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Scleroderma
	615.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Dyspigmentation
	616.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Contractures
	617.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Alopecia
	618.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Other skin/hair involvement, specify: _____
Eyes:	619.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Dry eyes
	620.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Corneal erosion/conjunctivitis
	621.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Other eye involvement, specify: _____
Mouth:	622.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Lichenoid changes
	623.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Mucositis/ulcers
	624.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Other mouth involvement, specify: _____
Lung:	625.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Bronchiolitis obliterans
	626.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Other lung involvement, specify: _____
GI Tract:	627.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Esophageal involvement
	628.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Chronic nausea/vomiting
	629.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Chronic diarrhea
	630.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Malabsorption
	631.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Other GI tract involvement, specify: _____
Liver:	632.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Liver involvement, specify: _____
GU Tract:	633.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Vaginitis/stricture
	634.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Other GU involvement, specify: _____
Musculoskeletal:	635.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Arthritis
	636.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Myositis
	637.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Myasthenia
	638.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Other musculoskeletal involvement, specify: _____
Hematologic:	639.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Thrombocytopenia
	640.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Eosinophilia
	641.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Autoantibodies
	642.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Other hematologic involvement, specify: _____
Other:	643.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8 <input type="checkbox"/> Specify: _____

TEAM

IUBMID

644. Was specific therapy used to treat chronic GVHD? 1  Yes 0  No Go to Q.679

For each agent listed below indicate whether or not it was used to treat chronic GVHD:

	No, drug not given	Drug continued at prophylactic dose	Yes, drug started		Yes, dose increased	Still taking?	
			1	2		3	Yes
645. ALS, ALG, ATS, ATG	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	646.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
647. Azathioprine	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	648.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
649. Cyclosporine	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	650.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
651. FK 506 (Tacrolimus)	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	652.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
653. Systemic Corticosteroids	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	654.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
655. Topical Corticosteroids	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	656.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
657. Cyclophosphamide	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	658.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
659. Thalidomide	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	660.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
In vivo anti-T-lymphocyte monoclonal antibody:							
661. Anti IL-2	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	662.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
663. Anti CD 25	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	664.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
665. Campath	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	666.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
667. OKT3	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	668.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
669. Other, specify: _____	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	670.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
671. In vivo immunotoxin, specify: _____	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	672.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
673. Blinded randomized trial; specify agent being studied: _____	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	674.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
675. Other, specify: _____	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	676.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
677. Is patient still receiving treatment for chronic GVHD?							
1 <input type="checkbox"/> Yes							
0 <input type="checkbox"/> No							
678. Date last treatment was administered: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>							
Month Day Year							

TEAM

IUBMID

679. Is chronic GVHD still present?

- 1  Yes
- 0  No
- 2  No symptoms, but patient still receiving treatment

### Other Treatment and Clinical Status After Start of Conditioning

680. Were transfusions given at any time after the start of conditioning to present?

- 1  Yes
- 0  No

	<u>Yes</u>	<u>No</u>	
681.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Did patient receive only CMV-negative blood products?
682.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Were blood products filtered to remove leukocytes?
683.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Were all transfusions irradiated?
684.	RBC (from conditioning to 60 days posttransplant):		<input type="text"/> <input type="text"/> <input type="text"/> Units
685.	Platelet (from conditioning to 60 days posttransplant):		
	Single donor		<input type="text"/> <input type="text"/> <input type="text"/> Number of aphereses
	Random donor		<input type="text"/> <input type="text"/> <input type="text"/> Number of donors
685. <sup>2</sup>	Irradiated granulocyte infusions (from conditioning to 60 days posttransplant):		<input type="text"/> <input type="text"/> <input type="text"/> Number of infusions

686. Did patient receive any of the following agents for infection prophylaxis after start of conditioning?

- 1  Yes
- 0  No

	<u>Yes</u>	<u>No</u>	
686. <sup>2</sup>	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Systemic antibacterial antibiotics
686. <sup>3</sup>	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Nonabsorbable antibiotics
687.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Polyclonal IV gamma globulin (not ATG)
688.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	CMV/hyperimmune gamma globulin
689.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	IV amphotericin
690.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Fluconazole
691.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Itraconazole
692.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other systemic antifungal agent, specify: _____
693.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Acyclovir
694.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Ganciclovir (DHPG)
695.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Foscarnet
696.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other antiviral agent, specify: _____
697.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Trimethoprim-sulfamethoxazole (Bactrim/Septra)
698.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Pentamidine inhaled
699.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Pentamidine IV
700.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Dapsone
701.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other pneumocystis prophylaxis, specify: _____
702.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

TEAM

IUBMID

703. Did patient develop clinically significant infection after start of conditioning? 1  Yes 0  No

Select site and organism from lists shown on the next page and place number in the appropriate spaces. If more than one site or organism was involved, list one site of infection and organism on the first line; second site and/or organism on second line.

If more than two infections of any category, check here  and copy page to provide information on 3rd or subsequent infection (do not report in Q.763-771).

	Site	Organism	Date of Onset			Did infection resolve?	
			Month	Day	Year	Yes	No
704. <input type="checkbox"/> Bacterial							
<u>Typical</u> First	705. <input type="text"/>	706. _____	707. <input type="text"/>	<input type="text"/>	<input type="text"/>	708. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
Second	709. <input type="text"/>	710. _____	711. <input type="text"/>	<input type="text"/>	<input type="text"/>	712. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
<u>Atypical</u> First	716. <input type="text"/>	717. B <input type="text"/>	718. <input type="text"/>	<input type="text"/>	<input type="text"/>	719. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
Second	720. <input type="text"/>	721. B <input type="text"/>	722. <input type="text"/>	<input type="text"/>	<input type="text"/>	723. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
	724. Other atypical bacterium, specify: _____						
727. <input type="checkbox"/> Fungal							
First	728. <input type="text"/>	729. F <input type="text"/>	730. <input type="text"/>	<input type="text"/>	<input type="text"/>	731. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
Second	732. <input type="text"/>	733. F <input type="text"/>	734. <input type="text"/>	<input type="text"/>	<input type="text"/>	735. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
	736. Other fungus, specify: _____						
739. <input type="checkbox"/> Viral							
First	740. <input type="text"/>	741. V <input type="text"/>	742. <input type="text"/>	<input type="text"/>	<input type="text"/>	743. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
Second	744. <input type="text"/>	745. V <input type="text"/>	746. <input type="text"/>	<input type="text"/>	<input type="text"/>	747. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
	748. Other virus, specify: _____						
751. <input type="checkbox"/> Parasitic							
First	752. <input type="text"/>	753. P <input type="text"/>	754. <input type="text"/>	<input type="text"/>	<input type="text"/>	755. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
Second	756. <input type="text"/>	757. P <input type="text"/>	758. <input type="text"/>	<input type="text"/>	<input type="text"/>	759. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
	760. Other parasite, specify: _____						
763. <input type="checkbox"/> Other infections							
First	764. <input type="text"/>	765. O <input type="text"/>	766. <input type="text"/>	<input type="text"/>	<input type="text"/>	767. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
Second	768. <input type="text"/>	769. O <input type="text"/>	770. <input type="text"/>	<input type="text"/>	<input type="text"/>	771. 1 <input type="checkbox"/>	0 <input type="checkbox"/>

TEAM IUBMID 

### Codes for Common Sites of Infection

- |  |  |
|--|--|
| 1 Blood/buffy coat   | 40 <u>Genito-Urinary Tract unspecified</u>                     |
| 2 Disseminated – generalized, isolated at 3 or more distinct sites | 41 Kidneys, renal pelvis, ureters and bladder                  |
| 3 <u>Central Nervous System unspecified</u>                        | 42 Prostate  |
| 4 Brain  | 43 Testes  |
| 5 Spinal cord  | 44 Fallopian tubes, uterus, cervix                             |
| 6 Meninges and CSF   | 45 Vagina  |
| 10 <u>Gastrointestinal Tract unspecified</u>                       | 50 <u>Skin unspecified</u>                                     |
| 11 Lips  | 51 Genital area  |
| 12 Tongue, oral cavity and oro-pharynx                             | 52 Cellulitis  |
| 13 Esophagus   | 53 Herpes Zoster   |
| 14 Stomach   | 54 Rash, pustules or abscesses not typical of any of the above |
| 15 Gallbladder and biliary tree (not hepatitis), pancreas          | 60 <u>Central venous catheter unspecified</u>                  |
| 16 Small intestine   | 61 Catheter insertion or exit site                             |
| 17 Large intestine   | 62 Catheter tip  |
| 18 Feces/stool   | 70 Eyes  |
| 19 Peritoneum  | 75 Ear   |
| 20 Liver   | 81 Joints  |
| 30 <u>Respiratory unspecified</u>                                  | 82 Bone marrow   |
| 31 Upper airway and nasopharynx                                    | 83 Bone cortex (osteomyelitis)                                 |
| 32 Laryngitis/larynx   | 84 Muscle (excluding cardiac)                                  |
| 33 Lower respiratory tract (lung)                                  | 85 Cardiac (endocardium, myocardium, pericardium)              |
| 34 Pleural cavity, pleural fluid                                   | 86 Lymph nodes   |
| 35 Sinuses   | 87 Spleen  |

### Codes for Commonly Reported Organisms

- |   |  |
|---|--|
| <b>1. Bacteria</b> (Indicate code for atypical bacteria; list bacterium for non-atypical bacteria in <b>Q.706, 710.</b> ) | <b>3. Viral Infections</b>   |
| 100 Atypical bacteria, not otherwise specified  | 301 Herpes Simplex (HSV1, HSV2)  |
| 101 Coxiella  | 302 Herpes Zoster (Chicken pox, Varicella)   |
| 102 Legionella  | 303 Cytomegalovirus (CMV)  |
| 103 Leptospira  | 304 Adenovirus   |
| 104 Listeria  | 305 Enterovirus (Coxsackie, Echo, Polio)   |
| 105 Mycoplasma  | 306 Hepatitis A (HAV)  |
| 106 Nocardia  | 307 Hepatitis B (HBV, Australian antigen)  |
| 107 Rickettsia  | 308 Hepatitis C (HCV)  |
| 110 Tuberculosis, NOS (AFB, acid fast bacillus, Koch bacillus)  | 309 HIV-1 (HTLV-III)   |
| 111 Typical tuberculosis (TB, Tuberculosis)   | 310 Influenza  |
| 112 Mycobacteria (avium, bovis, intracellulare)   | 311 Measles (Rubeola)  |
| 113 Chlamydia   | 312 Mumps  |
| 119 Other atypical bacteria, <i>specify in Q.724</i>  | 313 Papovavirus  |
| <b>2. Fungal Infections</b>   | 314 Respiratory syncytial virus (RSV)  |
| 200 Candida, not otherwise specified  | 315 Rubella (German Measles)   |
| 201 Candida albicans  | 316 Parainfluenza  |
| 202 Candida krusei  | 317 Human herpesvirus-6 (HHV-6)  |
| 203 Candida parapsilosis  | 318 Epstein-Barr virus (EBV)   |
| 204 Candida tropicalis  | 319 Polyomavirus   |
| 205 Torulopsis glabrata (a subspecies of candida)   | 320 Rotavirus  |
| 209 Other Candida, <i>specify in Q.736</i>  | 321 Rhinovirus   |
| 210 Aspergillus, not otherwise specified  | 329 Other viral, <i>specify in Q.748</i>   |
| 211 Aspergillus flavus  | <b>4. Parasite Infections</b>  |
| 212 Aspergillus fumigatus   | 401 Pneumocystis (PCP)   |
| 213 Aspergillus niger   | 402 Toxoplasma   |
| 219 Other Aspergillus, <i>specify in Q.736</i>  | 403 Giardia  |
| 220 Cryptococcus species  | 404 Cryptosporidium  |
| 230 Fusarium species  | 409 Other parasite (amebiasis, echinococcal cyst, trichomonas – either vaginal or gingivitis), <i>specify in Q.760</i> |
| 240 Mucormycosis (zygomycetes, rhizopus)  | <b>5. Other Infections</b>   |
| 250 Yeast, not otherwise specified  | 501 Suspected atypical bacterial infection   |
| 259 Other fungus, <i>specify in Q.736</i>   | 502 Suspected bacterial infection  |
|   | 503 Suspected fungal infection   |
|   | 504 Suspected viral infection  |
|   | 505 Suspected parasite infection   |
|   | 509 No organism identified   |



TEAM

IUBMID

**Pulmonary function**

775. Has patient developed interstitial pneumonitis (IPn)?

*Interstitial pneumonitis is characterized by hypoxia and diffuse interstitial infiltrates on chest x-ray not caused by fluid overload.*

- 1  Yes
- 0  No

776. How many episodes of IPn occurred?

*Note: If more than one episode of IPn, photocopy this page and complete Q.777-795 for subsequent episode(s).*

777. Date of onset of IPn:        
Month Day Year

778. Were diagnostic tests other than radiographic studies done?

- 1  Yes
- 0  No

Diagnosis was evaluated by:

	Yes	No	
779.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Bronchoalveolar lavage
780.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Transbronchial biopsy
781.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Open lung biopsy
782.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Autopsy
783.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

784. Was an organism isolated?

- 1  Yes
- 0  No (idiopathic, or no organism isolated)

Etiology:

	Yes	No	
785.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Pneumocystis carinii
786.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Aspergillus
787.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Candida
787. <sup>2</sup>	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Toxoplasma
788.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Respiratory syncytial virus
789.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cytomegalovirus
790.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Herpes simplex
791.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Adenovirus
792.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Human herpes virus 6
793.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other virus, specify: _____
794.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

795. Has interstitial pneumonitis resolved?

- 1  Yes
- 0  No
- 8  Unknown

TEAM

IUBMID

796. Did patient develop pulmonary abnormalities other than interstitial pneumonitis after start of conditioning?

- 1  Yes  
0  No

797. Did patient develop Acute Respiratory Distress Syndrome (ARDS)?

- 1  Yes  
0  No

798. Date of onset of ARDS:        
Month Day Year

799. Were diagnostic tests done?

- 1  Yes  
0  No

Diagnosis was evaluated by:

Yes No

800. 1  0  Bronchoalveolar lavage

801. 1  0  Transbronchial biopsy

802. 1  0  Open lung biopsy

803. 1  0  Autopsy

804. 1  0  Other, specify: \_\_\_\_\_

805. Did patient develop bronchiolitis obliterans?

- 1  Yes  
0  No

806. Date of onset:        
Month Day Year

807. Were diagnostic tests done?

- 1  Yes  
0  No

Diagnosis was evaluated by:

Yes No

808. 1  0  Bronchoalveolar lavage

809. 1  0  Transbronchial biopsy

810. 1  0  Open lung biopsy

811. 1  0  Autopsy

812. 1  0  Other, specify: \_\_\_\_\_

813. Did patient develop pulmonary hemorrhage?

- 1  Yes  
0  No

814. Date of onset:        
Month Day Year

815. Were diagnostic tests done?

- 1  Yes  
0  No

Diagnosis was evaluated by:

Yes No

816. 1  0  Bronchoalveolar lavage

817. 1  0  Transbronchial biopsy

818. 1  0  Open lung biopsy

819. 1  0  Autopsy

820. 1  0  Other, specify: \_\_\_\_\_

821. Did patient develop other non-infectious pulmonary abnormalities?

- 1  Yes  
0  No

822. Specify: \_\_\_\_\_

TEAM

IUBMID

**Liver function**

**Units for bilirubin**

823. Patient's maximum total bilirubin in the first 100 days posttransplant: .

824. 1  mg/dL 2   $\mu$ mol/L

825. Date of maximum total bilirubin in the first 100 days posttransplant: / /   
Month Day Year

826. Patient's bilirubin on day of last contact: .   
(Refer to page 1 for date, or value obtained closest to last contact)

827. 1  mg/dL 2   $\mu$ mol/L

827.<sup>2</sup> Date of last bilirubin (if different from last contact): / /   
Month Day Year

828. Did patient develop any of the following clinical signs/symptoms of abnormal liver function (excluding GVHD)?

1  Yes

0  No

	Yes	No	
829.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Jaundice
830.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Hepatomegaly
831.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Right upper quadrant pain
832.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Ascites
833.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Weight gain (>5%)
834.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

835. Did patient develop non-infectious liver toxicity after conditioning (excluding GVHD)?

1  Yes

0  No

836.	What was the date of onset?	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> Month Day Year		
Etiology:				
837.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Veno-occlusive disease	
838.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____	
839.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Unknown	
Diagnosis in Q.837-839 was confirmed by:				
<b>Yes No Not Done</b>				
840.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Clinical signs and symptoms (see Q.828)
841.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Elevated liver enzymes (e.g., Alk Phos, ALT, AST, LDH, GGT)
842.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Biopsy
843.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Autopsy
844.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Ultrasonography
845.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Doppler
846.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Other, specify: _____
847.	Has liver toxicity resolved?			
	1 <input type="checkbox"/>	Yes		
	0 <input type="checkbox"/>	No		

TEAM

IUBMID

848. Did patient develop any other non-infectious clinically significant organ impairment or disorder after conditioning?

- 1  Yes  
0  No

	Yes	No		
849.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Renal failure requiring dialysis	If yes, received dialysis: 1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
850.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Posttransplant microangiopathy/thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS) or similar syndrome	
851.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Hemorrhage, if yes specify site	
856.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Hemorrhagic cystitis	
857.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Seizures	
858.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cataracts	
859.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Avascular necrosis	
860.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Hypothyroidism	
861.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Gonadal dysfunction	
862.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Growth hormone deficiency/growth disturbance	
863.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____	

	Yes	No	
852.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	CNS
853.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Upper GI tract
854.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Lower GI tract
855.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

864. Did a new malignancy, lymphoproliferative or myeloproliferative disorder appear?

- 1  Yes  
0  No

864.<sup>2</sup> Did more than one new malignancy develop?  
1  Yes *Copy page and answer Q.865-878 for each new malignancy*  
0  No

865. Date of diagnosis:        
Month Day Year

866. Origin of cells: 1  Host 2  Donor 7  Not tested 8  Unknown

Diagnosis (*send copy of pathology report/other documentation*):

	Yes	No	
867.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Clonal cytogenetic abnormality without leukemia or MDS
868.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Acute myeloid leukemia
869.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other leukemia, specify: _____
870.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Myelodysplasia
871.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Lymphoma or lymphoproliferative disease
			872. EBV positive? 1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No 8 <input type="checkbox"/> Unknown
873.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Hodgkin disease
875.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other cancer
			876. Primary site: _____
			877. Histologic type: _____
			878. Behavior: 1 <input type="checkbox"/> Benign 2 <input type="checkbox"/> In situ 3 <input type="checkbox"/> Malignant/invasive 8 <input type="checkbox"/> Unknown

TEAM

IUBMID

### Survival and Functional Status

879. Was patient discharged from hospital after transplant?

- 1  Yes
- 0  No
- 7  Not applicable,  
high-dose therapy and transplant/infusion given as outpatient

880. Date of first discharge from hospital after transplant:

<input type="text"/>	<input type="text"/>	<input type="text"/>
Month	Day	Year

881. *Autografts only:* Total number inpatient days in first 60 days after start of high-dose therapy:

882. *Allografts only:* Total number inpatient days in first 100 days after start of high-dose therapy:

883. Was patient alive on the day of last contact? (Refer to page 1 for date):

- 1  Yes
- 0  No

884. *If the patient is 16 years of age or older, complete the Karnofsky Scale.  
If the patient is younger than 16 years of age, complete the Lansky Scale.*

Go to Q.895

#### Karnofsky Scale (age ≥16 yrs)

Select the phrase in the Karnofsky Scale which best describes the activity status of the patient:

**Able to carry on normal activity; no special care is needed.**

- 100 Normal; no complaints; no evidence of disease
- 90 Able to carry on normal activity
- 80 Normal activity with effort

**Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed.**

- 70 Cares for self; unable to carry on normal activity or to do active work
- 60 Requires occasional assistance but is able to care for most needs
- 50 Requires considerable assistance and frequent medical care

**Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.**

- 40 Disabled; requires special care and assistance
- 30 Severely disabled; hospitalization indicated, although death not imminent
- 20 Very sick; hospitalization necessary
- 10 Moribund; fatal process progressing rapidly

#### Lansky Scale (age <16 yrs)

Select the phrase in the Lansky Play-Performance Scale which best describes the activity status of the patient:

**Normal range.**

- 100 Fully active
- 90 Minor restriction in physically strenuous play
- 80 Restricted in strenuous play, tires more easily, otherwise active

**Mild to moderate restriction.**

- 70 Both greater restrictions of, and less time spent in, active play
- 60 Ambulatory up to 50% of time, limited active play with assistance/supervision
- 50 Considerable assistance required for any active play; fully able to engage in quiet play

**Moderate to severe restriction.**

- 40 Able to initiate quiet activities
- 30 Needs considerable assistance for quiet activity
- 20 Limited to very passive activity initiated by others (i.e., TV)
- 10 Completely disabled, not even passive play

TEAM

IUBMID

(If patient is alive, answer Q.885-894; if dead, skip to Q.895)

885. Patient (age  $\geq$  6 years) currently attends school:

- 1  Yes
- 0  No

886. 1  Part-time    2  Full-time    8  Unknown, whether part-time or full-time

887. Date returned to school:      Date unknown  
Month    Year

888. Patient was employed outside the home prior to current illness:

- 1  Yes
- 0  No

889. Patient has returned to work:

- 1  Yes

890. Date returned to work:      Date unknown  
Month    Year

- 0  No

891. Patient able to work but is not employed: 1  Yes    0  No

- 8  Unknown

892. Patient has resumed all household activities:

- 1  Yes

893. Date resumed all activities:      Date unknown  
Month    Year

- 0  No

- 8  Unknown

894. Patient is now employed:

- 1  Yes

894.<sup>2</sup> Date began work:      Date unknown  
Month    Year

- 0  No

- 8  Unknown

TEAM

IUBMID

### Death Information

895. Date of death:          
Month Day Year

**Cause(s) of death:**

Enter appropriate cause of death below.  
*If a code number for "Other, specify" (codes 29, 39, 88, 89, 109, 129, 900) is entered, write the cause in the space provided.*

896. Primary:    Specify: \_\_\_\_\_

Contributing or secondary causes:

897.    Specify: \_\_\_\_\_

898.    Specify: \_\_\_\_\_

899.    Specify: \_\_\_\_\_

900.    Specify: \_\_\_\_\_

901.    Specify: \_\_\_\_\_

902. Was cause of death confirmed by autopsy?

- 1  Yes
- 0  No
- 8  Unknown
- 6  Pending

**Send copy of autopsy report when available**  
 Autopsy included with this report:  
 1  Yes 0  No

Cause of Death Codes*
10 Graft rejection or failure
Infection (other than interstitial pneumonia) 20 Infection, organism not identified 21 Bacterial 22 Fungal 23 Viral 24 Protozoal 29 Other infection, specify
Interstitial pneumonia 30 IPn, idiopathic 31 Cytomegalovirus (CMV) 32 Viral, other 33 Pneumocystis (PCP) 34 Fungal 39 Other IPn, specify
40 Adult Respiratory Distress Syndrome, ARDS (other than IPn)
50 Acute GVHD 60 Chronic GVHD
70 Recurrence or persistence of primary disease  <i>* NOTE: Code "70" may only be used as a primary cause of death, not a contributing or secondary cause.</i>
Organ failure (not due to GVHD or infection) 80 Organ failure, not otherwise specified 81 Liver (not VOD) 82 VOD 83 Cardiac (Cardiomyopathy) 84 Pulmonary 85 CNS 86 Renal 87 Gastrointestinal (not liver) 88 Multiple organ failure, specify 89 Other organ failure, specify
90 Secondary malignancy <i>(malignancy other than one for which transplant performed includes post transplant lymphoproliferative disease and MDS)</i>
Hemorrhage 100 Hemorrhage, not otherwise specified 101 Pulmonary 102 Intracranial 103 Gastrointestinal 109 Other hemorrhage, specify
110 Accidental death
Vascular 120 Vascular, not otherwise specified 121 Thromboembolic 122 Diffused intravascular conglutation (DIC) 123 Thrombotic thrombocytopenic purpura 129 Other vascular, specify
130 In utero death (for in utero transplants)
140 Prior malignancy <i>(malignancy existing before disease for which transplant performed as reported in Q.41)</i>
900 Other, specify

TEAM

IUBMID

**FOR REGISTRY USE ONLY:**

I.D. --

Date received:

Registry: *IBMTR* *ABMTR* (circle one)

**Confidential/Socioeconomic Information**

903. Patient's First Name:

904. Patient's Last Name:

905. Patient's state of residence (US only):

906. Zip code for place of patient's residence (US only): -

907. Country of residence (check one):

- |  |  |   |  |   |
|--|--|---|--|---|
| 1 <input type="checkbox"/> United States | 10 <input type="checkbox"/> Cuba           | 18 <input type="checkbox"/> India       | 27 <input type="checkbox"/> New Zealand  | 36 <input type="checkbox"/> Switzerland         |
| 2 <input type="checkbox"/> Argentina     | 42 <input type="checkbox"/> Czech Republic | 48 <input type="checkbox"/> Iran        | 28 <input type="checkbox"/> Norway       | 37 <input type="checkbox"/> Taiwan              |
| 3 <input type="checkbox"/> Austria       | 11 <input type="checkbox"/> Denmark        | 19 <input type="checkbox"/> Ireland     | 50 <input type="checkbox"/> Peru         | 45 <input type="checkbox"/> Turkey              |
| 4 <input type="checkbox"/> Australia     | 44 <input type="checkbox"/> Egypt          | 20 <input type="checkbox"/> Israel      | 29 <input type="checkbox"/> Poland       | 47 <input type="checkbox"/> Uruguay             |
| 5 <input type="checkbox"/> Belgium       | 12 <input type="checkbox"/> England        | 21 <input type="checkbox"/> Italy       | 30 <input type="checkbox"/> Portugal     | 39 <input type="checkbox"/> Venezuela           |
| 41 <input type="checkbox"/> Bosnia       | 13 <input type="checkbox"/> Finland        | 22 <input type="checkbox"/> Japan       | 38 <input type="checkbox"/> Russia       | 40 <input type="checkbox"/> Wales               |
| 6 <input type="checkbox"/> Brazil        | 14 <input type="checkbox"/> France         | 23 <input type="checkbox"/> Jordan      | 31 <input type="checkbox"/> Saudi Arabia | 88 <input type="checkbox"/> Unknown/Unspecified |
| 7 <input type="checkbox"/> Canada        | 15 <input type="checkbox"/> Germany        | 24 <input type="checkbox"/> Korea       | 32 <input type="checkbox"/> Scotland     | 90 <input type="checkbox"/> Other Country       |
| 8 <input type="checkbox"/> Chile         | 49 <input type="checkbox"/> Greece         | 25 <input type="checkbox"/> Malaysia    | 33 <input type="checkbox"/> South Africa | specify: _____                                  |
| 9 <input type="checkbox"/> China         | 46 <input type="checkbox"/> Hong Kong      | 43 <input type="checkbox"/> Mexico      | 34 <input type="checkbox"/> Spain        |   |
| 51 <input type="checkbox"/> Croatia      | 17 <input type="checkbox"/> Hungary        | 26 <input type="checkbox"/> Netherlands | 35 <input type="checkbox"/> Sweden       |   |

908. Does patient have a US Social Security Number or Canadian Social Insurance Number?

- 1  Yes
- 0  No
- 8  Unknown
- 7  Not applicable

909. Social Security or Social Insurance Number:

909.<sup>2</sup> Patient ≥18 years old:

- 1  Yes
- 0  No

910. Patient's marital status: (check one)

- 1  Single, never married
- 2  Married
- 3  Separated
- 4  Divorced
- 5  Widowed
- 8  Unknown

911. Highest grade patient finished in school:

- 1  1 - 8 grades
- 2  9 - 11 grades
- 3  High School graduate
- 4  Some college
- 5  Junior college degree
- 6  College degree (BA/BS)
- 7  Some post-college work
- 8  Advanced degree
- 88  Unknown



TEAM     IUBMID

**912.** Type of health insurance: (check all that apply)

- No Insurance
- Medicaid
- Medicare (US)
- Disability Insurance
- HMO
- Individual Health Insurance
- Group Health Insurance
- National Health Insurance (non-US)
- V.A./Military
- Other, specify: \_\_\_\_\_

**913.** (U.S. patients only) Type of fee reimbursement:

- 1  Fee for service
- 2  Capitation
- 7  Other, specify: \_\_\_\_\_
- 8  Unknown

**914.** Which category best describes patient's occupation?

*If not currently employed, which best describes patient's LAST job? (check only one)*

- 1  Professional, Technical, & Related Occupations (teacher/professor, nurse, lawyer, physician or engineer)
- 2  Manager, Administrator or Proprietor (sales manager, real estate agent, or postmaster)
- 3  Clerical & Related Occupations (secretary, clerk, or mail carrier)
- 4  Sales Occupation (salesperson, demonstrator, agent or broker)
- 5  Service Occupation (police, cook or hairdresser)
- 6  Skilled crafts & Related Occupations (carpenter, repairer or telephone line worker)
- 7  Equipment or Vehicle Operator & Related Occupations (driver, railroad brakeman, or sewer worker)
- 8  Laborer (helper, longshoreman or warehouse worker)
- 9  Farmer (owner, manager, operator, or tenant)
- 10  Member of the military
- 11  Homemaker
- 90  Other, please describe: \_\_\_\_\_
- 88  Unknown

**915.** (US patients only) What is patient's yearly income, earned by all family members living in household, before taxes? (check one)

- |  |  |
|--|--|
| 1 <input type="checkbox"/> Less than \$5,000   | 6 <input type="checkbox"/> \$40,000 – \$49,999 |
| 2 <input type="checkbox"/> \$ 5,000 – \$9,999  | 7 <input type="checkbox"/> \$50,000 – \$59,999 |
| 3 <input type="checkbox"/> \$10,000 – \$19,999 | 8 <input type="checkbox"/> \$60,000 – \$79,999 |
| 4 <input type="checkbox"/> \$20,000 – \$29,999 | 9 <input type="checkbox"/> \$80,000 and over   |
| 5 <input type="checkbox"/> \$30,000 – \$39,999 | 88 <input type="checkbox"/> Unknown            |

## INSTITUTIONAL INFORMATION

TEAM

IUBMID          
*(Institutional Unique Blood or Marrow Transplant Identification Number)*

Date of transplant for which this form is being completed:        
 Month Day Year

### FOR REGISTRY USE ONLY:

I.D.  -      -

Date received:

Registry: IBMTR ABMTR (circle one)

Date of report:        
 Month Day Year

1. Signed: \_\_\_\_\_ / \_\_\_\_\_  
 Person completing this form / Please print name

3. Name of doctor for correspondence: \_\_\_\_\_

Institution: \_\_\_\_\_

Address: \_\_\_\_\_

Telephone:

Ext:

Fax:

4. Make reimbursement check payable to: \_\_\_\_\_

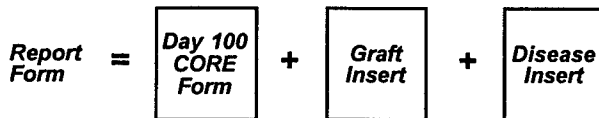
*Payment for data forms is contingent on the availability of funds that have been obtained from sources external to the Medical College of Wisconsin for purposes of these payments.*

5. Patient or authorized family member/guardian is aware of, and has consented to, the fact that this case is being entered into the Registry database: \_\_\_\_\_ (physician's initials).

6. Determining cut-off for all parts of this report:

A complete report of transplant consists of the following three parts (all 3 parts should have the same date of report and date of transplant):

- A (white) Day 100 CORE form
- An appropriate (blue or pink) graft-specific insert (Insert ALLOBM, ALLOPB, ALLOCB, AUTOPB, or AUTOBM)
- An appropriate (ivory) disease-specific insert (Inserts I through XVIII)



Enter date 100 days from transplant (e.g., Month, Day, Year):

The cut-off for **ALL** parts of this Report Form should be the date of the follow-up exam approximately 100 days post transplant, unless (a) patient died prior to day 100, or (b) patient received a subsequent transplant or infusion >14 days but <100 days post transplant which requires a separate Report Form. (See pages 17 & 18 of the 100 day CORE Form to determine if the re-infusions is considered another transplant requiring a separate Report Form.)

The date of Last Contact is the date of the 100 day follow-up exam or (a) the date of death (if death occurred before 100 days) or (b) one day prior to conditioning for subsequent transplant or one day prior to subsequent transplant/infusion if no conditioning given.

Enter Last Contact date (e.g., Month, Day, Year):

Enter these dates on page 1 of the CORE Form. Report information in the 100 day CORE Form and disease-specification insert only up to Last Contact date. Later information should be reported in a Follow-up Form or Report Form for a subsequent transplant when it is due.



TEAM

IUBMID

6. Is patient (age  $\geq 6$  years) currently attending school?

- 1  Yes
- 0  No

7. Specify status: 1  Part-time 2  Full-time 8  Unknown, whether part-time or full-time

8. Date returned to school:   /   or  Reported previously  
Month Year

9. Was patient employed outside the home prior to current illness?

- 1  Yes
- 0  No

10. Has patient been employed outside the home since last report?

- 1  Yes
- 0  No

11. Date returned to work:   /   or  Reported previously  
Month Year

12. Patient able to work but is not employed: 1  Yes 0  No

- 8  Unknown

13. Has patient resumed all household activities?

- 1  Yes
- 0  No
- 8  Unknown

14. Approximate date all activities were resumed:   /   or  Reported previously  
Month Year

TEAM

IUBMID

15. Did patient receive a blood or marrow infusion since the date of last report (*other than peripheral blood leukocytes or T-lymphocytes from original allogeneic donor*)?

- 1  Yes  
0  No

**Subsequent transplant**

Answers to all questions in this report should reflect clinical status immediately prior to start of conditioning for subsequent infusion.

**A separate report covering the subsequent transplant must be submitted unless the subsequent transplant is autologous for treatment of graft failure posttransplant.**

16. Date of subsequent infusion:        
Month Day Year

17. Reason for subsequent infusion:

- 1  No engraftment  
2  Partial engraftment  
3  Late graft failure

**Autologous re-infusions for these reasons do not require separate report completion**

- 4  Persistent malignancy  
5  Relapse  
6  Planned second transplant, per protocol  
8  Secondary malignancy

**Complete new malignancy Q.456-469**

90  Other, specify: \_\_\_\_\_

18. Type of graft:

- 1  Allogeneic, related  
2  Allogeneic, unrelated  
3  Autologous

19. Donor:

- 1  Same donor  
2  Different donor  
3  Not applicable, initial transplant was autologous

Source of cells:

20. 1  Fresh  
2  Cryopreserved

Check all that apply:

**Yes No**

21. 1  0  Bone marrow  
22. 1  0  Peripheral blood  
23. 1  0  Cord blood  
24. 1  0  Fetal tissue  
25. 1  0  Other, specify: \_\_\_\_\_

TEAM

IUBMID

26. *Allografts only:* Has patient received an infusion of peripheral blood leukocytes or T-lymphocytes from the original donor since date of last report?

- 1  Yes  
0  No

27. Date first infusion given:        
Month Day Year

28. Patient weight within 2 weeks of first infusion:   kg    pounds

29. Total number of infusions:

30. Total dose of mononuclear cells infused:     x 10   (supply exponent)

31. Were cells manipulated prior to infusion?

- 1  Yes  
0  No

32. Indicate method:

Yes No

1  0  T-cell depletion

1  0  CD34 selection

1  0  Incubated with cytokines

1  0  Other, specify: \_\_\_\_\_

33. Indication for the infusion(s) of donor cells:

- 1  Prophylaxis against B-cell lymphoproliferative disorder (or viral infection)  
2  Prophylaxis against relapse

3  Treatment of relapse

4  Treatment of B-cell lymphoproliferative disorder

5  Treatment of viral infection, specify: \_\_\_\_\_

6  Graft failure

7  Other, specify: \_\_\_\_\_

*If answers 3-7 were selected, then answers to all questions in this report should reflect clinical status immediately prior to infusion. This is considered a transplant and a separate report covering this infusion and post-infusion events must be submitted.*

TEAM

IUBMID

### Hematopoietic Reconstitution

34. Has patient received hematopoietic growth factors or cytokines since last report? 1  Yes 0  No Go to Q.88

**Coding for Indication of Therapy (below)**

1. Intervention for delay/decline in Absolute Neutrophil Count (ANC)
2. Intervention for delay/decline in platelets
3. Intervention for delay/decline in both ANC and platelets
4. Intervention for delay/decline in red blood cell counts
5. Anti-leukemic or tumor agent to prevent relapse
6. Anti-leukemic or tumor agent to treat relapse
7. Other indication

*Specify agents given:*

			Date Started			Date Stopped			Indication
	Yes	No	Month	Day	Year	Month	Day	Year	
G-CSF	35. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	36. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	37. <input type="text"/>	<input type="text"/>	<input type="text"/>	38. <input type="checkbox"/>
GM-CSF	39. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	40. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	41. <input type="text"/>	<input type="text"/>	<input type="text"/>	42. <input type="checkbox"/>
Erythropoietin	43. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	44. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	45. <input type="text"/>	<input type="text"/>	<input type="text"/>	46. <input type="checkbox"/>
Thrombopoietin	47. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	48. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	49. <input type="text"/>	<input type="text"/>	<input type="text"/>	50. <input type="checkbox"/>
Interleukin-2	51. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	52. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	53. <input type="text"/>	<input type="text"/>	<input type="text"/>	54. <input type="checkbox"/>
Interleukin-3	55. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	56. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	57. <input type="text"/>	<input type="text"/>	<input type="text"/>	58. <input type="checkbox"/>
Interleukin-6	59. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	60. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	61. <input type="text"/>	<input type="text"/>	<input type="text"/>	62. <input type="checkbox"/>
PIXY-321	63. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	64. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	65. <input type="text"/>	<input type="text"/>	<input type="text"/>	66. <input type="checkbox"/>
Stem Cell Factor (SCF)	67. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	68. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	69. <input type="text"/>	<input type="text"/>	<input type="text"/>	70. <input type="checkbox"/>
Interferon-alpha	71. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	72. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	73. <input type="text"/>	<input type="text"/>	<input type="text"/>	74. <input type="checkbox"/>
Interferon-gamma	75. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	76. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	77. <input type="text"/>	<input type="text"/>	<input type="text"/>	78. <input type="checkbox"/>
Blinded growth factor trial, specify agent(s) being studied:	79. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	80. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	81. <input type="text"/>	<input type="text"/>	<input type="text"/>	82. <input type="checkbox"/>
Other, specify:	83. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	84. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	85. <input type="text"/>	<input type="text"/>	<input type="text"/>	86. <input type="checkbox"/>

87. Did patient receive other courses of growth factors or cytokines since last report?

- 1  Yes Photocopy Q.35-86 and answer for each additional course given.
- 0  No
- 8  Unknown

**NOTE:** A new course includes starting a new agent, restarting a previously administered agent for a new indication or restarting a previously administered agent for the same indication but  $\geq 30$  days after discontinuing the agent.

TEAM

IUBMID

## Granulopoiesis

88. Did patient achieve an initial hematopoietic recovery (ANC  $\geq 500/\text{mm}^3$  for 3 consecutive days) since last report?

1  Yes

89. Date ANC  $\geq 500/\text{mm}^3$ :        Date unknown  
(First of 3 consecutive days) Month Day Year

90. Was ANC  $\geq 1000/\text{mm}^3$  achieved and sustained for 3 consecutive days?

1  Yes

0  No

**Go to Q.92**

91. Date achieved:        Date unknown  
(First of 3 consecutive days) Month Day Year

2  No, patient's initial hematopoietic recovery was recorded on a previous report

**Go to Q.92**

3  No, patient has never achieved an ANC  $\geq 500/\text{mm}^3$  for three consecutive days and there is no evidence of recurrent disease

**Go to Q.92**

4  No, patient has never achieved an ANC  $\geq 500/\text{mm}^3$  for three consecutive days and there was documented persistent malignant disease posttransplant

**Go to Q.92**

92. Following initial hematopoietic recovery (ANC  $\geq 500/\text{mm}^3$  for three consecutive days) did the patient experience a subsequent decline in ANC to  $< 500/\text{mm}^3$  for greater than three days since last report?

1  Yes

0  No

**Go to Q.117**

93. Date of decline in ANC to  $< 500/\text{mm}^3$  for greater than 3 days:        Date unknown  
(First of 3 days that ANC declined) Month Day Year

94. Did patient recover and maintain ANC  $\geq 500/\text{mm}^3$  following the decline?

1  Yes

0  No

**Go to Q.96**

95. Date of ANC recovery:        Date unknown  
Month Day Year



TEAM

IUBMID

Suspected etiology of failure to achieve ANC >500/mm<sup>3</sup> or of a decline in ANC:

96. Persistent disease or relapse: 1  Yes 0  No 8  Unknown
97. Graft versus host disease: 1  Yes 0  No 8  Unknown
98. Immune-mediated rejection: 1  Yes 0  No 8  Unknown
99. Non-viral infection: 1  Yes 0  No 8  Unknown
100. Suspected viral infection: 1  Yes 0  No 8  Unknown

Virus suspected:

Yes No

101. 1  0  Cytomegalovirus (CMV)
102. 1  0  Human Herpes Virus Type 6 (HHV6)
103. 1  0  Herpes Simplex Virus (HSV)
104. 1  0  Varicella
105. 1  0  Other, specify: \_\_\_\_\_

106. Documented viral infection: 1  Yes 0  No 8  Unknown

Virus involved:

Yes No

107. 1  0  Cytomegalovirus (CMV)
108. 1  0  Human Herpes Virus Type 6 (HHV6)
109. 1  0  Herpes Simplex Virus (HSV)
110. 1  0  Varicella
111. 1  0  Other, specify: \_\_\_\_\_

112. Drugs: 1  Yes 0  No 8  Unknown

Specify:

Yes No

113. 1  0  Ganciclovir
114. 1  0  Bactrim, Septra, Trimethoprim-sulfamethoxazole
115. 1  0  Other, specify: \_\_\_\_\_

116. Etiology undetermined: 1  Yes 0  No

TEAM

IUBMID

### Megakaryopoiesis

The following questions relate to initial platelet recovery. All dates should reflect no transfusions in previous 7 days, and the first of 3 consecutive laboratory results.

117. Did recipient achieve an initial platelet count of  $\geq 20 \times 10^9/L$  since last report?

- 1  Yes — **Go to Q.118**
- 2  No, recipient achieved a platelet count of  $\geq 20 \times 10^9/L$  but  $< 50 \times 10^9/L$  prior to last report — **Go to Q.119**
- 3  No, recipient achieved a platelet count of  $\geq 50 \times 10^9/L$  but  $< 100 \times 10^9/L$  prior to last report — **Go to Q.121**
- 4  No, recipient achieved a platelet count of  $\geq 100 \times 10^9/L$  prior to last report — **Go to Q.125**
- 0  No, recipient never achieved a platelet count of  $\geq 20 \times 10^9/L$  — **Go to Q.123**

118. Date platelets  $\geq 20 \times 10^9/L$ :        Date unknown  
Month Day Year

119. Was a platelet count of  $\geq 50 \times 10^9/L$  achieved?

- 1  Yes — **Go to Q.120**
- 0  No — **Go to Q.123**
- 8  Unknown — **Go to Q.123**

120. Date platelets  $\geq 50 \times 10^9/L$ :        Date unknown  
Month Day Year

121. Was a platelet count of  $\geq 100 \times 10^9/L$  achieved?

- 1  Yes — **Go to Q.122**
- 0  No
- 8  Unknown

122. Date platelets  $\geq 100 \times 10^9/L$ :        Date unknown  
Month Day Year

123. Was recipient ever platelet transfusion independent?

- 1  Yes
- 0  No — **Go to Q.125 if platelet count of  $\geq 20 \times 10^9/L$  achieved; otherwise go to Q.133**

124. Date of the last platelet transfusion\*:

- Reported on last report        Date unknown  
Month Day Year

\*If recipient was platelet transfusion independent for  $\geq 14$  days but subsequently experienced a decline in platelet count and required platelet transfusions, record date of last platelet transfusion before decline in counts. If recipient has not required platelet transfusions since initial platelet recovery record date of last platelet transfusion.

TEAM

IUBMID

125. After initial recovery to platelet count  $\geq 20 \times 10^9/L$  did the platelet count decline to  $< 20 \times 10^9/L$  for 3 consecutive laboratory values or decline to  $< 20 \times 10^9/L$  for one laboratory value and the recipient received a platelet transfusion?

1  Yes

0  No

*Go to Q.159  
if platelet count  
of  $\geq 100 \times 10^9/L$   
achieved;  
otherwise go to  
Q.133*

126. Date of the first day that platelet count declined below  $20 \times 10^9/L$ :     Date unknown  
Month Day Year

127. Has platelet count recovered? 1  Yes 0  No **Go to Q.133**

The following date questions relate to subsequent platelet recovery following a decline of platelet count to below  $20 \times 10^9/L$ . All dates should reflect no transfusions in previous 7 days, and the first of 3 consecutive laboratory values.

128. Was a platelet count of  $\geq 20 \times 10^9/L$  achieved? 1  Yes 0  No **Go to Q.131**

129. Was a platelet count of  $\geq 50 \times 10^9/L$  achieved? 1  Yes 0  No **Go to Q.131**

130. Was a platelet count of  $\geq 100 \times 10^9/L$  achieved? 1  Yes 0  No

131. Was patient ever transfusion independent following recovery from decline? 1  Yes 0  No

132. Date of the last platelet transfusion (following recovery from decline):     Date unknown  
Month Day Year

TEAM

IUBMID

Suspected etiology of failure to achieve a platelet count  $\geq 100 \times 10^9/L$  or decline in platelet count to  $< 20 \times 10^9/L$ :

133. Persistent disease or relapse: 1  Yes 0  No 8  Unknown

134. Graft versus host disease: 1  Yes 0  No 8  Unknown

135. Non-viral infection: 1  Yes 0  No 8  Unknown

136. Immune-mediated:  
(includes graft rejection) 1  Yes 0  No 8  Unknown

Immune mediated etiology:

Yes No

137. 1  0  Cellular

138. 1  0  Antibody

139. 1  0  Third party engraftment

140. 1  0  Unknown

141. Suspected viral infection: 1  Yes 0  No 8  Unknown

Virus involved:

Yes No

142. 1  0  Cytomegalovirus (CMV)

143. 1  0  Human Herpes Virus Type 6 (HHV6)

144. 1  0  Herpes Simplex Virus (HSV)

145. 1  0  Varicella

146. 1  0  Other, specify: \_\_\_\_\_

147. Documented viral infection: 1  Yes 0  No 8  Unknown

Virus involved:

Yes No

148. 1  0  Cytomegalovirus (CMV)

149. 1  0  Human Herpes Virus Type 6 (HHV6)

150. 1  0  Herpes Simplex Virus (HSV)

151. 1  0  Varicella

152. 1  0  Other, specify: \_\_\_\_\_

153. Drugs: 1  Yes 0  No 8  Unknown

Therapy:

Yes No

154. 1  0  Ganciclovir

155. 1  0  Bactrim, Septra, Trimethoprim-sulfamethoxazole

156. 1  0  Other, specify: \_\_\_\_\_

157. Venous-occlusive disease (VOD): 1  Yes 0  No 8  Unknown

158. Etiology undetermined: 1  Yes 0  No 2  Autologous recovery

158.<sup>2</sup> Other etiology: 1  Yes 0  No If yes, specify: \_\_\_\_\_

TEAM

IUBMID

### Erythropoiesis

159. Has patient received red blood cell (RBC) transfusions since last report?

- 1  Yes  
0  No

160. Date of last RBC transfusion:\*        Date unknown  
Month Day Year

*\* If patient was RBC transfusion independent for  $\geq 1$  month but subsequently experienced a decline in RBC count and required RBC transfusions, record date of last RBC transfusion before decline in counts. If patient has not required RBC transfusions since initial date of recovery, record date of last RBC transfusion.*

### Current Hematologic Findings

161. Date of most recent CBC:        
Month Day Year

**Actual CBC results**

		<u>Specify Units</u>	<u>Transfused</u>	<u>Not Tested</u>
162. WBC:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> $\times 10^9/L$ 2 <input type="checkbox"/> $\times 10^6/L$	<input type="checkbox"/>	<input type="checkbox"/>
163. Neutrophils:	<input type="text"/> <input type="text"/> %		<input type="checkbox"/>	<input type="checkbox"/>
164. Lymphocytes:	<input type="text"/> <input type="text"/> %		<input type="checkbox"/>	<input type="checkbox"/>
165. Hemoglobin:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> g/dL 2 <input type="checkbox"/> g/L 3 <input type="checkbox"/> mmol/L	<input type="checkbox"/>	<input type="checkbox"/>
166. Hematocrit:	<input type="text"/> <input type="text"/> %		<input type="checkbox"/>	<input type="checkbox"/>
167. Platelets:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	1 <input type="checkbox"/> $\times 10^9/L$ 2 <input type="checkbox"/> $\times 10^6/L$	<input type="checkbox"/>	<input type="checkbox"/>

168. Were chimerism studies performed since last report?

- 1  Yes — **Complete following page**  
0  No — **Go to Q.169**



TEAM

IUBMID

### Graft-vs-Host Disease (GVHD)

169. Was specific therapy used since last report to prevent or induce GVHD, or promote engraftment?

- 1  Yes
- 0  No
- 8  Unknown

**Allografts:**  
Go to Q.186

**Autografts:**  
Go to Q.326

For each agent listed below indicate whether or not it was used to prevent or induce GVHD since last report:

	Yes	No	
170.	<input type="checkbox"/>	<input type="checkbox"/>	Methotrexate
171.	<input type="checkbox"/>	<input type="checkbox"/>	Cyclosporine
172.	<input type="checkbox"/>	<input type="checkbox"/>	FK 506 (Tacrolimus)
173.	<input type="checkbox"/>	<input type="checkbox"/>	Corticosteroids
174.	<input type="checkbox"/>	<input type="checkbox"/>	ALS, ALG, ATS, ATG
175.	<input type="checkbox"/>	<input type="checkbox"/>	Azathioprine
176.	<input type="checkbox"/>	<input type="checkbox"/>	Cyclophosphamide
177.	<input type="checkbox"/>	<input type="checkbox"/>	In vivo anti T-lymphocyte monoclonal antibody: _____
183.	<input type="checkbox"/>	<input type="checkbox"/>	In vivo immunotoxin, specify: _____
184.	<input type="checkbox"/>	<input type="checkbox"/>	Blinded randomized trial; specify agent being studied: _____
185.	<input type="checkbox"/>	<input type="checkbox"/>	Other, specify: _____

Specify:

	Yes	No	
178.	<input type="checkbox"/>	<input type="checkbox"/>	Anti IL-2
179.	<input type="checkbox"/>	<input type="checkbox"/>	Anti CD 25
180.	<input type="checkbox"/>	<input type="checkbox"/>	Campath
181.	<input type="checkbox"/>	<input type="checkbox"/>	OKT3
182.	<input type="checkbox"/>	<input type="checkbox"/>	Other, specify: _____

186. Was acute GVHD present at time of last report?

- 1  Yes Go to Q.195
- 0  No

187. Did acute GVHD develop since date of last report?

- 1  Yes
- 0  No
- 8  Unknown

Go to Q.238

188. Date of onset:    /    /      
Month Day Year

What was diagnosis based on?

189. Histologic evidence:

- 1  Yes
- 0  No

Specify sites:

	Yes	No	
190.	<input type="checkbox"/>	<input type="checkbox"/>	Skin
191.	<input type="checkbox"/>	<input type="checkbox"/>	Gut
192.	<input type="checkbox"/>	<input type="checkbox"/>	Liver
193.	<input type="checkbox"/>	<input type="checkbox"/>	Other, specify: _____

194. Clinical evidence:

- 1  Yes
- 0  No

TEAM

IUBMID

195. Maximum overall grade since last report: 1  I 2  II 3  III 4  IV

List the maximum severity of organ involvement attributed to acute GVHD:

196. Skin:

<u>Stage 0</u>	<u>Stage 1</u>	<u>Stage 2</u>	<u>Stage 3</u>	<u>Stage 4</u>
1 <input type="checkbox"/> No rash	2 <input type="checkbox"/> Maculopapular rash, <25% of body surface	3 <input type="checkbox"/> Maculopapular rash, 25-50% of body surface	4 <input type="checkbox"/> Generalized erythroderma	5 <input type="checkbox"/> Generalized erythroderma with bullae formation and desquamation

197. Intestinal tract (use ml/day for adult patients and ml/m<sup>2</sup>/day for pediatric patients):

0 <input type="checkbox"/> No diarrhea	2 <input type="checkbox"/> Diarrhea >500 but <1000 ml/day or 280-555 ml/m <sup>2</sup> /day	3 <input type="checkbox"/> Diarrhea >1000 but <1500 ml/day or 556-833 ml/m <sup>2</sup> /day	4 <input type="checkbox"/> Diarrhea >1500 ml/day or >833 ml/m <sup>2</sup> /day	5 <input type="checkbox"/> Severe abdominal pain, with or without ileus
1 <input type="checkbox"/> Diarrhea <500 ml/day or <280 ml/m <sup>2</sup> /day				

198. Liver:

1 <input type="checkbox"/> Bilirubin <2.0 mg/dL or <35 μmol/L	2 <input type="checkbox"/> Bilirubin 2.0-3.0 mg/dL or 35-52 μmol/L	3 <input type="checkbox"/> Bilirubin 3.1-6.0 mg/dL or 53-103 μmol/L	4 <input type="checkbox"/> Bilirubin 6.1-15.0 mg/dL or 104-256 μmol/L	5 <input type="checkbox"/> Bilirubin >15.0 mg/dL or >256 μmol/L
---	--	---	---	---

199. Other organ involvement?

1  Yes  
0  No

Specify:

Yes No  
200. 1  0  Upper GI tract  
201. 1  0  Lung  
202. 1  0  Other, specify: \_\_\_\_\_



TEAM

IUBMID

203. Was specific therapy used to treat acute GVHD since last report? 1  Yes 0  No

For each agent listed below indicate whether or not it was used to treat acute GVHD:

	No, drug not given	Drug continued at prophylactic dose	Yes, drug started or continued for treatment	Yes, dose increased for treatment	Still taking?	
					Yes	No
204. Methotrexate	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	205. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
206. Cyclosporine	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	207. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
208. FK 506 (Tacrolimus)	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	209. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
210. Systemic Corticosteroids	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	211. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
212. Topical Corticosteroids	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	213. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
214. ALS, ALG, ATS, ATG	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	215. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
216. Azathioprine	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	217. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
218. Cyclophosphamide	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	219. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
220. Thalidomide	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	221. 1 <input type="checkbox"/>	0 <input type="checkbox"/>

In vivo anti-T-lymphocyte monoclonal antibody:

222. Anti IL-2	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	223. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
224. Anti CD 25	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	225. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
226. Campath	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	227. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
228. OKT3	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	229. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
230. Other antibody,	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	231. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify: _____						
232. In vivo immunotoxin,	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	233. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify: _____						
234. Blinded randomized trial;	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	235. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify agent being studied: _____						
236. Other,	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	237. 1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify: _____						

TEAM     IUBMID

238. Was chronic GVHD present at time of last report?

- 1  Yes  
0  No

239. Chronic GVHD is still present or was present at time of death:  
1  Yes — **Go to Q.256**  
0  No

240. Did clinical chronic GVHD develop since date of last report?

- 1  Yes  
0  No  
8  Unknown — **Go to Q.326**

241. Date of onset:       
Month Day Year

242. Progressed from acute GVHD? 1  Yes 0  No

243. Karnofsky/Lansky score (see page 1) at diagnosis of chronic GVHD:

244. Platelet count at diagnosis of chronic GVHD:               $\times 10^9/L$  2   $\times 10^6/L$

245. Total serum bilirubin at diagnosis of chronic GVHD:        mg/dL 2   $\mu\text{mol/L}$

What was diagnosis based on?

246. Histologic evidence:

- 1  Yes  
0  No

Specify sites:

**Yes No**

247. 1  0  Skin

248. 1  0  Gut

249. 1  0  Liver

250. 1  0  Buccal mucosa/lip

251. 1  0  Conjunctiva

252. 1  0  Lung

253. 1  0  Muscle

254. 1  0  Other, specify: \_\_\_\_\_

255. Clinical evidence:

- 1  Yes  
0  No

256. Maximum grade of chronic GVHD:

- 1  Limited (*Localized skin involvement and/or hepatic dysfunction due to chronic GVHD*)  
2  Extensive (*Generalized skin involvement; or localized skin involvement and/or hepatic dysfunction due to chronic GVHD, plus:*  
-Liver histology showing chronic aggressive hepatitis, bridging necrosis or cirrhosis; or,  
-Involvement of eye: Schirmer's test with < 5 mm wetting; or,  
-Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy; or,  
-Involvement of any other target organ)

257. Overall severity: 1  Mild 2  Moderate 3  Severe

Continued on next page

TEAM

--	--	--	--

IUBMID

--	--	--	--	--	--

Continued from previous page

Indicate organ involvement with chronic GVHD from list below:

		Absent	Mild	Moderate	Severe	Present, but unknown Severity	Unknown whether Involved	
Skin/Hair:	258.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Subclinical (biopsy findings only)
	259.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Rash
	260.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Scleroderma
	261.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Dyspigmentation
	262.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Contractures
	263.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Alopecia
	264.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Other skin/hair involvement, specify: _____
Eyes:	265.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Dry eyes
	266.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Corneal erosion/conjunctivitis
	267.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Other eye involvement, specify: _____
Mouth:	268.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Lichenoid changes
	269.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Mucositis/ulcers
	270.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Other mouth involvement, specify: _____
Lung:	271.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Bronchiolitis obliterans
	272.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Other lung involvement, specify: _____
GI Tract:	273.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Esophageal involvement
	274.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Chronic nausea/vomiting
	275.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Chronic diarrhea
	276.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Malabsorption
	277.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Other GI tract involvement, specify: _____
Liver:	278.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Liver involvement, specify: _____
GU Tract:	279.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Vaginitis/stricture
	280.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Other GU involvement, specify: _____
Musculoskeletal:	281.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Arthritis
	282.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Myositis
	283.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Myasthenia
	284.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Other musculoskeletal involvement, specify: _____
Hematologic:	285.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Thrombocytopenia
	286.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Eosinophilia
	287.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Autoantibodies
	288.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Other hematologic involvement, specify: _____
Other:	289.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Specify: _____

TEAM

IUBMID

290. Was specific therapy used to treat chronic GVHD since last report? 1  Yes 0  No Go to Q.325

For each agent listed below indicate whether or not it was used to treat chronic GVHD:

	No, drug not given	Drug continued at prophylactic dose	Yes, drug started or continued for treatment	Yes, dose increased for treatment		Still taking?	
	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>		Yes	No
291. ALS, ALG, ATS, ATG	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	292.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
293. Azathioprine	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	294.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
295. Cyclosporine	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	296.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
297. FK 506 (Tacrolimus)	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	298.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
299. Systemic Corticosteroids	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	300.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
301. Topical Corticosteroids	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	302.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
303. Cyclophosphamide	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	304.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
305. Thalidomide	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	306.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
In vivo anti-T-lymphocyte monoclonal antibody:							
307. Anti IL-2	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	308.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
309. Anti CD 25	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	310.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
311. Campath	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	312.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
313. OKT3	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	314.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
315. Other antibody,	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	316.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify: _____							
317. In vivo immunotoxin,	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	318.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify: _____							
319. Blinded randomized trial;	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	320.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify agent being studied: _____							
321. Other,	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	322.	1 <input type="checkbox"/>	0 <input type="checkbox"/>
specify: _____							

TEAM     IUBMID

323. Is patient still receiving treatment for chronic GVHD?

1  Yes

0  No

324. Date last treatment was administered:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Month	Day	Year	

325. Is chronic GVHD still present?

1  Yes

0  No

8  No symptoms, but patient still receiving treatment

TEAM     IUBMID

326. Did patient develop clinically significant infection since date of last report? 1  Yes 0  No

Select site and organism from lists shown on the next page and place number in the appropriate spaces. If more than one site or organism was involved, list one site of infection and organism on the first line; second site and/or organism on second line.

	Site	Organism	Date of Onset			Did infection resolve?	
			Month	Day	Year	Yes	No
327. <input type="checkbox"/> Bacterial							
<u>Typical</u> First	328. <input type="text"/>	329. _____	330. <input type="text"/>	<input type="text"/>	<input type="text"/>	331. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
Second	332. <input type="text"/>	333. _____	334. <input type="text"/>	<input type="text"/>	<input type="text"/>	335. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
<u>Atypical</u> First	337. <input type="text"/>	338. B <input type="text"/>	339. <input type="text"/>	<input type="text"/>	<input type="text"/>	340. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
Second	341. <input type="text"/>	342. B <input type="text"/>	343. <input type="text"/>	<input type="text"/>	<input type="text"/>	344. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
		345. Other atypical bacterium, specify: _____					
346. <input type="checkbox"/> Fungal							
First	347. <input type="text"/>	348. F <input type="text"/>	349. <input type="text"/>	<input type="text"/>	<input type="text"/>	350. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
Second	351. <input type="text"/>	352. F <input type="text"/>	353. <input type="text"/>	<input type="text"/>	<input type="text"/>	354. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
		355. Other fungus, specify: _____					
356. <input type="checkbox"/> Viral							
First	357. <input type="text"/>	358. V <input type="text"/>	359. <input type="text"/>	<input type="text"/>	<input type="text"/>	360. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
Second	361. <input type="text"/>	362. V <input type="text"/>	363. <input type="text"/>	<input type="text"/>	<input type="text"/>	364. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
		365. Other virus, specify: _____					
366. <input type="checkbox"/> Parasitic							
First	367. <input type="text"/>	368. P <input type="text"/>	369. <input type="text"/>	<input type="text"/>	<input type="text"/>	370. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
Second	371. <input type="text"/>	372. P <input type="text"/>	373. <input type="text"/>	<input type="text"/>	<input type="text"/>	374. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
		375. Other parasite, specify: _____					
376. <input type="checkbox"/> No organism identified							
First	377. <input type="text"/>	378. O <input type="text"/>	379. <input type="text"/>	<input type="text"/>	<input type="text"/>	380. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	
Second	381. <input type="text"/>	382. O <input type="text"/>	383. <input type="text"/>	<input type="text"/>	<input type="text"/>	384. 1 <input type="checkbox"/> 0 <input type="checkbox"/>	

TEAM

--	--	--	--	--

IUBMID

--	--	--	--	--	--	--	--

### Codes for Common Sites of Infection

- |  |  |
|--|--|
| 1 Blood/buffy coat   | 40 <u>Genito-Urinary Tract unspecified</u>                     |
| 2 Disseminated – generalized, isolated at 3 or more distinct sites | 41 Kidneys, renal pelvis, ureters and bladder                  |
| 3 <u>Central Nervous System unspecified</u>                        | 42 Prostate  |
| 4 Brain  | 43 Testes  |
| 5 Spinal cord  | 44 Fallopian tubes, uterus, cervix                             |
| 6 Meninges and CSF   | 45 Vagina  |
| 10 <u>Gastrointestinal Tract unspecified</u>                       | 50 <u>Skin unspecified</u>                                     |
| 11 Lips  | 51 Genital area  |
| 12 Tongue, oral cavity and oro-pharynx                             | 52 Cellulitis  |
| 13 Esophagus   | 53 Herpes Zoster   |
| 14 Stomach   | 54 Rash, pustules or abscesses not typical of any of the above |
| 15 Gallbladder and biliary tree (not hepatitis), pancreas          | 60 <u>Central venous catheter unspecified</u>                  |
| 16 Small intestine   | 61 Catheter insertion or exit site                             |
| 17 Large intestine   | 62 Catheter tip  |
| 18 Feces/stool   | 70 Eyes  |
| 19 Peritoneum  | 75 Ear   |
| 20 Liver   | 81 Joints  |
| 30 <u>Respiratory unspecified</u>                                  | 82 Bone marrow   |
| 31 Upper airway and nasopharynx                                    | 83 Bone cortex (osteomyelitis)                                 |
| 32 Laryngitis/larynx   | 84 Muscle (excluding cardiac)                                  |
| 33 Lower respiratory tract (lung)                                  | 85 Cardiac (endocardium, myocardium, pericardium)              |
| 34 Pleural cavity, pleural fluid                                   | 86 Lymph nodes   |
| 35 Sinuses   | 87 Spleen  |

### Codes for Commonly Reported Organisms

- |   |  |
|---|--|
| <b>1. Bacteria</b> (Indicate code for atypical bacteria; list bacterium for non-atypical bacteria in Q.329, 330.) | <b>3. Viral Infections</b>   |
| 100 Atypical bacteria, not otherwise specified  | 301 Herpes Simplex (HSV1, HSV2)  |
| 101 Coxiella  | 302 Herpes Zoster (Chicken pox, Varicella)   |
| 102 Legionella  | 303 Cytomegalovirus (CMV)  |
| 103 Leptospira  | 304 Adenovirus   |
| 104 Listeria  | 305 Enterovirus (Coxsackie, Echo, Polio)   |
| 105 Mycoplasma  | 306 Hepatitis A (HAV)  |
| 106 Nocardia  | 307 Hepatitis B (HBV, Australian antigen)  |
| 107 Rickettsia  | 308 Hepatitis C (HCV)  |
| 110 Tuberculosis, NOS (AFB, acid fast bacillus, Koch bacillus)  | 309 HIV-1 (HTLV-III)   |
| 111 Typical tuberculosis (TB, Tuberculosis)   | 310 Influenza  |
| 112 Mycobacteria (avium, boviium, intracellulare)   | 311 Measles (Rubeola)  |
| 113 Chlamydia   | 312 Mumps  |
| 119 Other atypical bacteria, <i>specify in Q.345</i>  | 313 Papovavirus  |
| <b>2. Fungal Infections</b>   | 314 Respiratory syncytial virus (RSV)  |
| 200 Candida, not otherwise specified  | 315 Rubella (German Measles)   |
| 201 Candida albicans  | 316 Parainfluenza  |
| 202 Candida krusei  | 317 Human herpesvirus-6 (HHV-6)  |
| 203 Candida parapsilosis  | 318 Epstein-Barr virus (EBV)   |
| 204 Candida tropicalis  | 319 Polyomavirus   |
| 205 Torulopsis glabrata (a subspecies of candida)   | 320 Rotavirus  |
| 209 Other Candida, <i>specify in Q.355</i>  | 321 Rhinovirus   |
| 210 Aspergillus, not otherwise specified  | 329 Other viral, <i>specify in Q.365</i>   |
| 211 Aspergillus flavus  | <b>4. Parasite Infections</b>  |
| 212 Aspergillus fumigatus   | 401 Pneumocystis (PCP)   |
| 213 Aspergillus niger   | 402 Toxoplasma   |
| 219 Other Aspergillus, <i>specify in Q.355</i>  | 403 Giardia  |
| 220 Cryptococcus species  | 404 Cryptosporidium  |
| 230 Fusarium species  | 409 Other parasite (amebiasis, echinococcal cyst, trichomonas – either vaginal or gingivitis), <i>specify in Q.375</i> |
| 240 Mucormycosis (zygomycetes, rhizopus)  | <b>5. Other Infections</b>   |
| 250 Yeast, not otherwise specified  | 501 Suspected atypical bacterial infection   |
| 259 Other fungus, <i>specify in Q.355</i>   | 502 Suspected bacterial infection  |
|   | 503 Suspected fungal infection   |
|   | 504 Suspected viral infection  |
|   | 505 Suspected parasite infection   |
|   | 509 No organism identified   |

TEAM

IUBMID

### Pulmonary function

385. Has patient developed interstitial pneumonitis (IPn) since date of last report?

*Interstitial pneumonitis is characterized by hypoxia and diffuse interstitial infiltrates on chest x-ray not caused by fluid overload.*

- 1  Yes  
0  No

386. How many episodes of IPn occurred since date of last report?

*Note: If more than one episode of IPn, photocopy this page and complete Q.387-406 for subsequent episode(s).*

387. Date of onset of IPn:     
Month Day Year

388. Were diagnostic tests other than radiographic studies done?

- 1  Yes  
0  No

Diagnosis was evaluated by:

Yes No

389. 1  0  Bronchoalveolar lavage  
390. 1  0  Transbronchial biopsy  
391. 1  0  Open lung biopsy  
392. 1  0  Autopsy  
393. 1  0  Other, specify: \_\_\_\_\_

394. Was an organism isolated?

- 1  Yes  
0  No (idiopathic, or no organism isolated)

Etiology:

Yes No

395. 1  0  Pneumocystis carinii  
396. 1  0  Aspergillus  
397. 1  0  Candida  
398. 1  0  Toxoplasma  
399. 1  0  Respiratory syncytial virus  
400. 1  0  Cytomegalovirus  
401. 1  0  Herpes simplex  
402. 1  0  Adenovirus  
403. 1  0  Human herpes virus 6  
404. 1  0  Other virus, specify: \_\_\_\_\_  
405. 1  0  Other, specify: \_\_\_\_\_

406. Has interstitial pneumonitis resolved?

- 1  Yes  
0  No  
8  Unknown



TEAM

IUBMID

407. Did patient develop pulmonary abnormalities other than interstitial pneumonitis since date of last report?

- 1  Yes
- 0  No

<p>408. Did patient develop Acute Respiratory Distress Syndrome (ARDS) since last report?</p> <p>1 <input type="checkbox"/> Yes</p> <p>0 <input type="checkbox"/> No</p>	<p>409. Date of onset of ARDS: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/></p> <p style="margin-left: 100px;">Month      Day      Year</p> <p>410. Were diagnostic tests done?</p> <p>1 <input type="checkbox"/> Yes</p> <p>0 <input type="checkbox"/> No</p> <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"><p>Diagnosis was evaluated by:</p><table style="width: 100%; border-collapse: collapse;"><thead><tr><th style="width: 5%;"></th><th style="width: 5%;"></th><th style="width: 5%; text-align: center;"><u>Yes</u></th><th style="width: 5%; text-align: center;"><u>No</u></th><th style="width: 80%;"></th></tr></thead><tbody><tr><td>411.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Bronchoalveolar lavage</td></tr><tr><td>412.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Transbronchial biopsy</td></tr><tr><td>413.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Open lung biopsy</td></tr><tr><td>414.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Autopsy</td></tr><tr><td>415.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Other, specify: _____</td></tr></tbody></table></div>			<u>Yes</u>	<u>No</u>		411.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Bronchoalveolar lavage	412.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Transbronchial biopsy	413.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Open lung biopsy	414.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Autopsy	415.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Other, specify: _____
		<u>Yes</u>	<u>No</u>																												
411.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Bronchoalveolar lavage																											
412.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Transbronchial biopsy																											
413.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Open lung biopsy																											
414.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Autopsy																											
415.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Other, specify: _____																											
<p>416. Did patient develop bronchiolitis obliterans since last report?</p> <p>1 <input type="checkbox"/> Yes</p> <p>0 <input type="checkbox"/> No</p>	<p>417. Date of onset: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/></p> <p style="margin-left: 100px;">Month      Day      Year</p> <p>418. Were diagnostic tests done?</p> <p>1 <input type="checkbox"/> Yes</p> <p>0 <input type="checkbox"/> No</p> <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"><p>Diagnosis was evaluated by:</p><table style="width: 100%; border-collapse: collapse;"><thead><tr><th style="width: 5%;"></th><th style="width: 5%;"></th><th style="width: 5%; text-align: center;"><u>Yes</u></th><th style="width: 5%; text-align: center;"><u>No</u></th><th style="width: 80%;"></th></tr></thead><tbody><tr><td>419.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Bronchoalveolar lavage</td></tr><tr><td>420.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Transbronchial biopsy</td></tr><tr><td>421.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Open lung biopsy</td></tr><tr><td>422.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Autopsy</td></tr><tr><td>423.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Other, specify: _____</td></tr></tbody></table></div>			<u>Yes</u>	<u>No</u>		419.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Bronchoalveolar lavage	420.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Transbronchial biopsy	421.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Open lung biopsy	422.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Autopsy	423.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Other, specify: _____
		<u>Yes</u>	<u>No</u>																												
419.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Bronchoalveolar lavage																											
420.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Transbronchial biopsy																											
421.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Open lung biopsy																											
422.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Autopsy																											
423.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Other, specify: _____																											
<p>424. Did patient develop pulmonary hemorrhage since last report?</p> <p>1 <input type="checkbox"/> Yes</p> <p>0 <input type="checkbox"/> No</p>	<p>425. Date of onset: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/></p> <p style="margin-left: 100px;">Month      Day      Year</p> <p>426. Were diagnostic tests done?</p> <p>1 <input type="checkbox"/> Yes</p> <p>0 <input type="checkbox"/> No</p> <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"><p>Diagnosis was evaluated by:</p><table style="width: 100%; border-collapse: collapse;"><thead><tr><th style="width: 5%;"></th><th style="width: 5%;"></th><th style="width: 5%; text-align: center;"><u>Yes</u></th><th style="width: 5%; text-align: center;"><u>No</u></th><th style="width: 80%;"></th></tr></thead><tbody><tr><td>427.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Bronchoalveolar lavage</td></tr><tr><td>428.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Transbronchial biopsy</td></tr><tr><td>429.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Open lung biopsy</td></tr><tr><td>430.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Autopsy</td></tr><tr><td>431.</td><td>1 <input type="checkbox"/></td><td>0 <input type="checkbox"/></td><td></td><td>Other, specify: _____</td></tr></tbody></table></div>			<u>Yes</u>	<u>No</u>		427.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Bronchoalveolar lavage	428.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Transbronchial biopsy	429.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Open lung biopsy	430.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Autopsy	431.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Other, specify: _____
		<u>Yes</u>	<u>No</u>																												
427.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Bronchoalveolar lavage																											
428.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Transbronchial biopsy																											
429.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Open lung biopsy																											
430.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Autopsy																											
431.	1 <input type="checkbox"/>	0 <input type="checkbox"/>		Other, specify: _____																											
<p>432. Did patient develop other non-infectious pulmonary abnormalities since last report?</p> <p>1 <input type="checkbox"/> Yes</p> <p>0 <input type="checkbox"/> No</p>	<p>433. Specify: _____</p>																														

TEAM

IUBMID

**Liver function**

434. Did patient develop non-infectious liver toxicity since last report?

- 1  Yes
- 0  No

435. What was the date of onset?     
Month Day Year

Etiology:

**Yes No**

436. 1  0  Veno-occlusive disease

437. 1  0  Other, specify: \_\_\_\_\_

438. 1  0  Unknown

439. Has liver toxicity resolved?

1  Yes

0  No

8  Unknown

440. Did patient develop any other non-infectious clinically significant organ impairment or disorder since last report?

- 1  Yes
- 0  No

**Yes No**

441. 1  0  Renal failure requiring dialysis—  If yes, received dialysis? 1  Yes 0  No

442. 1  0  Posttransplant microangiopathy/thrombotic thrombocytopenic purpura (TTP)/ hemolytic uremic syndrome (HUS) or similar syndrome

443. 1  0  Hemorrhage, if yes specify site: \_\_\_\_\_

448. 1  0  Hemorrhagic cystitis

449. 1  0  Seizures

450. 1  0  Cataracts

451. 1  0  Avascular necrosis

452. 1  0  Hypothyroidism

453. 1  0  Gonadal dysfunction

454. 1  0  Growth hormone deficiency/growth disturbance

455. 1  0  Other, specify: \_\_\_\_\_

**Yes No**

444. 1  0  CNS

445. 1  0  Upper GI tract

446. 1  0  Lower GI tract

447. 1  0  Other, specify: \_\_\_\_\_

TEAM

IUBMID

456. Did a new malignancy, lymphoproliferative or myeloproliferative disorder appear since last report?

- 1  Yes  
0  No

456.2 Did more than one new malignancy develop?

- 1  Yes  
0  No

*Copy page and answer Q.457-469 for each new malignancy*

457. Date of diagnosis:        
Month Day Year

458. Origin of cells: 1  Host 2  Donor 7  Not tested 8  Unknown

Diagnosis (*send copy of pathology report/other documentation*):

Yes No

459. 1  0  Clonal cytogenetic abnormality without leukemia or MDS

460. 1  0  Acute myeloid leukemia

461. 1  0  Other leukemia, specify: \_\_\_\_\_

462. 1  0  Myelodysplasia

463. 1  0  Lymphoma or lymphoproliferative disease

464. EBV positive? 1  Yes 0  No 8  Unknown

465. 1  0  Hodgkin disease

466. 1  0  Other cancer

467. Primary site: \_\_\_\_\_

468. Histologic type: \_\_\_\_\_

469. Behavior:

- 1  Benign  
2  In situ  
3  Malignant/invasive  
8  Unknown

TEAM

IUBMID

### Death Information

470. Date of death:        
Month Day Year

Cause(s) of death:

<p>Enter appropriate cause of death below.</p> <p><i>If a code number for "Other, specify" (codes 29, 39, 88, 89, 109, 129, 900) is entered, write the cause in the space provided.</i></p> <p>471. Primary: <input type="text"/> <input type="text"/> <input type="text"/> Specify: _____</p> <p>Contributing or secondary causes:</p> <p>472. <input type="text"/> <input type="text"/> <input type="text"/> Specify: _____</p> <p>473. <input type="text"/> <input type="text"/> <input type="text"/> Specify: _____</p> <p>474. <input type="text"/> <input type="text"/> <input type="text"/> Specify: _____</p> <p>475. <input type="text"/> <input type="text"/> <input type="text"/> Specify: _____</p> <p>476. <input type="text"/> <input type="text"/> <input type="text"/> Specify: _____</p>	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center; padding: 2px;">Cause of Death Codes*</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">10 Graft rejection or failure</td> </tr> <tr> <td style="padding: 2px;">Infection (other than interstitial pneumonia)                      20 Infection, organism not identified                      21 Bacterial                      22 Fungal                      23 Viral                      24 Protozoal                      29 Other infection, specify</td> </tr> <tr> <td style="padding: 2px;">Interstitial pneumonia                      30 IPn, idiopathic                      31 Cytomegalovirus (CMV)                      32 Viral, other                      33 Pneumocystis (PCP)                      34 Fungal                      39 Other IPn, specify</td> </tr> <tr> <td style="padding: 2px;">40 Adult Respiratory Distress Syndrome, ARDS (other than IPn)</td> </tr> <tr> <td style="padding: 2px;">50 Acute GVHD 60 Chronic GVHD</td> </tr> <tr> <td style="padding: 2px;">70 Recurrence or persistence of primary disease                       * NOTE: Code "70" may only be used as a primary cause of death, not a contributing or secondary cause.</td> </tr> <tr> <td style="padding: 2px;">Organ failure (not due to GVHD or infection)                      80 Organ failure, not otherwise specified                      81 Liver (not VOD)                      82 VOD                      83 Cardiac (Cardiomyopathy)                      84 Pulmonary                      85 CNS                      86 Renal                      87 Gastrointestinal (not liver)                      88 Multiple organ failure, specify                      89 Other organ failure, specify</td> </tr> <tr> <td style="padding: 2px;">90 Secondary malignancy                       (malignancy other than one for which transplant performed includes post transplant lymphoproliferative disease and MDS)</td> </tr> <tr> <td style="padding: 2px;">Hemorrhage                      100 Hemorrhage, not otherwise specified                      101 Pulmonary                      102 Intracranial                      103 Gastrointestinal                      109 Other hemorrhage, specify</td> </tr> <tr> <td style="padding: 2px;">110 Accidental death</td> </tr> <tr> <td style="padding: 2px;">Vascular                      120 Vascular, not otherwise specified                      121 Thromboembolic                      122 Diffused intravascular coagulation (DIC)                      123 Thrombotic thrombocytopenic purpura                      129 Other vascular, specify</td> </tr> <tr> <td style="padding: 2px;">130 In utero death (for in utero transplants)</td> </tr> <tr> <td style="padding: 2px;">140 Prior malignancy                       (malignancy existing before disease for which transplant performed as reported in 095-COR Form Q.41)</td> </tr> <tr> <td style="padding: 2px;">900 Other, specify</td> </tr> </tbody> </table>	Cause of Death Codes*	10 Graft rejection or failure	Infection (other than interstitial pneumonia) 20 Infection, organism not identified 21 Bacterial 22 Fungal 23 Viral 24 Protozoal 29 Other infection, specify	Interstitial pneumonia 30 IPn, idiopathic 31 Cytomegalovirus (CMV) 32 Viral, other 33 Pneumocystis (PCP) 34 Fungal 39 Other IPn, specify	40 Adult Respiratory Distress Syndrome, ARDS (other than IPn)	50 Acute GVHD 60 Chronic GVHD	70 Recurrence or persistence of primary disease  * NOTE: Code "70" may only be used as a primary cause of death, not a contributing or secondary cause.	Organ failure (not due to GVHD or infection) 80 Organ failure, not otherwise specified 81 Liver (not VOD) 82 VOD 83 Cardiac (Cardiomyopathy) 84 Pulmonary 85 CNS 86 Renal 87 Gastrointestinal (not liver) 88 Multiple organ failure, specify 89 Other organ failure, specify	90 Secondary malignancy  (malignancy other than one for which transplant performed includes post transplant lymphoproliferative disease and MDS)	Hemorrhage 100 Hemorrhage, not otherwise specified 101 Pulmonary 102 Intracranial 103 Gastrointestinal 109 Other hemorrhage, specify	110 Accidental death	Vascular 120 Vascular, not otherwise specified 121 Thromboembolic 122 Diffused intravascular coagulation (DIC) 123 Thrombotic thrombocytopenic purpura 129 Other vascular, specify	130 In utero death (for in utero transplants)	140 Prior malignancy  (malignancy existing before disease for which transplant performed as reported in 095-COR Form Q.41)	900 Other, specify
Cause of Death Codes*																
10 Graft rejection or failure																
Infection (other than interstitial pneumonia) 20 Infection, organism not identified 21 Bacterial 22 Fungal 23 Viral 24 Protozoal 29 Other infection, specify																
Interstitial pneumonia 30 IPn, idiopathic 31 Cytomegalovirus (CMV) 32 Viral, other 33 Pneumocystis (PCP) 34 Fungal 39 Other IPn, specify																
40 Adult Respiratory Distress Syndrome, ARDS (other than IPn)																
50 Acute GVHD 60 Chronic GVHD																
70 Recurrence or persistence of primary disease  * NOTE: Code "70" may only be used as a primary cause of death, not a contributing or secondary cause.																
Organ failure (not due to GVHD or infection) 80 Organ failure, not otherwise specified 81 Liver (not VOD) 82 VOD 83 Cardiac (Cardiomyopathy) 84 Pulmonary 85 CNS 86 Renal 87 Gastrointestinal (not liver) 88 Multiple organ failure, specify 89 Other organ failure, specify																
90 Secondary malignancy  (malignancy other than one for which transplant performed includes post transplant lymphoproliferative disease and MDS)																
Hemorrhage 100 Hemorrhage, not otherwise specified 101 Pulmonary 102 Intracranial 103 Gastrointestinal 109 Other hemorrhage, specify																
110 Accidental death																
Vascular 120 Vascular, not otherwise specified 121 Thromboembolic 122 Diffused intravascular coagulation (DIC) 123 Thrombotic thrombocytopenic purpura 129 Other vascular, specify																
130 In utero death (for in utero transplants)																
140 Prior malignancy  (malignancy existing before disease for which transplant performed as reported in 095-COR Form Q.41)																
900 Other, specify																

477. Was cause of death confirmed by autopsy?

- 1  Yes
- 0  No
- 8  Unknown
- 6  Pending

**Send copy of autopsy report when available**

Autopsy included with this report:  
 1  Yes    0  No

# FOLLOW-UP INSTITUTIONAL INFORMATION

TEAM

IUBMID   
*(Institutional Unique Blood or Marrow Transplant Identification Number)*

Date of transplant for which this form is being completed:     
 Month Day Year

**FOR REGISTRY USE ONLY:**

I.D.  -  -

Date received:

Registry: *IBMTR* *ABMTR* (circle one)

Date of report:     
 Month Day Year

1. Signed: \_\_\_\_\_ / \_\_\_\_\_  
 Person completing this form / Please print name

3. Name of doctor for correspondence: \_\_\_\_\_

Institution: \_\_\_\_\_

Address: \_\_\_\_\_

Telephone:

Ext:

Fax:

4. Make reimbursement check payable to: \_\_\_\_\_  
*Payment for data forms is contingent on the availability of funds that have been obtained from sources external to the Medical College of Wisconsin for purposes of these payments.*

5. Patient or authorized family member/guardian is aware of, and has consented to, the fact that this case is being entered into the Registry database: \_\_\_\_\_ (physician's initials).

6. Determining cut-off for all parts of this report:  
 A complete follow-up report of transplant consists of the following two parts (both parts should have the same date of report, date of transplant and contact date):

- A (white) CORE Follow-up form
- An appropriate (ivory) disease-specific insert (Inserts I through XVIII)



The cut-off for **ALL** parts of this Report Form should be the date of the follow-up exam closest to the transplant anniversary date, unless (a) patient died, or (b) patient received a subsequent transplant or infusion >14 days but <100 days post transplant which requires a separate Report Form. (See pages 3 & 4 of the CORE Follow-up Form to determine if the re-infusions is considered another transplant requiring a separate Report Form.)

The date of Last Contact is the date of the follow-up exam or (a) the date of death, or (b) one day prior to conditioning for subsequent transplant or one day prior to subsequent transplant/infusion if no conditioning given.

Enter Last Contact date (e.g., Month, Day, Year):

Enter these dates on page 1 of the CORE Follow-up Form. Report information in the CORE Follow-up Form and disease-specific insert only up to Last Contact date. Later information should be reported in the next Follow-up Form or Report Form for a subsequent transplant when it is due.

***If completing Follow-up Form for >2 years of data, report all data on one Follow-up Form. Begin completing annual Follow-up Forms thereafter.***



TEAM

IUBMID

4. Was bone marrow cryopreserved?

- 1  Yes  
0  No

5. Cryopreservative was:

- 1  DMSO  
2  Hydroxyethylstarch  
7  Other, specify: \_\_\_\_\_

Indicate whether or not tumor involvement of bone marrow or circulating cells was detected prior to transplant by each of the indicated methods:

	<u>Detected in circulating cells*</u>			<u>Detected in bone marrow, prior to harvest*</u>			<u>Detected in harvested bone marrow (before purging)</u>		
	<u>Yes</u>	<u>No</u>	<u>Not Tested</u>	<u>Yes</u>	<u>No</u>	<u>Not Tested</u>	<u>Yes</u>	<u>No</u>	<u>Not Tested</u>
Routine histopathology	6. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	7. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	8. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>
Polymerase chain reaction (PCR)	9. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	10. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	11. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>
Other molecular technique	12. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	13. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	14. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>
Immunohistochemistry	15. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	16. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	17. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>
Cell culture technique	18. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	19. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	20. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>
Other, specify: _____	21. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	22. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	23. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>

\* Refers to detection of tumor cells in circulation or bone marrow in the interval between last chemotherapy and harvest.

24. Was bone marrow treated to remove malignant cells (purged)?

- 1  Yes  
0  No

Which of the following were used for purging?

- |     | <u>Yes</u>                 | <u>No</u>                  |  |
|-----|----------------------------|----------------------------|--|
| 25. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Monoclonal antibody, specify: _____  |
| 26. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 4-hydroperoxycyclophosphamide (4HC)  |
| 27. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Mafofosamide   |
| 28. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other drug, specify: _____   |
| 29. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Elutriation  |
| 30. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Immunomagnetic column  |
| 31. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Toxin, specify: _____  |
| 32. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Positive stem cell selection (other than preparation of mononuclear fraction)<br>Specify method: _____ |
| 33. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other, specify: _____  |

continued on next page

TEAM

IUBMID

Indicate whether or not tumor involvement of harvested bone marrow was detected after purging by each of the indicated methods:

- |     | <u>Yes</u>                 | <u>No</u>                  | <u>Not Tested</u>          |                                 |
|-----|----------------------------|----------------------------|----------------------------|---------------------------------|
| 34. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Routine histopathology          |
| 35. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Polymerase chain reaction (PCR) |
| 36. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Other molecular technique       |
| 37. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Immunohistochemistry            |
| 38. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Cell culture technique          |
| 39. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Other, specify: _____           |

40. Were cells (or a portion of cells) expanded ex vivo prior to infusion?

- 1  Yes  
0  No

41. Days of expansion culture:

Growth factors used:

- |     | <u>Yes</u>                 | <u>No</u>                  |                       |
|-----|----------------------------|----------------------------|-----------------------|
| 42. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | G-CSF                 |
| 43. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | GM-CSF                |
| 44. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | IL-2                  |
| 45. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | IL-3                  |
| 46. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | IL-6                  |
| 47. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | SCF                   |
| 48. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Thrombopoietin        |
| 49. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | M-CSF                 |
| 50. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | PIXY 321              |
| 51. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other, specify: _____ |

52. Number of nucleated cells pre-expansion:    .  x 10<sup>10</sup>

53. Number of nucleated cells post-expansion:    .  x 10<sup>10</sup>

54. Total number of nucleated cells infused:    .  x 10<sup>10</sup>

55. Total number of mononucleated cells infused:    .  x 10<sup>10</sup>

56. Were bone marrow progenitor assays done?

- 1  Yes  
0  No

57. Number of CD34+ cells infused:    .  x 10<sup>7</sup> -s  Unknown



**INSERT AUTOPB**

**FOR REGISTRY USE ONLY:**  
I.D. -  
Date received:

TEAM  IUBMID

(Institutional Unique Blood or Marrow Transplant Identification Number)

Registry: IBMTR ABMTR (circle one)

Date of transplant for which this form is being completed:     
Month Day Year

Date of report:     
Month Day Year

### Autologous Blood Collection and Processing

1. What was the reason for using blood rather than bone marrow for hematopoietic reconstitution?

- 1  All patients receive peripheral blood cells, per protocol
- 2  Bone marrow involvement with tumor
- 3  Prior radiation to pelvis
- 4  Inadequate bone marrow cellularity
- 7  Other, specify: \_\_\_\_\_

2. Date of first stem cell collection:     
Month Day Year

3. Date of last stem cell collection:     
Month Day Year

4. Number of collections:

5. Did patient receive treatment prior to harvesting to enhance stem cell collection?

- 1  Yes
- 0  No

What treatment did patient receive?

6. Chemotherapy:  
1  Yes  
0  No

7. Growth factors:  
1  Yes  
0  No

	Yes	No	
8.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	G-CSF
9.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	GM-CSF
10.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

11. 1  Yes 0  No Other, specify: \_\_\_\_\_

TEAM

IUBMID

**12. For leukemia/lymphoma patients only:**

What was disease state at time of stem cell collections?

1 <input type="checkbox"/> First remission	Date of remission: <input type="text"/> <input type="text"/> <input type="text"/> Month Day Year
2 <input type="checkbox"/> Second remission	
3 <input type="checkbox"/> Third remission	
4 <input type="checkbox"/> First relapse	
5 <input type="checkbox"/> Second relapse	
7 <input type="checkbox"/> Other, specify: _____	

**13. Were cells cryopreserved?**

- 1  Yes  
0  No

**14. Cryopreservative was:**

- 1  DMSO  
2  Hydroxyethylstarch  
7  Other, specify: \_\_\_\_\_

Indicate whether or not tumor involvement of bone marrow or circulating cells was detected prior to transplant by each of the indicated methods:

	<u>Detected in circulating cells*</u>			<u>Detected in bone marrow, prior to harvest*</u>			<u>Detected in harvested cells (before purging)</u>		
	Yes	No	Not Tested	Yes	No	Not Tested	Yes	No	Not Tested
Routine histopathology	15. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	16. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	17. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>
Polymerase chain reaction (PCR)	18. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	19. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	20. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>
Other molecular technique	21. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	22. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	23. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>
Immunohistochemistry	24. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	25. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	26. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>
Cell culture technique	27. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	28. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	29. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>
Other, specify: _____	30. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	31. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	32. <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>

\* Refers to detection of tumor cells in circulation or bone marrow in the interval between last chemotherapy and stem cell collection.

TEAM

IUBMID

33. Were cells treated to remove malignant cells (purged)? 1  Yes 0  No

Which of the following were used for purging?

- |     | Yes                        | No                         |  |
|-----|----------------------------|----------------------------|--|
| 34. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Monoclonal antibody, specify: _____  |
| 35. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 4-hydroperoxycyclophosphamide (4HC)  |
| 36. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Mafosfamide  |
| 37. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other drug, specify: _____   |
| 38. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Elutriation  |
| 39. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Immunomagnetic column  |
| 40. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Toxin, specify: _____  |
| 41. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Positive stem cell selection (other than preparation of mononuclear fraction)<br>Specify method: _____ |
| 42. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other, specify: _____  |

Indicate whether or not tumor cells were detected in the graft after purging by each of the indicated methods:

- |     | Yes                        | No                         | Not Tested                 |                                 |
|-----|----------------------------|----------------------------|----------------------------|---------------------------------|
| 43. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Routine histopathology          |
| 44. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Polymerase chain reaction (PCR) |
| 45. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Other molecular technique       |
| 46. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Immunohistochemistry            |
| 47. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Cell culture technique          |
| 48. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | 7 <input type="checkbox"/> | Other, specify: _____           |

49. Were cells expanded ex vivo prior to infusion?

1  Yes  
0  No

50. Days of expansion culture:

Growth factors used:

- |     | Yes                        | No                         |                       |
|-----|----------------------------|----------------------------|-----------------------|
| 51. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | G-CSF                 |
| 52. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | GM-CSF                |
| 53. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | IL-2                  |
| 54. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | IL-3                  |
| 55. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | IL-6                  |
| 56. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | SCF                   |
| 57. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Thrombopoietin        |
| 58. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | M-CSF                 |
| 59. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | PIXY 321              |
| 60. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other, specify: _____ |

61. Number of nucleated cells pre-expansion:    .  x 10<sup>10</sup>

62. Number of nucleated cells post-expansion:    .  x 10<sup>10</sup>

TEAM

IUBMID

63. Total number of nucleated cells infused:     .  x 10<sup>10</sup>

64. Total number of mononucleated cells infused:     .  x 10<sup>10</sup>

65. Were progenitor cell assays done?

1  Yes

0  No

66. Number of CD34+ cells infused:     .  x 10<sup>7</sup> -s  Unknown

**INSERT VIII**  
**Breast Cancer**

**FOR REGISTRY USE ONLY:**

I.D.  -  -

Date received: \_\_\_\_\_

TEAM  IUBMID

(Institutional Unique Blood or Marrow Transplant Identification Number)

Registry:  IBMTR  ABMTR (circle one)

Date of transplant for which this form is being completed:

Month      Day      Year

Date of report:

Month      Day      Year

**Pretransplant Information**

**\* If this is a report of a second (or subsequent) transplant, check here  and go to Q.168**

1. Date of pathologic diagnosis of breast cancer:

Month      Year

**Append copy of pathology report if available.**

*If transplant was done after occurrence of a second primary breast cancer, report staging and treatment [Q.1-75] of each primary separately by copying pages 1-4.*

2. Stage of breast cancer at diagnosis:

0  In situ

1  I - T<sub>1</sub>N<sub>0</sub>M<sub>0</sub>

2  II - T<sub>0,1</sub>N<sub>1</sub>M<sub>0</sub> or T<sub>2</sub>N<sub>0,1</sub>M<sub>0</sub> or T<sub>3</sub>N<sub>0</sub>M<sub>0</sub>

3  IIIA - T<sub>0-2</sub>N<sub>2</sub>M<sub>0</sub> or T<sub>3</sub>N<sub>1-2</sub>M<sub>0</sub>

4  IIIB - T<sub>4</sub>N<sub>Any</sub>M<sub>0</sub>, T<sub>Any</sub>N<sub>3</sub>M<sub>0</sub>, Inflammatory

5  IV - T<sub>Any</sub>N<sub>Any</sub>M<sub>1</sub>

8  Unknown

3. Breast cancer histology at diagnosis:

1  Invasive/infiltrating ductal

2  Invasive lobular

3  Inflammatory

4  Other, specify: \_\_\_\_\_

8  Unknown

4. Location of breast cancer at diagnosis:

1  Right breast

2  Left breast

3  Bilateral

5. Menopausal status at diagnosis:

1  Premenopausal

2  Postmenopausal

7  Not applicable, male patient

8  Unknown

6. Age at menopause:   years

7. Did patient have a history of prior cancer (other than breast cancer)?

1  Yes

0  No

8. Cite prior disease:

1  Hodgkin lymphoma

2  Non-Hodgkin lymphoma

7  Other, specify: \_\_\_\_\_

9. Date of diagnosis of prior cancer:

Month      Year

TEAM

IUBMID

10. Were metastases (other than ipsilateral axillary lymph nodes) present at diagnosis?

- 1  Yes  
0  No

	<u>Yes</u>	<u>No</u>	<u>Unknown</u>	
11.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Bone
12.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Bone marrow
13.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Lung
14.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Liver
15.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Skin
16.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Chest wall
17.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Other lymph nodes, specify site: _____
18.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	Other, specify: _____

19. Did patient receive neoadjuvant treatment (includes chemotherapy, hormones and/or radiation) prior to definitive surgery?

- 1  Yes  
0  No

### Neoadjuvant Treatment

Size of primary tumor (largest diameter before neoadjuvant treatment)

20. Was tumor multicentric?

- 1  Yes  
0  No  
8  Unknown

Give size of largest tumor in Q.21 – 22

21. Clinical size:   cm -7  Not measurable -8  Unknown

22. Radiographic size:   cm -7  Not measurable -8  Unknown

23. Did patient receive neoadjuvant **chemotherapy**?

- 1  Yes  
0  No

Specify chemotherapy:

- |     | <u>Yes</u>                 | <u>No</u>                  |                       |
|-----|----------------------------|----------------------------|-----------------------|
| 24. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Adriamycin alone      |
| 25. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | CAF                   |
| 26. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | CMF                   |
| 27. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | AFM                   |
| 28. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other, specify: _____ |

29. Number of cycles:

30. Did patient receive neoadjuvant **hormone therapy**?

- 1  Yes  
0  No

Specify hormones:

- |     | <u>Yes</u>                 | <u>No</u>                  |                       |
|-----|----------------------------|----------------------------|-----------------------|
| 31. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Tamoxifen             |
| 32. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other, specify: _____ |

33. Duration of pre-surgical treatment was:   .  mos.

Continued on next page

TEAM  IUBMID

34. Did patient receive neoadjuvant radiation therapy?

- 1  Yes  
0  No

35. Specify radiation field: \_\_\_\_\_

36. Total dose:  cGy (rads)

37. Best clinical response (at time of surgery) to neoadjuvant treatment:

- 1  Complete response  
2  Partial response  
3  Stable disease  
4  Progressive disease  
8  Not evaluable, specify why not evaluable: \_\_\_\_\_

38. Did patient have surgery as part of initial management (include surgery done after neoadjuvant treatment)?

- 1  Yes  
0  No

39. Type of surgery was:

- 1  Mastectomy  
2  Lumpectomy  
7  Other, specify: \_\_\_\_\_

Size of primary tumor at time of definitive surgery; or, if surgery was not done, prior to initial non-surgical treatment

40. Was tumor multicentric?

- 1  Yes  
0  No

Give size of largest tumor in Q.41 - 43

41. Clinical size:  cm -8  Unknown

42. Radiographic size:  cm -8  Unknown

43. Pathologic size:  cm -8  Unknown

44. How many axillary nodes were examined?  -8  Unknown

45. How many axillary nodes were positive for breast cancer?  -8  Unknown

46. Were estrogen receptor assays done?

- 1  Yes  
0  No  
8  Unknown

47. Results:

- 1  Positive 3  Borderline  
2  Negative 8  Unknown

48. Actual value if available (specify units):

49. Units:

- 1  fmol/mg  
7  Other, specify: \_\_\_\_\_

50. Were progesterone receptor assays done?

- 1  Yes  
0  No  
8  Unknown

51. Results:

- 1  Positive 3  Borderline  
2  Negative 8  Unknown

52. Actual value if available (specify units):

53. Units:

- 1  fmol/mg  
7  Other, specify: \_\_\_\_\_

TEAM

IUBMID

54. Did patient receive radiation, chemotherapy and/or hormone treatment (excluding neoadjuvant) after definitive surgery as part of initial management?

- 1  Yes  
0  No

55. Did patient receive radiation treatment?

- 1  Yes  
0  No

Radiation field:

Yes No

56. 1  0  local/regional  
57. 1  0  sites of distant metastatic disease  
58. 1  0  Other, specify: \_\_\_\_\_

59. Total dose:     cGy (rads)

60. Did patient receive hormones?

- 1  Yes  
0  No

Specify hormones:

Yes No

61. 1  0  Tamoxifen  
62. 1  0  Other, specify: \_\_\_\_\_

63. Date started:      
Month Year

64. Date ended:      
Month Year

65. Did patient receive chemotherapy?

- 1  Yes  
0  No

66. Reason for chemotherapy:

- 1  Adjuvant  
2  For metastatic disease — [Go to Q.79](#)

Chemotherapy given:

Yes No

67. 1  0  CMF  
68. 1  0  CAF  
69. 1  0  Adriamycin-containing regimen  
70. 1  0  Taxol alone  
71. 1  0  Taxol plus other drugs  
72. 1  0  Other chemotherapy, specify:  
\_\_\_\_\_

73. Number of cycles:   -8  Unknown

74. Date started:      
Month Year

75. Date ended:      
Month Year



TEAM     IUBMID

76. Did breast cancer recur?

- 1  Yes  
0  No

77. Date:      
Month Year

78. Site(s): \_\_\_\_\_

79. Did patient receive treatment for persistent, recurrent or metastatic disease? 1  Yes 0  No

Regimen	Date Started	Date Stopped	Number cycles (chemotherapy)	Total dose (radiation)	Non-bone Response (see below)	Bone Response (see below)	Date Relapse/Progression		
1st	80. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year	81. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year	82. <input type="text"/> <input type="text"/>	83. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cGy (rads)	84. <input type="checkbox"/>	85. <input type="checkbox"/>	86. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year		
Treatment, specify all drugs given:									
Yes No									
87.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Adriamycin	91.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Methotrexate	94.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Thiotepa	
88.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Cytosin	92.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Mitoxantrone	95.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Vinblastine	
89.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Cisplatin	93.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Taxol	96.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Other, specify: _____	
90.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	5-fluorouracil (5-FU)							
2nd	97. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year	98. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year	99. <input type="text"/> <input type="text"/>	100. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cGy (rads)	101. <input type="checkbox"/>	102. <input type="checkbox"/>	103. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year		
Treatment, specify all drugs given:									
Yes No									
104.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Adriamycin	108.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Methotrexate	111.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Thiotepa	
105.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Cytosin	109.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Mitoxantrone	112.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Vinblastine	
106.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Cisplatin	110.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Taxol	113.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Other, specify: _____	
107.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	5-fluorouracil (5-FU)							
3rd	114. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year	115. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year	116. <input type="text"/> <input type="text"/>	117. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cGy (rads)	118. <input type="checkbox"/>	119. <input type="checkbox"/>	120. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year		
Treatment, specify all drugs given:									
Yes No									
121.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Adriamycin	125.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Methotrexate	128.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Thiotepa	
122.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Cytosin	126.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Mitoxantrone	129.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Vinblastine	
123.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Cisplatin	127.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Taxol	130.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	Other, specify: _____	
124.	1 <input type="checkbox"/> 0 <input type="checkbox"/>	5-fluorouracil (5-FU)							

**Non-bone response codes:**

- 1 = CR
- 2 = PR
- 3 = stable disease
- 4 = progressive disease

**Bone response codes:**

- 1 = no prior bone disease
- 2 = symptomatic improvement, no progression
- 3 = symptomatic and radiographic (not bone scan only) improvement
- 4 = no response
- 5 = progressive disease
- 6 = not evaluable (radiographic data not available)

Continued on next page

TEAM

IUBMID

Regimen	Date Started	Date Stopped	Number cycles (chemotherapy)	Total dose (radiation)	Non-bone Response (see below)	Bone Response (see below)	Date Relapse/Progression																																												
4th	131. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year	132. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year	133. <input type="text"/> <input type="text"/>	134. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cGy (rads)	135. <input type="text"/>	136. <input type="text"/>	137. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year																																												
Treatment, specify all drugs given:																																																			
<table border="0"> <tr> <td><u>Yes</u></td> <td><u>No</u></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>138. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Adriamycin</td> <td>142. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Methotrexate</td> <td>145. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Thiotepa</td> </tr> <tr> <td>139. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Cytosan</td> <td>143. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Mitoxantrone</td> <td>146. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Vinblastine</td> </tr> <tr> <td>140. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Cis-platin</td> <td>144. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Taxol</td> <td>147. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Other, specify: _____</td> </tr> <tr> <td>141. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>5-fluorouracil (5-FU)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>								<u>Yes</u>	<u>No</u>							138. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Adriamycin	142. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Methotrexate	145. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Thiotepa	139. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cytosan	143. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Mitoxantrone	146. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Vinblastine	140. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cis-platin	144. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Taxol	147. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____	141. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	5-fluorouracil (5-FU)						
<u>Yes</u>	<u>No</u>																																																		
138. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Adriamycin	142. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Methotrexate	145. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Thiotepa																																											
139. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cytosan	143. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Mitoxantrone	146. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Vinblastine																																											
140. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cis-platin	144. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Taxol	147. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____																																											
141. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	5-fluorouracil (5-FU)																																																	
5th	148. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year	149. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year	150. <input type="text"/> <input type="text"/>	151. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cGy (rads)	152. <input type="text"/>	153. <input type="text"/>	154. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Month Year																																												
Treatment, specify all drugs given:																																																			
<table border="0"> <tr> <td><u>Yes</u></td> <td><u>No</u></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>155. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Adriamycin</td> <td>159. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Methotrexate</td> <td>162. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Thiotepa</td> </tr> <tr> <td>156. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Cytosan</td> <td>160. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Mitoxantrone</td> <td>163. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Vinblastine</td> </tr> <tr> <td>157. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Cis-platin</td> <td>161. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Taxol</td> <td>164. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>Other, specify: _____</td> </tr> <tr> <td>158. 1 <input type="checkbox"/></td> <td>0 <input type="checkbox"/></td> <td>5-fluorouracil (5-FU)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>								<u>Yes</u>	<u>No</u>							155. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Adriamycin	159. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Methotrexate	162. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Thiotepa	156. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cytosan	160. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Mitoxantrone	163. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Vinblastine	157. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cis-platin	161. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Taxol	164. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____	158. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	5-fluorouracil (5-FU)						
<u>Yes</u>	<u>No</u>																																																		
155. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Adriamycin	159. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Methotrexate	162. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Thiotepa																																											
156. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cytosan	160. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Mitoxantrone	163. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Vinblastine																																											
157. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Cis-platin	161. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Taxol	164. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____																																											
158. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	5-fluorouracil (5-FU)																																																	
Non-bone response codes:				Bone response codes:																																															
1 = CR				1 = no prior bone disease																																															
2 = PR				2 = symptomatic improvement, no progression																																															
3 = stable disease				3 = symptomatic and radiographic (not bone scan only) improvement																																															
4 = progressive disease				4 = no response																																															
				5 = progressive disease																																															
				6 = not evaluable (radiographic data not available)																																															

What was the total dose of anthracyclines prior to start of high-dose therapy (conditioning)?

165. Doxorubicin:    mg/m<sup>2</sup> -8  Unknown -7  Not given  
(Adriamycin)
166. Mitoxantrone:    mg/m<sup>2</sup> -8  Unknown -7  Not given
167. Other    mg/m<sup>2</sup> -8  Unknown -7  Not given  
anthracycline,  
specify: \_\_\_\_\_

TEAM

IUBMID

168. Was bone marrow biopsy done prior to high-dose conditioning?

- 1  Yes  
0  No

169. Date of most recent biopsy        
Month Day Year

170. Was breast cancer present?  
1  Yes  
0  No

How was it detected?

	Yes	No	Not tested	
171.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	Routine histopathology
172.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	PCR (polymerase chain reaction)
173.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	Other molecular technique
174.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	Immunohistochemistry
175.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	Cell culture technique
176.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	Other, specify: _____

177. Did patient ever have bone marrow involvement with breast cancer other than involvement indicated in Q.168?

- 1  Yes  
0  No

How was it detected?

	Yes	No	Not tested	
178.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	Routine histopathology
179.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	PCR (polymerase chain reaction)
180.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	Other molecular technique
181.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	Immunohistochemistry
182.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	Cell culture technique
183.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	7 <input type="checkbox"/>	Other, specify: _____

184. What was status of disease immediately prior to start of conditioning?

- 1  Complete response - no evidence of disease  
2  Complete response with exception of bone scan abnormalities of unknown significance  
3  Partial response  
4  Stable  
5  Progressive disease

Indicate all sites of disease involvement:

	<u>At any time between diagnosis and transplant</u>			<u>Immediately prior to start of conditioning</u>		
	Yes	No	Unknown	Yes	No	Unknown
Breast	185.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	185.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Chest wall	186.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	186.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Bone - symptomatic	187.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	187.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Bone - radiographic	188.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	188.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Axillary lymph nodes	189.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	189.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Other lymph nodes	190.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	190.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Brain	191.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	191.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Lung	192.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	192.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Pleura	193.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	193.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Liver	194.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	194.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Skin	195.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	195.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>
Other, specify:	196.1. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>	196.2. 1 <input type="checkbox"/>	0 <input type="checkbox"/>	8 <input type="checkbox"/>

TEAM

IUBMID

197. What was sensitivity of breast cancer to chemotherapy prior to conditioning? (*Response to last chemotherapy given prior to transplant; chemotherapy must include  $\geq 2$  cycles treatment given  $\leq 6$  months prior to transplant*)

- 1  Sensitive:  $\geq 50\%$  reduction in bidimensional diameter of all disease sites with no new sites of disease
- 2  Resistant:  $< 50\%$  reduction in diameter of all disease sites or development of new disease sites
- 3  Untreated
- 8  Unknown

### Outcome

198. What was patient's best response to transplant excluding planned posttransplant treatment?

- 1  Complete response: complete disappearance of all known disease for  $\geq 4$  weeks
- 2  Complete response with persistent bone scan/x-ray abnormalities of unknown significance
- 3  Partial response:  $\geq 50\%$  reduction in greatest diameter of all sites of known disease and no new sites of disease for  $\geq 4$  weeks
- 4  No response:  $< 50\%$  reduction in greatest diameter of all sites of known disease and no new sites of disease
- 5  Progressive disease: increase in size of sites of known disease or new sites of disease
- 6  Not evaluable, toxic death
- 7  Not evaluable, other reason, specify: \_\_\_\_\_

199. Was planned treatment (treatment before progressive disease) given posttransplant?

- 1  Yes
- 0  No

Go to Q.207

200. Was disease restaged prior to planned posttransplant treatment?

- 1  Yes
- 0  No

Specify treatment given whether restaged or not:

- |      | Yes                        | No                         |                                   |
|------|----------------------------|----------------------------|-----------------------------------|
| 201. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Chemotherapy, specify: _____      |
| 202. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Hormone therapy, specify: _____   |
| 203. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Radiation therapy, specify: _____ |
| 204. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Immune therapy, specify: _____    |
| 205. | 1 <input type="checkbox"/> | 0 <input type="checkbox"/> | Other, specify: _____             |

206. What was patient's best response to transplant including planned posttransplant treatment?

- 1  Complete response: complete disappearance of all known disease for  $\geq 4$  weeks
- 2  Complete response with persistent bone scan/x-ray abnormalities of unknown significance
- 3  Partial response:  $\geq 50\%$  reduction in greatest diameter of all sites of known disease and no new sites of disease for  $\geq 4$  weeks
- 4  No response:  $< 50\%$  reduction in greatest diameter of all sites of known disease and no new sites of disease
- 5  Progressive disease: increase in size of sites of known disease or new sites of disease
- 6  Not evaluable, toxic death
- 7  Not evaluable, other reason, specify: \_\_\_\_\_

TEAM     IUBMID

**207. Status of breast cancer: (at time of this report or at time of death)**

- 1  Free of breast cancer; no recurrence posttransplant
- 2  Free of breast cancer except for persistent scan abnormalities of unknown significance, no recurrence posttransplant
- 3  Persistent breast cancer without progression (*never achieved complete response*)
- 4  Progressive disease (*never achieved complete response*)

Date of progression       Site(s): \_\_\_\_\_  
 Month Day Year

- 5  Recurrent disease (relapse after complete response)

Date of recurrence       Site(s): \_\_\_\_\_  
 Month Day Year

- 6  Free of breast cancer after posttransplant recurrence

Date of recurrence       Site(s): \_\_\_\_\_  
 Month Day Year

- 7  Not evaluable; explain: \_\_\_\_\_

**First site(s) of progression/recurrence:**

	Yes	No	
208.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Lymph node
209.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Bone marrow
210.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	CNS
211.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Liver
212.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Lung
213.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Local
214.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Contralateral breast
215.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

216. Date status established:        
 Month Day Year

**FOLLOW-UP: INSERT VIII**  
**Breast Cancer**

**FOR REGISTRY USE ONLY:**  
I.D. --  
Date received: \_\_\_\_\_

TEAM   
IUBMID   
*(Institutional Unique Blood or Marrow Transplant Identification Number)*

Registry: IBMTR ABMTR (circle one)

Date of transplant for which this form is being completed:     
Month Day Year

Date of report:     
Month Day Year

**Follow-up Information**

**\* Report data for date of last contact as reported in Q.3 of Follow-up Core Form or immediately prior to death.**

1. Was planned post transplant treatment (treatment before progressive disease) given since date of last report?

- 1  Yes  
0  No

**Go to Q.9**

2. Was disease restaged prior to planned posttransplant treatment?  
1  Yes  
0  No

Specify treatment given whether restaged or not:

	<u>Yes</u>	<u>No</u>	
3.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Chemotherapy, specify: _____
4.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Hormone therapy, specify: _____
5.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Radiation therapy, specify: _____
6.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Immune therapy, specify: _____
7.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____

8. Specify best response to transplant including planned posttransplant treatment:

- 1  Complete response (*complete disappearance of all known disease for  $\geq 4$  weeks*)  
2  Complete response with persistent bone scan or x-ray abnormalities of unknown significance  
3  Partial response ( *$\geq 50\%$  reduction in greatest diameter of all sites of known disease and no new sites of disease for  $\geq 4$  weeks*)  
4  No response: *< 50% reduction in greatest diameter of all sites of known disease and no new sites of disease*  
5  Progressive disease: increase in size of sites of known disease or new sites of disease  
Specify site(s) of persistent/new disease: \_\_\_\_\_  
6  Not evaluable, toxic death  
7  Not evaluable, other reason, specify: \_\_\_\_\_

TEAM

IUBMID

9. Most recent status of breast cancer: (for patients who died, report status at time of death)

- 1  Free of breast cancer; no recurrence posttransplant
- 2  Free of breast cancer except for persistent scan abnormalities of unknown significance, no recurrence posttransplant
- 3  Persistent breast cancer without progression (never achieved CR or PR)
- 4  Progressive disease (never achieved CR or PR)

Date of progression       Site(s): \_\_\_\_\_  
Month Day Year

- 5  Recurrent disease (relapse after complete remission)

Date of progression       Site(s): \_\_\_\_\_  
Month Day Year

- 6  Free of breast cancer after posttransplant recurrence

Date of recurrence       Site(s): \_\_\_\_\_  
Month Day Year

- 7  Not evaluable; explain: \_\_\_\_\_

10. Date current status established     
Month Day Year

First site(s) of progression/recurrence:

	Yes	No	
11.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Lymph node
12.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Bone marrow
13.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	CNS
14.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Liver
15.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Lung
15.2	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Local (chest wall)
15.3	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Contralateral breast
16.	1 <input type="checkbox"/>	0 <input type="checkbox"/>	Other, specify: _____



## Transplant Essential Data

### First Report: 100 Days Post Transplant



Primary Disease Diagnosis: \_\_\_\_\_

Graft:  Auto  Allo  Syngeneic

Date of This Report: \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

**CENTRE IDENTIFICATION**

Centre Identification Code:  
 EBMT \_\_\_\_\_  
 IBMTR/ABMTR \_\_\_\_\_

National (specify) \_\_\_\_\_  
 Other (specify) \_\_\_\_\_

Hospital: \_\_\_\_\_  
 Unit: \_\_\_\_\_  
 Contact person: \_\_\_\_\_  
 Phone #: \_\_\_\_\_  
 Fax #: \_\_\_\_\_  
 Email: \_\_\_\_\_

**PATIENT IDENTIFICATION**

Hospital Unique Patient Number: \_\_\_\_\_

Last/Family Name: \_\_\_\_\_

First/Given Name: \_\_\_\_\_

~or~ Initials: \_\_\_\_\_  
                                   First Name    Last Name

Date of Birth: \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

Sex:  Male  Female

Ethnicity:  White/Caucasian  Black  Oriental  
 Other, specify: \_\_\_\_\_

Postal Code of Patient's Residence: \_\_\_\_\_

**BEFORE TRANSPLANTATION**

Performance Score Pretransplant:  
 Good (KPS ≥80 ~or~ ECOG 0-1 ~or~ Lansky ≥80)  
 Poor (KPS <80 ~or~ ECOG 2-4 ~or~ Lansky <80)

Did conditioning regimen contain Total Body Irradiation?  
 Yes  No

**DISEASE**

*(complete appropriate disease classification sheet)*

Date of initial diagnosis of primary disease:  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

**AFTER TRANSPLANTATION**

Engraftment (Neutrophils ≥0.5 x 10<sup>9</sup>/L)?  
 Yes  No  Unknown  
 If yes, date Neutrophils ≥0.5 x 10<sup>9</sup>/L:  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

If no, date of latest assessment:  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

Maximum Grade of Acute Graft Versus Host Disease (GVHD):  
 0  1  2  3  4  Unknown  NA

Best disease response to transplant:  
 Continued CR  CR achieved, date achieved:  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

Never in CR, date assessed:  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

Unknown  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

Did the disease for which the patient was transplanted relapse or progress after the transplant?  
 Yes  No  Unknown  
 If yes, check all that apply to describe relapse/progression:  
 Molecular  Cytogenetic  Hematological/Clinical  
 If yes, date of earliest relapse or progression:  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

If no, date of latest assessment:  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

Survival status after transplant:  
 Alive  Dead  Died before transplant  
 Date of latest follow-up or death:  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

Main cause of death (check one):  
 Relapse or Progression  
 Transplantation related causes:  
 Rejection/Poor graft function  GVHD  
 Pulmonary toxicity  Cardiac toxicity  
 Infection  VOD  
 Posttransplant lymphoproliferative disorder  Other: \_\_\_\_\_

Other: \_\_\_\_\_  
 Unknown

**TRANSPLANTATION**

Date of this transplant: \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

Chronological number of this transplant for this patient: \_\_\_\_\_

If >1, date of most recent previous transplant for this patient:  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD

Source of Stem Cells (check all that apply):  
 Bone marrow  Peripheral blood  
 Cord blood  Other: \_\_\_\_\_

Donor Type (check one):  
 Autologous (self)  Syngeneic (monozygotic twin)  
 Allogeneic:  
 HLA-identical sibling (not monozygotic twin)  
 HLA-matched other relative  
 HLA-mismatched sibling or other relative  
 HLA-matched unrelated donor  
 HLA-mismatched unrelated donor  
 Multiple donors

(For allotransplants) donor sex:  Male  Female

Was the graft manipulated ex vivo other than for RBC removal or volume reduction?  Yes  No

Was this transplant part of a planned sequential transplant protocol?  Yes  No

Additional cell therapy given?  Yes  No  Unknown  
 If yes, type of cell(s) (check all that apply):  
 Lymphocytes  Fibroblasts  Dendritic cells  
 Other: \_\_\_\_\_

If yes, date of first infusion of additional cell therapy (may be the same as transplant date):  
 \_\_\_\_-\_\_\_\_-\_\_\_\_  
                                   YYYY          MM          DD





**Transplant Essential Data  
First Report: 100 Days Post Transplant  
Disease Classification Sheet 1**



**ACUTE LEUKEMIAS**

**Classification:**

**Acute Myelogenous Leukemia (AML)**

- M1
- M2
- M3
- M4
- M5
- M6
- M7
- AML unspecified
- Other, specify: \_\_\_\_\_

**Acute Lymphoblastic Leukemia (ALL)**

- ALL B-lineage
- ALL T-lineage
- Mature B cell (L3)
- ALL unspecified
- Other, specify: \_\_\_\_\_

**Other Acute Leukemias**

- Acute undifferentiated
- Acute biphenotypic
- Acute mast cell leukemia
- Other, specify: \_\_\_\_\_

**Status at Transplantation:**

- Primary Induction Failure (PIF)
- CR 1
- Rel 1
- CR 2-
- Rel 2-

**For Complete Remission**

- Y N Unk**
- Hematological remission
  - Cytogenetic remission
  - Molecular remission

**CHRONIC MYELOGENOUS LEUKEMIA (CML)**

**Classification:**

- Juvenile CML
- CML, Ph+
- CML, Ph-
- CML, not otherwise specified

**Status at Transplantation:**

- CP 1
- CP 2+
- AP
- BP

**Chronic Phase Only (check all that apply)**

- Stable, not hematological remission
- Hematological remission
- Partial cytogenetic remission
- Complete cytogenetic remission
- Molecular remission
- Cytogenetics unknown
- bcr/abl unknown

**OTHER LEUKEMIAS**

**Classification:**

- Chronic Lymphoblastic Leukemia (CLL), B-cell
- CLL, T-cell
- CLL, not otherwise specified
- Prolymphocytic Leukemia
- Hairy Cell Leukemia
- Other leukemia, specify: \_\_\_\_\_

**Status at Transplantation:**

- CR
- PR
- No response/stable
- Progression

CR=complete remission, PR=partial remission, Rel=relapse, CP=chronic phase, AP accelerated phase, BP=blast phase



**Transplant Essential Data  
First Report: 100 Days Post Transplant  
Disease Classification Sheet 2**



**MYELOYDYSPLASTIC MYELOPROLIFERATIVE SYNDROMES**

**Classification:**

**Myelodysplastic Syndromes (MDS)**

- RA
- RAEB
- RAEB-t
- CMMoL
- RARS
- MDS not otherwise specified
- Other,  
specify: \_\_\_\_\_

**Myeloproliferative Syndromes (MPS)**

- Polycythemia vera
- Essential or primary thrombocythemia
- Myelofibrosis with myeloid metaplasia
- Acute myelofibrosis or myelosclerosis
- Paroxysmal nocturnal hemoglobinuria
- MPS not otherwise specified
- Other,  
specify: \_\_\_\_\_

**Status at Transplantation:**

- Untreated
- Treatment with intent to achieve a CR – CR not achieved
- Treatment with intent to achieve a CR – CR achieved
- Relapse after CR

**ANEMIA/HEMOGLOBINOPATHY**

**Classification:**

- Acquired Severe Aplastic Anemia (SAA), not otherwise specified
- Acquired SAA, secondary to hepatitis
- Acquired SAA, secondary to toxin/other drug
- Amegakaryocytosis acquired (not congenital)
- Acquired Pure Red Cell Aplasia (PRCA) (not congenital)
- Other acquired cytopenic syndrome,  
specify: \_\_\_\_\_
- Fanconi anemia
- Diamond-Blackfan anemia (congenital PRCA)
- Other constitutional anemia,  
specify: \_\_\_\_\_
- Thalassemia
- Sickle cell disease
- Other hemoglobinopathy,  
specify: \_\_\_\_\_

**PLATELET DISORDERS**

**Classification:**

- Amegakaryocytosis/congenital thrombocytopenia
- Glanzmann thrombasthenia
- Other inherited platelet abnormalities,  
specify: \_\_\_\_\_

**HISTIOCYTIC DISORDERS**

**Classification:**

- Histiocytic disorders, not otherwise specified
- Familial erythro/hemophagocytic lymphohistiocytosis(FELH)
- Histiocytosis-X
- Hemophagocytosis (reactive or viral associated)
- Malignant histiocytosis
- Other, specify: \_\_\_\_\_

CR=complete remission



**Transplant Essential Data  
First Report: 100 Days Post Transplant  
Disease Classification Sheet 3**



**LYMPHOMAS**

**Classification:**

Hodgkin Disease

- Lymphocyte predominant
- Nodular sclerosis
- Mixed cellularity
- Lymphocyte depleted
- Hodgkin disease, not otherwise specified
- Other,  
specify: \_\_\_\_\_

Non-Hodgkin Lymphoma (NHL)

- Follicular NHL
- Mantle cell NHL
- Marginal zone B-cell lymphoma of mucosa-associated tissue (MALT)
- Diffuse large B-cell NHL, centroblastic
- Diffuse large B-cell NHL, immunoblastic
- Diffuse large B-cell NHL, anaplastic
- Lymphoblastic/Burkitt
- Precursor B-cell lymphoblastic
- Angioblastic T-cell NHL
- Peripheral T-cell NHL
- Anaplastic large cell, T-cell and null cell
- Precursor T-cell lymphoblastic
- NHL, not otherwise specified
- Other,  
specify: \_\_\_\_\_

**Status at Transplantation:**

- At diagnosis
- Primary Induction Failure (PIF)
- CR 1
- CR 2
- CR 3+
- Rel 1
- Rel 2+

For Relapses & PIF

- Sensitive
- Resistant
- Untreated
- Unknown

**PLASMA CELL DISORDERS**

**Classification:**

- Multiple myeloma-Ig \_\_\_\_\_
- Multiple myeloma-IgA \_\_\_\_\_
- Multiple myeloma-IgD \_\_\_\_\_
- Multiple myeloma-IgE \_\_\_\_\_
- Multiple myeloma-light chain \_\_\_\_\_
- Multiple myeloma-non-secretory \_\_\_\_\_
- Multiple myeloma, not otherwise specified \_\_\_\_\_
- Plasma cell leukemia
- Solitary plasmacytoma
- Waldenstrom's macroglobulinemia
- Amyloidosis
- Other,  
specify: \_\_\_\_\_

Stage at Diagnosis  
(Multiple Myeloma only)

- 1 and  A
- 2  B
- 3

**Status at Transplantation:**

- CR
- PR
- MR
- No change/Stable
- Progression/Relapse

Number of remissions, relapses or progressions

- 1st
- 2nd
- >2nd

CR=complete remission, PR=partial remission, Rel=relapse, MR=minimal response



**Transplant Essential Data  
First Report: 100 Days Post Transplant  
Disease Classification Sheet 4**



**BREAST CANCER**

**Classification:**

Breast Cancer

- Inflammatory
- Non-inflammatory

Stage at Diagnosis  
(Breast Cancer only)

- II
- III
- Inflammatory, no distant metastases
- Metastatic

**Status at Transplantation:**

- Adjuvant (Stage II, III, inflamm)
- Metastatic

For Metastatic

- Untreated/Upfront
- Refractory
- CR
- PR
- Unknown

For Metastatic

- Patient had a prior CR?
- Yes
  - No

**OTHER MALIGNANCIES**

**Classification:**

- |   |   |
|---|---|
| <input type="checkbox"/> Head and neck                        | <input type="checkbox"/> Sarcoma not otherwise specified        |
| <input type="checkbox"/> Lung cancer, small cell              | <input type="checkbox"/> Soft tissue sarcoma                    |
| <input type="checkbox"/> Lung cancer, non-small cell          | <input type="checkbox"/> Bone sarcoma (excluding Ewing sarcoma) |
| <input type="checkbox"/> Lung cancer, not otherwise specified | <input type="checkbox"/> Rhabdomyosarcoma                       |
| <input type="checkbox"/> Thymoma                              | <input type="checkbox"/> Leiomyosarcoma                         |
| <input type="checkbox"/> Gastric                              | <input type="checkbox"/> Liposarcoma                            |
| <input type="checkbox"/> Colorectal                           | <input type="checkbox"/> Fibrosarcoma                           |
| <input type="checkbox"/> Pancreas                             | <input type="checkbox"/> Synovial sarcoma                       |
| <input type="checkbox"/> Hepatobiliary                        | <input type="checkbox"/> Hemangiosarcoma                        |
| <input type="checkbox"/> Kidney and urinary tract             | <input type="checkbox"/> Lymphangiosarcoma                      |
| <input type="checkbox"/> Wilm tumour                          | <input type="checkbox"/> Neurogenic sarcoma                     |
| <input type="checkbox"/> Prostate                             | <input type="checkbox"/> Melanoma                               |
| <input type="checkbox"/> Testicular                           | <input type="checkbox"/> Central nervous system tumors          |
| <input type="checkbox"/> External genitalia                   | <input type="checkbox"/> Medulloblastoma                        |
| <input type="checkbox"/> Cervical                             | <input type="checkbox"/> Neuroblastoma                          |
| <input type="checkbox"/> Uterus                               | <input type="checkbox"/> Retinoblastoma                         |
| <input type="checkbox"/> Ewing sarcoma                        | <input type="checkbox"/> PNET                                   |
| <input type="checkbox"/> Ovary                                | <input type="checkbox"/> Other                                  |
| <input type="checkbox"/> Vagina                               | specify: _____  |
| <input type="checkbox"/> Germ cell tumour                     |   |

**Status at Transplantation:**

- Primary refractory
- CR
- VGPR
- PR
- MR
- Relapse
- Primary treatment
- Adjuvant

For Responses

- 1st
- 2nd
- >2nd

For Relapses

- Sensitive
- Resistant
- Untreated
- Unknown

CR=complete remission, PR=partial remission, VGPR=very good partial response, MR=minimal response





**Transplant Essential Data**  
**First Report: 100 Days Post Transplant**  
**Disease Classification Sheet 6**



AUTOIMMUNE DISORDERS - I			
	Involved Organs/Clinical Problem	Reason for Transplant	Miscellaneous
<input type="checkbox"/> Scleroderma	<input type="checkbox"/> diffuse cutaneous	<input type="checkbox"/>	Scl 70 positive <input type="checkbox"/>
	<input type="checkbox"/> limited cutaneous	<input type="checkbox"/>	ACA positive <input type="checkbox"/>
	<input type="checkbox"/> lung parenchyma	<input type="checkbox"/>	
	<input type="checkbox"/> pulm. hypertension	<input type="checkbox"/>	
	<input type="checkbox"/> syst. hypertension	<input type="checkbox"/>	
	<input type="checkbox"/> renal (biopsy type: _____)	<input type="checkbox"/>	
	<input type="checkbox"/> oesophagus	<input type="checkbox"/>	
	<input type="checkbox"/> other GIT	<input type="checkbox"/>	
	<input type="checkbox"/> Raynaud	<input type="checkbox"/>	
	<input type="checkbox"/> CREST	<input type="checkbox"/>	
	<input type="checkbox"/> other (state: _____)	<input type="checkbox"/>	
<input type="checkbox"/> Systemic lupus erythematosus	<input type="checkbox"/> renal (biopsy type: _____)	<input type="checkbox"/>	ds DNA <input type="checkbox"/> (____)
	<input type="checkbox"/> CNS (type: _____)	<input type="checkbox"/>	complement <input type="checkbox"/> (____)
	<input type="checkbox"/> PNS (type: _____)	<input type="checkbox"/>	other <input type="checkbox"/> (____)
	<input type="checkbox"/> lung	<input type="checkbox"/>	
	<input type="checkbox"/> serositis	<input type="checkbox"/>	
	<input type="checkbox"/> arthritis	<input type="checkbox"/>	
	<input type="checkbox"/> skin (type: _____)	<input type="checkbox"/>	
	<input type="checkbox"/> haematological (type: _____)	<input type="checkbox"/>	
	<input type="checkbox"/> vasculitis (type: _____)	<input type="checkbox"/>	
<input type="checkbox"/> other (state: _____)	<input type="checkbox"/>		
<input type="checkbox"/> Sjogren syndrome	<input type="checkbox"/> SICCA	<input type="checkbox"/>	
	<input type="checkbox"/> exocrine gland swelling	<input type="checkbox"/>	
	<input type="checkbox"/> other organ lymphocytic infiltration	<input type="checkbox"/>	
	<input type="checkbox"/> lymphoma, paraproteinemia	<input type="checkbox"/>	
	<input type="checkbox"/> other (type: _____)	<input type="checkbox"/>	
<input type="checkbox"/> Antiphospholipid syndrome	<input type="checkbox"/> thrombosis (type: _____)	<input type="checkbox"/>	anticardiolipin IgG <input type="checkbox"/>
	<input type="checkbox"/> CNS (type: _____)	<input type="checkbox"/>	anticardiolipin IgM <input type="checkbox"/>
	<input type="checkbox"/> abortion	<input type="checkbox"/>	
	<input type="checkbox"/> skin (livido, vasculitis)	<input type="checkbox"/>	
	<input type="checkbox"/> haematological (type: _____)	<input type="checkbox"/>	
	<input type="checkbox"/> other (type: _____)	<input type="checkbox"/>	
<input type="checkbox"/> Polymyositis-dermatomyositis	<input type="checkbox"/> proximal weakness	<input type="checkbox"/>	CPK <input type="checkbox"/>
	<input type="checkbox"/> generalized weakness (including bulbar)	<input type="checkbox"/>	typical biopsy <input type="checkbox"/>
	<input type="checkbox"/> pulmonary fibrosis	<input type="checkbox"/>	typical EmG <input type="checkbox"/>
	<input type="checkbox"/> vasculitis (type: _____)	<input type="checkbox"/>	typical rash (DM) <input type="checkbox"/>
	<input type="checkbox"/> malignancy (type: _____)	<input type="checkbox"/>	
	<input type="checkbox"/> other (type: _____)	<input type="checkbox"/>	
<input type="checkbox"/> Polyarteritis nodosa	<input type="checkbox"/> renal (type: _____)	<input type="checkbox"/>	p-ANICA positive <input type="checkbox"/>
	<input type="checkbox"/> mononeuritis multiplex	<input type="checkbox"/>	c-ANA positive <input type="checkbox"/>
	<input type="checkbox"/> pulmonary haemorrhage	<input type="checkbox"/>	hepatitis serology <input type="checkbox"/>
	<input type="checkbox"/> GIT	<input type="checkbox"/>	
	<input type="checkbox"/> skin	<input type="checkbox"/>	
	<input type="checkbox"/> other (state: _____)	<input type="checkbox"/>	



**Transplant Essential Data**  
**First Report: 100 Days Post Transplant**  
**Disease Classification Sheet 7**



AUTOIMMUNE DISORDERS - II			
	Involved Organs/Clinical Problem	Reason for Transplant	Miscellaneous
<input type="checkbox"/> Wegener granulomatosis	<input type="checkbox"/> upper respiratory tract <input type="checkbox"/> pulmonary <input type="checkbox"/> renal (biopsy type: _____) <input type="checkbox"/> skin <input type="checkbox"/> other (state: _____)	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> c-ANCA positive <input type="checkbox"/>
<input type="checkbox"/> Other vasculitis	<input type="checkbox"/> Churg-Strauss <input type="checkbox"/> Giant cell arthritis <input type="checkbox"/> Takayasu <input type="checkbox"/> Bechet <input type="checkbox"/> overlap necrotising arteritis <input type="checkbox"/> other: ( _____ )	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<input type="checkbox"/> Rheumatoid arthritis	<input type="checkbox"/> destructive arthritis <input type="checkbox"/> necrotising vasculitis <input type="checkbox"/> eye (type: _____) <input type="checkbox"/> pulmonary <input type="checkbox"/> extrarticular (state: _____) <input type="checkbox"/> other: ( _____ )	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<input type="checkbox"/> Psoriatic arthritis/psoriasis	<input type="checkbox"/> destructive arthritis <input type="checkbox"/> psoriasis <input type="checkbox"/> other (state: _____)	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<input type="checkbox"/> Juvenile RA	<input type="checkbox"/> systemic (main feature: _____) <input type="checkbox"/> pauci, ANA positive (eye) <input type="checkbox"/> polyarticular <input type="checkbox"/> other (state: _____)	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<input type="checkbox"/> Multiple sclerosis	<input type="checkbox"/> primary progressive <input type="checkbox"/> secondary progressive <input type="checkbox"/> relapsing/reuniting	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<input type="checkbox"/> Other, specify:	<input type="checkbox"/> Inflammatory bowel disease <input type="checkbox"/> Myasthenia gravis <input type="checkbox"/> Idiopathic thrombocytopenic purpura (ITP) <input type="checkbox"/> Hemolytic anemic <input type="checkbox"/> Evan syndrome <input type="checkbox"/> other autoimmune cytopenia specify: _____	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	



## Transplant Essential Data

### Follow-up Report: 1 Year Post Transplant and Annually



#### PATIENT IDENTIFICATION

Hospital Unique Patient Number: \_\_\_\_\_

Last/Family Name: \_\_\_\_\_

First/Given Name: \_\_\_\_\_

~ or ~ Initials: \_\_\_\_\_  
First Name      Last Name

Date of Birth: \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
        YYYY                  MM                  DD

Sex:     Male     Female

#### CENTRE IDENTIFICATION

Centre Identification Code: \_\_\_\_\_

EBMT \_\_\_\_\_

IBMTR/ABMTR \_\_\_\_\_

National (specify) \_\_\_\_\_

Other (specify) \_\_\_\_\_

Hospital: \_\_\_\_\_

Unit: \_\_\_\_\_

Contact person: \_\_\_\_\_

Phone #: \_\_\_\_\_

Fax #: \_\_\_\_\_

Email: \_\_\_\_\_

Date of this Report: \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
                                YYYY                  MM                  DD

#### AFTER TRANSPLANTATION

Engraftment (Neutrophils  $\geq 0.5 \times 10^9/L$ ) achieved?  
 Yes     No     Unknown

If yes, date Neutrophils  $\geq 0.5 \times 10^9/L$ :  
 \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
                                YYYY                  MM                  DD

If no, date of latest assessment:  
 \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
                                YYYY                  MM                  DD

Did late graft failure occur?     Yes     No

Maximum Grade of Acute Graft Versus Host Disease (GVHD):  
 0     1     2     3     4     Unknown

Best disease status post-transplant:  
 Continued CR     CR achieved, date achieved:  
 \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
                                YYYY                  MM                  DD

Never in CR, date assessed:  
 \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
                                YYYY                  MM                  DD

Unknown

Did the disease for which the patient was transplanted relapse or progress after the transplant?  
 Yes     No     Unknown

A relapse or progression was previously reported

If yes, check all that apply to describe relapse/progression:  
 Molecular     Cytogenetic     Hematological/Clinical

If yes, date of earliest relapse:  
 \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
                                YYYY                  MM                  DD

Maximum extent of Chronic GVHD:  
 None     Limited     Extensive     Unknown

Current disease status:  
 Complete remission     Not in remission

Date of latest disease assessment:  
 \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
                                YYYY                  MM                  DD

#### SURVIVAL

Survival status at latest follow-up:  
 Alive     Dead     Unknown

Date of latest follow-up or death:  
 \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
                                YYYY                  MM                  DD

Main cause of death (check one):  
 Relapse or Progression

Transplantation-related causes:  
 Rejection/Poor graft function  
 Pulmonary toxicity  
 Infection  
 Posttransplant lymphoproliferative disorder  
 GVHD  
 Cardiac toxicity  
 VOD  
 Other:

Other:  
 Unknown

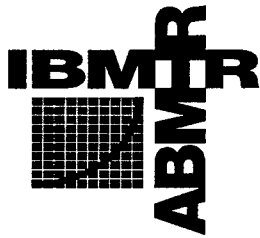
#### SECONDARY MALIGNANCY

Secondary malignancy or lymphoproliferative disorder?  
 Yes     No     Unknown

If yes, date of diagnosis:  
 \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
                                YYYY                  MM                  DD

If no, date of latest assessment:  
 \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
                                YYYY                  MM                  DD





## Appendix 2

### Institutions participating in the ABMTR

---

Albany Medical Center	Albany	United States
New York Oncology Hematology, PC	Albany	United States
Presbyterian Health Care Services	Albuquerque	United States
Don & Sybil Harrington Cancer Center	Amarillo	United States
Oncology Associates	Anchorage	United States
University of Michigan Medical Center	Ann Arbor	United States
Gulhane Military Medical Academy	Ankara	Turkey
Arlington Cancer Center	Arlington	United States
Blood and Marrow Transplant Group of Georgia	Atlanta	United States
Emory Clinic	Atlanta	United States
Emory University - Egleston Children's Hospital	Atlanta	United States
Northside Hospital	Atlanta	United States
Southwest Regional Cancer Center	Austin	United States
Greater Baltimore Medical Center	Baltimore	United States
Johns Hopkins Oncology Center	Baltimore	United States
Sinai Hospital of Baltimore Cancer Institute	Baltimore	United States
University of Maryland Cancer Center	Baltimore	United States
Hosp. General Vall d'Hebron	Barcelona	Spain
Institut Catala d'Oncologia	Barcelona	Spain
Mary Bird Perkins Cancer Center	Baton Rouge	United States
Our Lady of the Lake Regional Cancer Center	Baton Rouge	United States
Alta Bates Hospital	Berkeley	United States
University of Alabama at Birmingham	Birmingham	United States
St. Luke's RMC/Mountain State Tumor Institute	Boise	United States
Dana-Farber Cancer Institute	Boston	United States
Montefiore Medical Center	Bronx	United States
Alexander Fleming Institute	Buenos Aires	Argentina
Centro de Internacion e Investigacion	Buenos Aires	Argentina
Hospital Privado de Oncologia	Buenos Aires	Argentina
ITMO Fundacion Mainetti	Buenos Aires	Argentina
Navy Hospital "Pedro Mallo"	Buenos Aires	Argentina
Roswell Park Cancer Institute	Buffalo	United States
Lahey Hitchcock Clinic	Burlington	United States
Alberta Children's Hospital	Calgary	Canada
University of Calgary	Calgary	Canada
Royal Prince Alfred Hospital	Camperdown	Australia
Hemocentro UNICAMP	Campinas	Brazil
The Wynberg Hospital	Cape Town	South Africa
University of North Carolina Chapel Hill	Chapel Hill	United States
Medical University of South Carolina	Charleston	United States
Roper Care Alliance	Charleston	United States
Presbyterian Hospital Cancer Center	Charlotte	United States
Children's Memorial Hospital	Chicago	United States
Columbia Michael Reese Hospital	Chicago	United States

Institutions participating in the ABMTR, *continued.*

Mount Sinai Hospital Medical Center	Chicago	United States
Northwestern Memorial Hospital	Chicago	United States
Rush Presbyterian/St. Luke's Medical Center	Chicago	United States
University of Chicago Medical Center	Chicago	United States
University of Illinois	Chicago	United States
Children's Hospital Medical Center	Cincinnati	United States
Jewish Hospital of Cincinnati	Cincinnati	United States
Case Western Reserve University Hospital	Cleveland	United States
Cleveland Clinic Foundation	Cleveland	United States
Rainbow Babies & Children's Hospital	Cleveland	United States
Rocky Mountain Cancer Center	Colorado Springs	United States
University of South Carolina	Columbia	United States
Columbus Children's Hospital	Columbus	United States
Ohio State University Hospital	Columbus	United States
Hospital Privado de Cordoba	Cordoba	Argentina
Hospital de Clinicas	Curitiba	Brazil
Hospital Nossa Senhora das Gracias	Curitiba	Brazil
Baylor University Medical Center	Dallas	United States
Children's Medical Center of Dallas	Dallas	United States
Medical City Dallas Hospital	Dallas	United States
Miami Valley Hospital	Dayton	United States
Halifax Medical Center	Daytona Beach	United States
Oakwood Hospital and Medical Center	Dearborn	United States
Presbyterian St. Luke's Hospital	Denver	United States
Iowa Health System	Des Moines	United States
Henry Ford Hospital	Detroit	United States
Wayne State University	Detroit	United States
City of Hope National Medical Center	Duarte	United States
Duke University Medical Center	Durham	United States
North Shore Hematology/Oncology Associates	East Setauket	United States
Northwest Oncology & Hematology Associates	Elk Grove Village	United States
Fairfax Hospital	Falls Church	United States
University of Connecticut Health Center	Farmington	United States
Bone Marrow & Stem Cell Institute of Florida	Fort Lauderdale	United States
Cook-Fort Worth Children's Medical Center	Fort Worth	United States
Harris Methodist Oncology Program	Fort Worth	United States
University of Florida, Shands Hospital	Gainesville	United States
Cancer Center of the Carolinas	Greenville	United States
Hackensack Medical Center	Hackensack	United States
Queen Elizabeth II Health Sciences Center	Halifax	Canada
Institute de Hematologia e Immunologia	Havana	Cuba
Penn State Geisinger Health Systems	Hershey	United States
Hinsdale Hematology-Oncology Associates	Hinsdale	United States
Queen's Medical Center	Honolulu	United States
St. Francis Medical Center	Honolulu	United States
Baylor College of Medicine	Houston	United States
M.D. Anderson Cancer Center	Houston	United States
Indiana University Hospital & Outpatient Ctr.	Indianapolis	United States
Methodist Hospital of Indiana	Indianapolis	United States
Oncology/Hematology Associates	Indianapolis	United States
St. Vincent Hospital & Health Care Ctr.	Indianapolis	United States

Institutions participating in the ABMTR, *continued.*

Baptist Regional Cancer Center	Jacksonville	United States
Mayo Clinic Jacksonville	Jacksonville	United States
Nemours Children's Clinic/Wolfson Children's Hospital	Jacksonville	United States
University Medical Center	Jacksonville	United States
Children's Mercy Hospital	Kansas City	United States
Oncology/Hematology Associates of Kansas City	Kansas City	United States
University of Kansas Medical Center	Kansas City	United States
Thompson Cancer Survival Center	Knoxville	United States
Scripps Clinic & Research Foundation	La Jolla	United States
Dartmouth-Hitchcock Medical Center	Lebanon	United States
University of Kentucky Medical Center	Lexington	United States
Arkansas Cancer Research Center	Little Rock	United States
Saint Barnabas Medical Center	Livingston	United States
London Health Sciences Centre	London, Ontario	Canada
Kaiser Permanente of Southern California	Los Angeles	United States
UCLA Center for Health Sciences	Los Angeles	United States
USC/Norris Cancer Hospital	Los Angeles	United States
James Graham Brown Cancer Center	Louisville	United States
University of Wisconsin	Madison	United States
Hospital G.U. Gregorio Maranon	Madrid	Spain
North Shore University Hospital	Manhasset	United States
Marshfield Clinic	Marshfield	United States
Loyola University Medical Center	Maywood	United States
Methodist Hospital Central	Memphis	United States
Response Technologies	Memphis	United States
St. Jude Children's Research Hospital	Memphis	United States
Baptist Hospital of Miami	Miami	United States
Miami Children's Hospital	Miami	United States
University of Miami School of Medicine	Miami	United States
Froedtert Memorial Lutheran Hospital Cancer Center	Milwaukee	United States
Oncology of Wisconsin	Milwaukee	United States
St. Luke's Medical Center	Milwaukee	United States
Abbott Northwestern Hospital	Minneapolis	United States
University of Minnesota	Minneapolis	United States
Missoula Oncology & Infectious Disease	Missoula	United States
British Hospital & Faculty of Medicine	Montevideo	Uruguay
Hosp. Naciel Ministere of Public Health	Montevideo	Uruguay
IMPASA - Centro de Transplante de Medula Osea	Montevideo	Uruguay
Hôpital Ste. Justine	Montreal	Canada
Jewish General Hospital	Montreal	Canada
Montreal Children's Hospital	Montreal	Canada
Royal Victoria Hospital	Montreal	Canada
Sacre Coeur Hospital	Montreal	Canada
West Virginia University	Morgantown	United States
Vanderbilt University Medical Center	Nashville	United States
All India Institute of Medical Sciences	New Delhi	India
Louisiana State University Medical Center	New Orleans	United States
Memorial Medical Center	New Orleans	United States
Tulane University Medical Center	New Orleans	United States
Columbia University	New York	United States
Memorial Sloan-Kettering Cancer Center	New York	United States

Institutions participating in the ABMTR, *continued.*

Mt. Sinai Medical Center	New York	United States
New York Hospital Cornell Medical Center	New York	United States
New York University Medical Center	New York	United States
Medical Center of Delaware	Newark	United States
Hoag Cancer Center	Newport Beach	United States
Virginia Hematology/Oncology Associates	Newport News	United States
Virginia Oncology Associates	Norfolk	United States
Cancer Care Associates of Oklahoma City	Oklahoma City	United States
University of Oklahoma Health Sciences	Oklahoma City	United States
Immanuel Cancer Center	Omaha	United States
University of Nebraska Medical Center	Omaha	United States
Children's Hospital of Orange County	Orange	United States
Saint Joseph Hospital	Orange	United States
UCI Medical Center	Orange	United States
Walt Disney Memorial Cancer Institute	Orlando	United States
Ottawa General Hospital	Ottawa	Canada
The Desert Hospital Comprehensive Cancer Center	Palm Springs	United States
Clinica Univ. de Navarra	Pamplona	Spain
Lutheran General Hospital	Park Ridge	United States
Hematology Associates	Peoria	United States
Children's Hospital of Philadelphia	Philadelphia	United States
Hahnemann University Hospital	Philadelphia	United States
St. Christopher's Hospital for Children	Philadelphia	United States
Temple Univ. Comprehensive Cancer Center	Philadelphia	United States
Thomas Jefferson University Hospital	Philadelphia	United States
University of Pennsylvania Hospital	Philadelphia	United States
Children's Hospital of Pittsburgh	Pittsburgh	United States
Shadyside Hospital	Pittsburgh	United States
University of Pittsburgh	Pittsburgh	United States
Western Pennsylvania Hospital	Pittsburgh	United States
Legacy Good Samaritan Hospital	Portland	United States
Oregon Health Sciences Univ.	Portland	United States
Providence Portland Medical Center	Portland	United States
Instituto Portugues de Oncologia - Centro do Porto	Porto	Portugal
Alfred Hospital	Prahran	Australia
Roger Williams Medical Center	Providence	United States
Centro de Hematologia y Medicina Interna	Puebla	Mexico
Univ. of Puerto Rico School of Medicine	Puerto Rico	United States
Hôpital du Saint-Sacrement	Quebec City	Canada
Cancer & Blood Institute of the Desert	Rancho Mirage	United States
Riverview Medical Center	Red Bank	United States
Washow Regional Cancer Center	Reno	United States
Medical College of Virginia	Richmond	United States
Univ. Federal de Rio de Janeiro	Rio de Janeiro	Brazil
Mayo Clinic Rochester	Rochester	United States
University of Rochester	Rochester	United States
Universita Cattolica Sacro Cuore	Rome	Italy
Sutter Memorial Hospital	Sacramento	United States
Univ. of California Davis Cancer Center	Sacramento	United States
Cardinal Glennon Children's Hospital	St. Louis	United States
St. Louis Children's Hospital	St. Louis	United States

Institutions participating in the ABMTR, *continued.*

St. Louis University Medical Center	St. Louis	United States
Washington University School of Medicine	St. Louis	United States
Methodist Hospital/Nicollet Cancer Center	St. Louis Park	United States
All Children's Hospital	St. Petersburg	United States
Petrov Res. Inst. of Oncology	St. Petersburg	Russia
LDS Hospital	Salt Lake City	United States
University of Utah Medical Center	Salt Lake City	United States
Santa Rosa Children's Hospital	San Antonio	United States
South Texas Cancer Institute	San Antonio	United States
University of Texas Health Sciences Ctr.	San Antonio	United States
Children's Hospital San Diego	San Diego	United States
University of CA, San Diego	San Diego	United States
Inst. Nacional de Cancerologia	San Fernando	Mexico
University of CA, San Francisco Medical Ctr.	San Francisco	United States
University of California, San Francisco, Pediatrics	San Francisco	United States
Hosp. Especialidades Centro Medico	San Mateo	Mexico
Hospital do Cancer	Sao Paulo	Brazil
Mayo Clinic Scottsdale	Scottsdale	United States
LSU Medical Center-Shreveport	Shreveport	United States
Avera Cancer Institute	Sioux Falls	United States
Spartanburg Regional Medical Center	Spartanburg	United States
Baystate Medical Center	Springfield	United States
St. John's Regional Health Center	Springfield	United States
Bennett Cancer Center	Stamford	United States
Stanford University Hospital	Stanford	United States
State University of New York at Stone Brook	Stony Brook	United States
Northeastern Ontario Regional Cancer Centre	Sudbury	Canada
State University of New York Health Science Center	Syracuse	United States
H. Lee Moffitt Cancer Center	Tampa	United States
Scott & White Clinic	Temple	United States
St. Vincent Mercy Medical Center	Toledo	United States
Hospital for Sick Children	Toronto	Canada
The Toronto Hospital	Toronto	Canada
Arizona Cancer Center	Tucson	United States
Arizona Oncology Associates	Tucson	United States
St. Francis Hospital	Tulsa	United States
New York Medical College	Valhalla	United States
British Columbia's Children's Hospital	Vancouver	Canada
Vancouver General Hospital	Vancouver	Canada
Donauspital	Vienna	Austria
John Muir Medical Center	Walnut Creek	United States
Georgetown University Medical Center	Washington, DC	United States
George Washington University Medical Ctr.	Washington, DC	United States
Walter Reed Army Medical Center	Washington, DC	United States
Washington Cancer Institute	Washington, DC	United States
Waukesha Memorial Regional Cancer Center	Waukesha	United States
Good Samaritan Medical Center/Duke University	West Palm Beach	United States
St. Francis Hospital	Wichita	United States
Manitoba Cancer Treatment Center	Winnipeg	Canada
Piedmont Hematology/Oncology Associates	Winston-Salem	United States

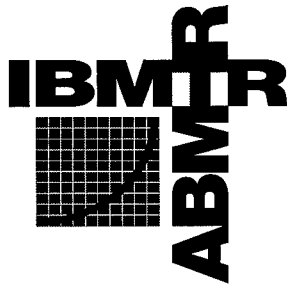
Institutions participating in the ABMTR, *continued.*

Wake Forest University  
University of Massachusetts Medical Center

Winston-Salem  
Worcester

United States  
United States

F:\ABMTR-1AD\DATA\_LISTS\ABMTR\ABMTRMS.LST



## ABMTR Breast Cancer Working Committee

---

### Chair:

Karen H. Antman

Columbia University, New York, NY

ABMTR Statistician: J. Douglas Rizzo, MD

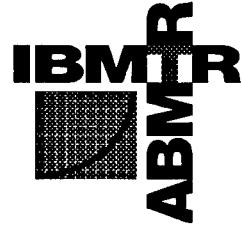
### Committee:

Martin D. Abeloff	Johns Hopkins Oncology Center, Baltimore, MD
Tauseef Ahmed	New York Medical College, Valhalla, NY
Luke Akard	Methodist Hospital of Indiana, Indianapolis, IN
Karen Antman	Columbia University, New York, NY
James O. Armitage	University of Nebraska Medical Center, Omaha, NE
Fikret Arpaci	Gulhane Military Medical Academy, Etlik, Ankara, TURKEY
Joao L. Ascensao	Washoe Regional Cancer Center, Reno, NV
Kerry Atkinson	SyStemix, Palo Alto, CA
Lois J. Ayash	University of Michigan Medical Center, Ann Arbor, MI
Asad Bashey	University of California, San Diego, La Jolla, CA
Murray Bern	Cancer Center of Boston, Plymouth, Plymouth, MA
Jacob D. Bitran	Cancer Care Center, Park Ridge, IL
Milan Blaha	Charles University, Hradec Kralove, CZECH REPUBLIC
Brian J. Bolwell	Cleveland Clinic Foundation, Cleveland, OH
Linda J. Burns	University of Minnesota, Minneapolis, MN
Rose Catchatourian	Michael Reese Hospital and Medical Center, Chicago, IL
Takaaki Chou	Niigata Cancer Center Hospital, Niigata, JAPAN
Neal Paul Christiansen	University of South Carolina, Columbia, SC
Perry C. Cook	Riverview Medical Center, Brooklyn, NY
Edward A. Copelan	A.G. James Cancer Hosp & Research Inst, Ohio State, Columbus, OH
Antonio De Laurenzi	Ospedale San Camillo, Roma, ITALY
Robert Drapkin	Florida Community Cancer Center, Clearwater, FL
Gerald J. Elfenbein	H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL
Leonardo Feldman	Inst Medicos Antartida, Hospital Privado, Buenos Aires, ARGENTINA
Karen Fields	H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL
Cesar O. Freytes	Univ of Texas, Health Science Center at San Antonio, San Antonio, TX
James Gajewski	MD Anderson Cancer Center, Houston, TX
Robert Peter Gale	Salick Health Care, Inc., Los Angeles, CA
Juan Jose Garcia	Hospital Privado de Cordoba, Cordoba, Peia, ARGENTINA
Stefan Gluck	Northeastern Ontario Regional Cancer Ctr, Sudbury, Ontario, CANADA
Stuart L. Goldberg	Temple University Hospital, Philadelphia, PA
Hildegard T. Greinix	University of Vienna, Vienna, AUSTRIA
Geoffrey P. Herzig	St. Vincent's Hospital and Medical Center, New York, NY
Roger H. Herzig	University of Louisville, Louisville, KY
Bruce E. Hillner	Medical College of Virginia, Richmond, VA
Winston G. Ho	UCI Medical Center, Clinical Cancer Center, Orange, CA
David D. Hurd	Bowman Gray School of Medicine, Winston-Salem, NC
Osman Ilhan	Ibni Sina Hospital, Ankara, TURKEY

ABMTR Breast Cancer Working Committee, continued

Nalini Janakiraman	Henry Ford Health Systems, Detroit, MI
Robert A. Joyce	Baptist Regional Cancer Center, Jacksonville, FL
John Kennedy	Johns Hopkins Hospital, Baltimore, MD
Thomas R. Klumpp	Temple University Cancer Center, Philadelphia, PA
Vladimir Koza	Charles University Hospital, Pilsen, CZECH REPUBLIC
Benjamin Koziner	Hospital Privado de Oncologia, Munro, ARGENTINA
Adrian Langleben	Royal Victoria Hospital, Montreal, Quebec, CANADA
Hillard M. Lazarus	University Hosp of Cleveland, Ireland Cancer Ctr, Cleveland, OH
Edward J. Lee	St. Joseph's Hospital, Milwaukee, WI
Charles F. LeMaistre	University of Texas, Health Science Ctr at San Antonio, San Antonio, TX
Mark R. Litzow	Mayo Clinic & Foundation, Rochester, MN
K.M. Steve Lo	Bennett Cancer Center, Stamford, CT
Joseph P. Lynch	West Virginia University Hospitals, Morgantown, WV
Dipnarine Maharaj	Bone Marrow/Stem Cell Institute of Florida, Ft. Lauderdale, FL
Kenneth F. Mangan	Temple University Comprehensive Cancer Center, Philadelphia, PA
James Mason	Scripps Clinic & Research Foundation, La Jolla, CA
Philip L. McCarthy	Roswell Park Cancer Institute, Buffalo, NY
Kenneth R. Meehan	Georgetown University Medical Ctr, Washington, DC
Rakesh Mehra	MD Anderson Cancer Center, Houston, TX
Letha E. Mills	Dartmouth-Hitchcock Medical Center, Lebanon, NH
Arturo Molina	City of Hope National Medical Center, Duarte, CA
Ahmet Ozet	Gulhane Military Medical Academy, Etlik, Ankara, TURKEY
Andrew L. Pecora	Hackensack Medical Center, Hackensack, NJ
Finn B. Petersen	University of Utah Medical Center, Salt Lake City, UT
Gordon L. Phillips	University of Kentucky Medical Center, Lexington, KY
Donna E. Reece	University of Kentucky Medical Center, Lexington, KY
Elizabeth C. Reed	University of Nebraska Medical Center, Omaha, NE
Gomez Rodolfo	Universidad de Antioquia, Medellin, COLOMBIA
Ruben A. Saez	Harris Methodist Hospital, Fort Worth, TX
Michael W. Schuster	North Shore University Hospital, Manhasset, NY
Dominik Selleslag	A.Z. Sint-Jan, Brugge, BELGIUM
Leonard S. Sender	St. Joseph Hospital, Irvine, CA
Thomas C. Shea	University of North Carolina, Chapel Hill, Chapel Hill, NC
Elizabeth Shpall	University of Colorado Health Sciences Center, Denver, CO
Barry S. Skikne	University of Kansas Medical Center, Kansas City, KS
Shimon Slavin	Hadassah Hebrew University Hospital, Jerusalem, ISRAEL
Gary Spitzer	Georgetown University Medical Center, Washington, DC
Edward A. Stadtmauer	University of Pennsylvania Hospital, Philadelphia, PA
Patrick J. Stiff	Loyola University Medical Center, Maywood, IL
Martin S. Tallman	Northwestern Memorial Hospital, Chicago, IL
Charles W. Taylor	University of Arizona Health Sciences Center, Tucson, AZ
Robert F. Taylor	St. Luke's Medical Center, Milwaukee, WI
L. Bik To	Hanson Centre for Cancer Research, Adelaide, South Aust, AUSTRALIA
Linda T. Vahdat	Columbia Presbyterian Medical Center, New York, NY
Koen van Besien	University of Illinois at Chicago, Chicago, IL
William P. Vaughan	University of Alabama at Birmingham, Birmingham, AL
David H. Vesole	Medical College of Wisconsin, Milwaukee, WI
B. Barry Weinberger	Louisiana State University Medical Center-Shreveport, Shreveport, LA
Roy S. Weiner	Tulane University Medical Center, New Orleans, LA
Stephanie F. Williams	University of Chicago Medical Center, Chicago, IL
John R. Wingard	University of Florida, Gainesville, FL
Jane N. Winter	Northwestern University Hospital, Chicago, IL
Steven N. Wolff	Vanderbilt University Medical Center, Nashville, TN





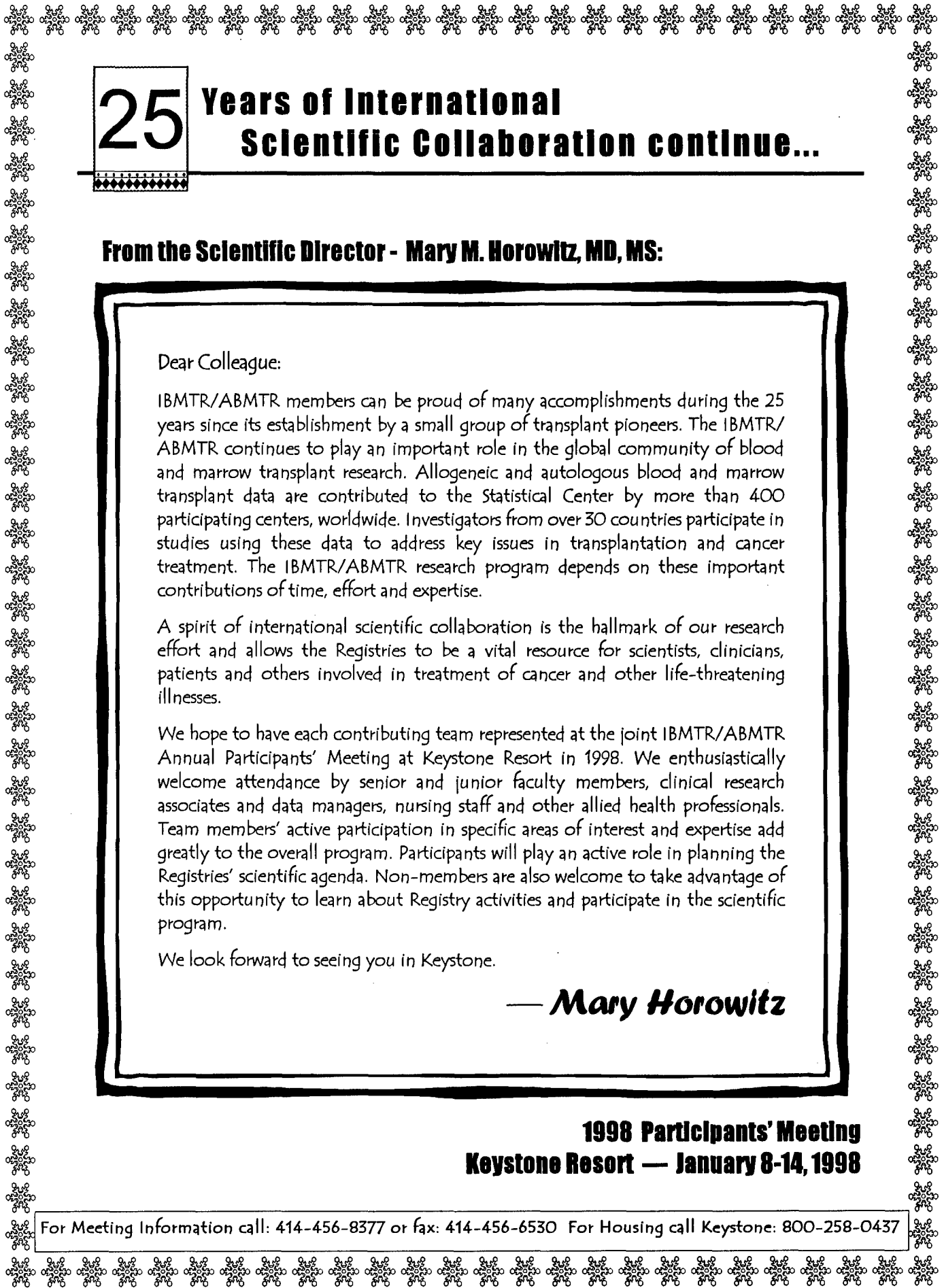
# 1998 Participants' Meeting



Keystone Resort, Colorado  
January 8 - 14, 1998



**CME**  
*program*



**25**

**Years of International  
Scientific Collaboration continue...**

---

**From the Scientific Director - Mary M. Horowitz, MD, MS:**

Dear Colleague:

IBMTR/ABMTR members can be proud of many accomplishments during the 25 years since its establishment by a small group of transplant pioneers. The IBMTR/ABMTR continues to play an important role in the global community of blood and marrow transplant research. Allogeneic and autologous blood and marrow transplant data are contributed to the Statistical Center by more than 400 participating centers, worldwide. Investigators from over 30 countries participate in studies using these data to address key issues in transplantation and cancer treatment. The IBMTR/ABMTR research program depends on these important contributions of time, effort and expertise.

A spirit of international scientific collaboration is the hallmark of our research effort and allows the Registries to be a vital resource for scientists, clinicians, patients and others involved in treatment of cancer and other life-threatening illnesses.

We hope to have each contributing team represented at the joint IBMTR/ABMTR Annual Participants' Meeting at Keystone Resort in 1998. We enthusiastically welcome attendance by senior and junior faculty members, clinical research associates and data managers, nursing staff and other allied health professionals. Team members' active participation in specific areas of interest and expertise add greatly to the overall program. Participants will play an active role in planning the Registries' scientific agenda. Non-members are also welcome to take advantage of this opportunity to learn about Registry activities and participate in the scientific program.

We look forward to seeing you in Keystone.

— *Mary Horowitz*

**1998 Participants' Meeting  
Keystone Resort — January 8-14, 1998**

For Meeting Information call: 414-456-8377 or fax: 414-456-6530 For Housing call Keystone: 800-258-0437

# Why you should attend the 1998 Participants' Meeting

**Keystone Resort — January 8-14, 1998**

## Meeting Objectives

- ◆ to report on the "state of the art" in blood and marrow transplantation;
- ◆ to review Registry accomplishments;
- ◆ to discuss the progress of current and ongoing scientific studies;
- ◆ to set the Registries' scientific agenda for the next year;
- ◆ to provide training in data management and analysis for data managers, nurses and other allied health professionals working in blood and marrow transplantation.

## Working Committee Meetings

IBMTR and ABMTR disease- and treatment-specific Working Committees are open to all interested in taking an ACTIVE role in ongoing and future studies. All Working Committee members should plan to attend.

Working Committees will review the past year's accomplishments, discuss current studies and plan future studies. Priorities for proposed studies will be established. Participation in these meetings is an opportunity to help determine the Registries' scientific agenda.

### 1998 IBMTR & ABMTR Working Committees

IBMTR/ABMTR Acute Leukemia	chairs:	Daniel Weisdorf - IBMTR Armand Keating - ABMTR
ABMTR Breast Cancer	chair:	Karen Antman
IBMTR/ABMTR CLL (Chronic Lymphocytic Leukemia)	chairs:	Emilio Montserrat - IBMTR Richard Champlin - ABMTR
IBMTR Chronic Myelogenous Leukemia	chair:	Phil McGlave
IBMTR GVH/GVL and Immune Reconstitution	chairs:	A John Barrett Olle Ringden
IBMTR Histocompatibility, Alternative Donors & Stem Cell Sources	chair:	Richard Champlin
IBMTR Immune Deficiencies & Metabolic Diseases	chair:	Alexandra Filipovich
IBMTR Late Effects	chair:	Gérard Socié
IBMTR/ABMTR Lymphoma	chairs:	Koen Van Besien - IBMTR Hillard Lazarus, Julie Vose - ABMTR
ABMTR Multiple Myeloma	chair:	Sundar Jagannath
IBMTR/ABMTR Pediatric Cancer	chair:	Bruce Camitta
IBMTR Severe Aplastic Anemia	chair:	Jill Hows
IBMTR/ABMTR Solid Tumors	chair:	Patrick Stiff

# R

## egistration Information

**Meeting registration is easy by fax!**

**Do It today!**

Complete the enclosed Registration Form, including your VISA or MasterCard number, and fax to the Statistical Center at 414-456-6530. Checks, made payable to "The Medical College of Wisconsin - IBMTR", may be mailed to the Statistical Center. We regret that we cannot accept American Express for meeting registration fees. International funds must be submitted in US Dollars. All credit cards are processed in US Dollars and are subject to current exchange rates.

Registration Forms received prior to November 1 qualify for a preregistration discount. Those received on or after December 1 must pay the full conference rate, as indicated. Payment is due with the Registration Form.

Registration fees include admission to all sessions and exhibits, all IBMTR/ABMTR conference materials, abstract book and program, breakfast, coffee breaks and refreshments, and evening poster session receptions. Confirmation for each registered participant will be returned by fax.

### 1997 IBMTR/ABMTR MEETING REGISTRATION FEES

	<u>before Nov1</u>	<u>before Dec1</u>	<u>on or after Dec1</u>
PARTICIPATING TEAM MEMBERS			
♦ MD/PhD	\$395	\$475	\$550
♦ Allied Health Professionals*	\$100	\$125	\$145
♦ Accompanying Persons	\$150	\$200	\$250
CORPORATE MEMBERS	\$400	\$500	\$600
NON-MEMBERS	\$575	\$675	\$775

**\*Data Management Grants:** A limited number of \$500 grants are available on a first-come, first-serve basis to data management personnel attending the Data Management Workshops. To be eligible, data managers must be from centers currently reporting, or planning to report, autotransplants for breast cancer. The enclosed application must be returned to the Statistical Center prior to November 1, 1997 for consideration. See application for additional details. For more information contact D'Etta Waldoch Severson, CMP, Associate Director-International Programs at the Statistical Center at: 414-456-8377.

**Conference Registration Cancellation:** Meeting registration is fully refundable until November 30. All cancellations must be made in writing and may be faxed to the Statistical Center at 414-456-6530. Cancellations made on or after December 1 will be assessed a non-refundable handling fee of US \$50; On January 1 the cancellation fee will increase to US \$75. "No shows" without written notification will be assessed the full prepaid registration fee with no refund provision.

**1998 Participants' Meeting  
Keystone Resort — January 8-14**

For Meeting Information call: 414-456-8377 or fax: 414-456-6530 For Housing call Keystone: 800-258-0437

# Housing & Accommodations

The IBMTR/ABMTR 1998 Participants' Meeting will be held at:  
Keystone Resort, Keystone, Colorado  
Reservations 800-258-0437 or 970-496-4242  
Reservations fax: 970-496-4343  
PO Box 38, Keystone, CO, 80435, USA

## Call or Fax Today for Reservations

## Housing Form Due: December 1

A limited number of guest rooms and condominiums at special conference rates are reserved for IBMTR/ABMTR Meeting participants. The rates are available for 3 days before and after the conference for those wishing to extend their stay in Colorado's picturesque Arapahoe region. Take advantage of these special room rates, which represent substantial discounts during peak season for Keystone-area resorts.

Please complete the enclosed Housing Form and return it directly to Keystone Resort prior to December 1, 1997. It is strongly recommended that reservations be made early, as accommodations will be difficult and more costly to obtain after the deadline. Please indicate a major credit card number for the first and last night's deposit and applicable taxes. Reservations will not be held without a deposit. Reservations made after the deadline may not be available at the discounted conference rate and last minute requests may be impossible to accommodate (see Housing Form for more information).

### 1998 KEYSTONE RESORT ROOM RATES — Subject to Availability

Keystone Lodge:	\$162/night single occupancy	\$177/night double
Inn at Keystone:	\$126/night single occupancy	\$141/night double
Village Studio:	\$163/night single or double	
Village 1 Bedroom:	\$178/night single or double	
Village 2 Bedroom:	\$262/single, double, triple or quad	
Resort Studio:	\$146/night single or double	
Resort 1 Bedroom:	\$168/night single or double	
Mountain Studio:	\$183/night single or double	

**Hotel Cancellation:** Call Keystone Resort directly to cancel housing reservations. No shows, late arrivals and early departures will be charged the full room rate for the entire reserved period. THE IBMTR/ABMTR WILL NOT BE HELD RESPONSIBLE FOR INDIVIDUAL HOUSING CANCELLATIONS OR "NO SHOWS". HOUSING IS THE INDIVIDUAL RESPONSIBILITY OF EACH MEETING PARTICIPANT.

For Meeting Information call: 414-456-8377 or fax: 414-456-6530 For Housing call Keystone: 800-258-0437



# **D**ata Management Workshops

## **Featuring 2 Learning Tracks...**

**Friday, January 9, 1998**

Due to enthusiastic feedback from participating IBMTR and ABMTR data management professionals, we are pleased to offer a full day of Data Management Workshops at the 1998 Participants' Meeting. Data managers, clinical research associates and research nurses will find topics of interest and opportunities for direct communication with on-site Statistical Center staff members leading informal, participatory Workshops on two tracks. Both tracks will discuss recent changes in IBMTR/ABMTR Registration and Reporting procedures.

- |                 |  |
|-----------------|--|
| <b>TRACK I</b>  | fundamental concepts for those attending the Workshops for the first time.   |
| <b>TRACK II</b> | designed for experienced data management and nursing professionals; features special topics related to clinical research and audit management. |

Additionally, StemCell Technologies Inc will demonstrate StemSoft software and their interrelated statistical analysis package. "Hands-on" training is available for those who preregister with StemCell Technologies Inc (details below). Data management personnel are invited to stay for the entire meeting.

## **\$500 Grants for Data Management Workshops**

The Statistical Center was awarded a grant from the US Department of Defense which will provide 30 data managers with \$500 each to offset some of the travel costs associated with attending the Workshops. To be eligible, data managers must be from centers currently reporting, or planning to report autotransplants for breast cancer.

Grants are awarded as they are received, with priority given to first-time attendees. Please complete the enclosed Grant Application Form and return it by fax with your completed Registration Form as soon as possible. The deadline for Grant Application submission is November 1, 1997.

*Grant awards go fast — do not delay!*

## **StemCell Technologies Inc**

StemCell Technologies Inc will offer full-day hands-on training sessions for their StemSoft line of products on Saturday - January 10, Sunday - January 11 and Monday - January 12. Training sessions will be limited to 20 participants each, on a first-come, first-serve basis, and are subject to cancellation if less than half full.

Data Managers and all 'end-users' of StemSoft software who want to achieve greater levels of performance and effectiveness with the software will benefit. The fee for participating in each session is \$400. Please contact Ellen Low at StemCell Technologies Inc in Vancouver, British Columbia (Canada) at 800-667-0322 or 604-877-0713, or [stemsoft@stemcell.com](mailto:stemsoft@stemcell.com).

For Meeting Information call: 414-456-8377 or fax: 414-456-6530 For Housing call Keystone: 800-258-0437



# More about Data Management

## General Sessions

### Introduction

Discuss Workshop format and dispell myths.

**Barbara McGary, Manager of Information Systems, IBMTR/ABMTR**

### Scoring Common Toxicities

Useful information for scoring common toxicities (GVHD, VOD) on IBMTR/ABMTR Report Forms.

**Phil Rowings, MD, Assistant Scientific Director, IBMTR/ABMTR**

### Overview of Statistics

What does the Statistical Center do with all those data? Discussion of outcome variables, in's and out's of working with the databases and basics of statistical analyses.

**Judith Veum Stone, Biostatistician, IBMTR/ABMTR**

### High-Dose Therapies

How high-dose drug therapy in BMT differs from other disciplines.

**Kathleen Kovatovic, RPh - Clinical Oncology & BMT Pharmacist  
Froedert Memorial Lutheran Hospital, Milwaukee**

### Update on StemSoft

Quick demonstration on newest products available from StemCell Technologies. Opportunity to ask questions and sign up for full-day training seminars (see page 6 for details).

**David Reeves - Sr Programmer/Analyst, StemCell Technologies Inc, Vancouver, BC**

## Two Learning Tracks...

### TRACK I: First Timers

#### Registration & Reporting: Why Both?

Valuable information for first-timers regarding IBMTR/ABMTR registration and reporting procedures, why it is necessary to complete both registration and reporting forms and stay up-to-date.

**Barbara McGary, Manager of Information Systems, IBMTR/ABMTR**

#### Hands-on Registration 101

How to complete IBMTR/ABMTR Registration Forms from A-Z, helpful for those just getting started, or with questions on Registration procedures; question & answer session will follow.

**Sharon Nell, Communications Coordinator, IBMTR/ABMTR**

#### Hands-on Reporting 101

Completing IBMTR/ABMTR Reporting Forms is not as difficult as it may first appear; obtain useful information to get started; opportunity to address specific questions on Reporting procedures.

**Diane Knutson, Systems Coordinator, IBMTR/ABMTR**

### TRACK II: For those who have attended IBMTR/ABMTR Workshops previously

#### Practical Aspects of Reporting: An Update

For those who have heard Diane present "Hands-on Reporting 101", an update on working with IBMTR/ABMTR Reporting Forms; practical tips and suggestions for time-saving measures.

**Diane Knutson, Systems Coordinator, IBMTR/ABMTR**

#### Registry Audit Survival Tactics

Ever wonder what an IBMTR/ABMTR Audit is like? Take it from Claudia! Practical tips for gathering data on a daily basis that will make audit day run like clockwork and sigh a gigantic breath of relief!

**Claudia Kahler-Babbitt, BSA, CCRC - Sr. Clinical Studies Coordinator  
Bone Marrow Transplant Program, Medical College of Wisconsin, Milwaukee**

For Meeting Information call: 414-456-8377 or fax: 414-456-6530

For Housing call Keystone: 800-258-0437

# P oster Sessions

1998 Participants' Meeting  
January 8-14  
Keystone Resort, Colorado, USA

## Poster Sessions Combined with Evening Receptions

The late afternoon poster session on Monday, January 12 will be combined with a hosted reception featuring Keystone Resort's award-winning light buffet-style cuisine and beverages.

A \$500 investigator award will be given for the best abstract submitted, as determined by IBMTR/ABMTR Committee Chairs.

## Abstract Instructions Submission Deadline: November 15, 1997

1. Abstract must be typed on the enclosed ABSTRACT FORM.
2. CAPITALIZE entire title and UNDERSCORE author's names (underscoring or capitalizing for emphasis in text is unacceptable. Single space all typing (no space between title and body or between paragraphs). Indent each paragraph three spaces. Do not indent title. Draw special symbols in black ink.
3. Please do not reduce the abstract on a photocopy machine! Type abstract in 12 point type or larger. Abstracts submitted in a reduced format may not be included in the Abstract Book. Abstracts must be received by November 15, 1997 to ensure publication in the Abstract Book. ABSTRACT WILL APPEAR EXACTLY AS SUBMITTED. Smudges, errors, misspellings, faint type, etc. should be avoided.
4. Make the TITLE brief, clearly indicating the nature of the investigation. After the title, list the authors' names and institutional affiliations. Omit degrees, titles, institutional appointments, street addresses and zip or postal code.
5. Organize the body of the abstract as follows:
  - A statement of the purpose of the study (preferably one sentence)
  - A statement of the methods used
  - A summary of the results presented in sufficient detail to support the conclusions
  - A statement of conclusions reached. It is not satisfactory to state, "The results will be discussed" or "Other data will be presented."
6. Simple tables or graphs, neat and in black ink, may be included if they fit within the Abstract Form.
7. Abbreviations must be defined by placing them in parentheses after the full word the first time they appear. Use numerals to indicate numbers except when beginning sentences.
8. The material must be in camera-ready form, i.e., type must be laser quality, 300 dpi or better (no dot matrix). USE BLACK INK. Practice fitting text into the Abstract Form.
9. NO abstract may be presented if previously presented orally at a national or international meeting.
10. Submit abstract (original plus 2 copies) BEFORE NOVEMBER 15, 1997.

For Meeting Information call: 414-456-8377 or fax: 414-456-6530 For Housing call Keystone: 800-258-0437



# **C**ontinuing Medical Education

The Medical College of Wisconsin (MCW) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. MCW designates this continuing medical education (CME) activity for 23.5 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent in the educational activity. MCW also designates this activity for 23.5 contact hours of continuing education for allied health professionals. Participants requesting credit should check the appropriate box on the enclosed Registration Form and must include social security number. A separate form will be available at the conference to designate actual hours attended which will be required for credit to be administered.

## **Disclosure**

The Statistical Center of the IBMTR/ABMTR is committed to providing unbiased, balanced and objective educational and scientific programs. In accordance with ACCME guidelines, all 1998 Annual Meeting speakers are asked to provide relevant disclosure statements. Disclosures are on file at the Medical College of Wisconsin Continuing Medical Education office and will be available on-site at the Registration Desk for review.

# **T**ravel Assistance

**CAUTION:** Weather at the Denver airport is not a good indication of driving conditions in the mountains. Before heading west on I-70, check the local forecast and road conditions. Those not familiar with driving in winter conditions should consider using Resort Express shuttle service.

## **Hertz - the official car rental company**

Hertz has been appointed the official car rental company for the 1998 IBMTR/ABMTR Participants' Meeting in Keystone. Special discount rates, with free unlimited mileage are guaranteed one week before and one week after the IBMTR/ABMTR meeting dates, subject to car availability. At the time of reservation booking, these rates will automatically be compared to Hertz published rates, assuring meeting participants are quoted the best comparable rates available at Denver International Airport. Standard rental conditions and qualifications apply, including minimum rental age. Check with your Hertz representative for further details.

For reservations, call Hertz at 1-800-654-2240 in the US, in Canada at 1-800-263-0600, or check with your travel agent. Refer to CV# 42539.

## **Resort Express**

Regularly scheduled shuttle service will meet you at the baggage claim level (level 5) at the Denver International Airport and deliver you to Keystone Lodge, with 16 daily departures. Mention the IBMTR/ABMTR Meeting at Keystone for discounted group fares: \$70 per person round trip; \$35 per person one way; \$285 for 10 passenger vans one way; \$395 for 6 passenger limosine one way.

For reservations, call Resort Express at 800-334-7433 or 970-468-7600

For Meeting Information call: 414-456-8377 or fax: 414-456-6530 For Housing call Keystone: 800-258-0437



## Questions About the Conference, Support/Exhibit Opportunities

For general questions about the Annual Participants'  
Meeting please contact:

D'Etta Waldoch Severson, CMP  
Associate Director-International Programs  
IBMTR/ABMTR Statistical Center  
414-456-8377  
fax: 414-456-6530

Corporations and others interested in meeting  
support and exhibit opportunities may contact:

Susan U. Ladwig, MA  
Associate Director of Development  
IBMTR/ABMTR Statistical Center  
c/o Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee, WI, 53226, USA  
414-456-8325  
fax: 414-456-6530



1998 Participants' Meeting  
January 8-14  
Keystone Resort, Colorado, USA

For Meeting Information call: 414-456-8377 or fax: 414-456-6530 For Housing call Keystone: 800-258-0437



1998 IBMTR/ABMTR Participants' Meeting  
Keystone Resort, Colorado  
January 8 - 14, 1998

---



Supported by unrestricted educational grants from:

- \* Aastrom Biosciences
- \* Amgen, Inc.
- \* Baxter Biotech Group, North America
- \* BioChem Pharma
- \* BIS Laboratories
- \* Bristol-Myers Squibb Oncology
- \* Cell Therapeutics, Inc.
- \* CellPro, Inc.
- \* Centeon
- \* Chiron Therapeutics
- \* COBE BCT
- \* Fujisawa USA
- \* Immunex Corporation
- \* ISHAGE
- \* The Liposome Company, Inc.
- \* Medical SafeTec
- \* NeXstar Pharmaceuticals, Inc.
- \* Novartis Pharmaceuticals
- \* OrthoBiotech, Inc.
- \* Pfizer, Inc.
- \* Pharmacia and Upjohn Company
- \* Roche Laboratories
- \* SangStat Medical Corporation
- \* Schering-Plough Corporation
- \* Searle
- \* SEQUUS Pharmaceuticals
- \* StemCell Technologies Inc
- \* SyStemix
- \* Therakos
- \* Wyeth-Ayerst Laboratories

# DATA MANAGEMENT WORKSHOP PROGRAM EVALUATION

**Keystone, CO January 8-14, 1998**

(Rating Scale: 1-poor 2-fair 3-good 4-very good 5-excellent)

## **Keystone Resort**

1) 2%      2) 0%      3) 19%      4) 27%      5) 52%

## **Overall Program**

1) 0%      2) 5%      3) 25%      4) 50%      5) 20%

## **Topics**

1) 0%      2) 4%      3) 31%      4) 40%      5) 25%

## **Audio Visual**

1) 4%      2) 12%      3) 35%      4) 25%      5) 24%

## **Handouts**

1) 2%      2) 13%      3) 34%      4) 28%      5) 23%

## **Meeting Room**

1) 2%      2) 4%      3) 34%      4) 26%      5) 34%

## **Food & Beverage**

1) 0%      2) 2%      3) 20%      4) 29%      5) 49%

## **Speakers (Overall)**

1) 0%      2) 7%      3) 33%      4) 40%      5) 20%

## **LeeAnn Baxter-Lowe**

1) 0%      2) 12%      3) 27%      4) 34%      5) 27%

## **Claudia Kabler-Babbitt**

1) 8%      2) 11%      3) 33%      4) 33%      5) 15%

## **Armand Keating for Carolyn Keever Taylor**

1) 0%      2) 3%      3) 16%      4) 32%      5) 49%

## **Diane Knutson**

1) 0%      2) 3%      3) 18%      4) 30%      5) 49%

## **Kathleen Kovatovic**

1) 0%      2) 16%      3) 35%      4) 33%      5) 16%

**Barbara McGary**

1) 2%      2) 11%      3) 39%      4) 37%      5) 11%

**Sandy Murphy**

1) 0%      2) 8%      3) 36%      4) 43%      5) 13%

**Sharon Nell**

1) 0%      2) 4%      3) 12%      4) 56%      5) 28%

**Jakob Passweg**

1) 0%      2) 0%      3) 20%      4) 50%      5) 30%

**David Reeves**

1) 0%      2) 9%      3) 46%      4) 26%      5) 19%

**Meeting Participants**

1) 3%      2) 7%      3) 29%      4) 32%      5) 29%

**Attention**

1) 0%      2) 11%      3) 31%      4) 33%      5) 25%

**Enthusiasm**

1) 0%      2) 16%      3) 31%      4) 31%      5) 22%

**Involvement in Discussion**

1) 2%      2) 19%      3) 38%      4) 26%      5) 15%

## 1998 DATA MANAGEMENT SESSION GRANTEES

Anderson, Jenni  
Northwest Oncology & Hematology  
820 W Biesterfield #120  
Elk Grove Village, IL 60007

Andrews, Doshia  
Bowman Gray School of Medicine  
Medical Center Blvd  
Winston-Salem, NC 27157

Aston, Susan  
Baylor University Medical Center  
3535 Worth Street  
Dallas, TX 75246

Batterson, LeAnn  
Mayo Clinic  
200 1st Street SW  
Rochester, WI 55905

Beale, Ruth  
Sutter Cancer Center  
2800 L Street #410  
Sacramento, CA 95816

Blackwell, Diane  
The Western Pennsylvania Hospital  
4800 Friendship Ave  
Pittsburgh, PA 15224

Brewer, Celeste  
University Hospitals of Cleveland  
11100 Euclid Ave Wearn 549  
Cleveland, OH 44106

Brockington, Daphne  
Vancouver General Hospital  
910 West 10th Avenue  
Vancouver, BC

Brown, Julie Marie  
Richland Memorial Hospital  
7 Richland Medical Park, Suite 600  
Columbia, SC 27203

Bunner, Pam  
West Virginia University  
1 Medical Center Drive P O Box 9162  
Morgantown, WV 26506-9162

Candler, Kathryn  
Medical College of Virginia  
1300 E Marshal St Box 980157  
Richmond, VA 23298

Caudill, Randall  
Greenebaum Cancer Center  
1307 Germander Dr  
Belcamp, MD 21017

Chilton, Joanne  
Sunny Health Science Center at  
Syracuse  
750 E Adams St  
Syracuse, NY 13210

Clark, Elisabeth  
McGill University / Royal Victoria  
Hospital  
687 Pine Ave West, Rm C6.80  
Montreal, Quebec

Cord, Kathy  
St Lukes Hospital of Kansas City  
4401 Wornall  
Kansas City, MO 64111

Creamer, Karen  
Allegheny Hahnemann  
Broad & Vine St Mail Stop 412  
Philadelphia, PA 19102

Crisp, Donna  
University of Louisville  
529 S Jackson St, Suite 230  
Louisville, KY 40202

Currie, Calla  
Vancouver Hospital & Health Sciences  
Center  
910 W 10th Ave  
Vancouver, BC

Dellinger, Elaine  
Wake Forest University  
Medical Center Blvd  
Winston-Salem, NC 27157-1082

Hadi, Abdul  
University of Nebraska Medical Center  
600 S 42nd Street  
Omaha, NE 68198-5135

Hartley, Eric  
Johns Hopkins Oncology Center  
600 N Wolfe St, Rm 3-101  
Baltimore, MD 21287-8985

Highbarger, Lori  
Cancer Care Associates/Oklahoma  
Hematology & Oncology  
6151 S Yale Suite 100  
Tulsa, OK 74106

Hopkins, Hans  
Shands Hospital  
1600 SW Archer Rd  
Gainesville, FL 32610

Horwath, Patrice  
University of Minnesota  
1300 S Second St, Suite 300  
Minneapolis, MN 55119

Jacobson, Esta Ann  
The Cancer Institute at Good Samaritan  
Medical Center  
1309 N Flagler Drive  
West Palm Beach, FL 33401

Jones, Dianna  
Methodist Hospital  
1265 Union Ave  
Memphis, TN 38104

Jones, Paula  
St Vincent Mercy Medical Center  
2213 Cherry  
Toledo, OH 43608-2691

Keuroghelian, Sosy  
UCI Medical Center  
101 The City Drive Rt-81  
Orange, CA 92686

Kronish, Lori  
H Lee Moffitt Cancer Center  
12902 Magnolia Dr  
Tampa, FL 33612

Kusuanco, Donato  
UCI Medical Center  
101 The City Drive South  
Orange, CA 92868

Larkin, Carol  
The Western Pennsylvania Hospital  
4800 Friendship Ave  
Pittsburgh, PA 15224

Larson, Jeanne  
Abbott Northwestern Hospital  
800 E 28th St Internal zip 39419  
Minneapolis, MN 55407

Lawrence, Joanne  
Hackensack Medical Center  
5 Summit Avenue  
Hackensack, NJ 07601

Litofsky, Irving  
University of TX, Health Science Center  
7703 Floyd Curl Dr  
San Antonio, TX 78284-7880

Manion, Karen  
Shands Hospital/University of Florida  
1600 SW Archer Rd Box 100335-BMTU  
Gainesville, FL 32610

McCrae, Jan  
The Toronto Hospital  
657 University Ave  
Toronto, Ontario

Morris, Mary  
UNMC  
600 S 42nd St  
Omaha, NE 68198-5735

Morrison, Carolyn  
University of Utah  
50 N Medical Drive  
Salt Lake City, UT 84132



Naert, Steven  
Medical University of South Carolina  
171 Ashley Avenue  
Charleston, SC 29425-2802

Nathwani, Mudra  
City of Hope National Medical Center  
1500 E Duarte Rd  
Duarte, CA 91010

Nemiroff, Suzanne  
St Francis Medical Center  
2230 Lilima St  
Honolulu, HI 96817

O'Toole, Kathleen  
Northside Hospital/Atlanta Cancer Care  
1000 Johnson Ferry Rd  
Atlanta, GA 30342

Oley, Chrystal  
Medical College of Virginia  
1300 E Marshal St Box 980157  
Richmond, VA 23298

Pantalena, Deborah  
Bennett Cancer Center at Stamford  
Hospital  
34 Shelburne Rd  
Stamford, CT 06902

Reilly, Pamela  
University of Nebraska Medical Center  
668 S 41st St  
Omaha, NE 68198

Sapo, Galina  
University Hospitals of Cleveland  
11100 Euclid Avenue  
Cleveland, OH 44106

Simpson, Linda  
Hoag Memorial Hospital  
One Hoag Drive  
Newport Beach, CA 92663

Soken, Lorraine  
St Francis Medical Center  
2230 Liliha Street  
Honolulu, HI 96817

Somanath, Sunitha  
Allegheny University-Hahnemann  
Broad & Vine St Mail Stop 412  
Philadelphia, PA 19102

Stein, Betsy  
Baylor University Medical Center  
3535 Worth Street, 5th Floor  
Dallas, TX 75246

Stryzak, John  
Johns Hopkins  
600 N Wolfe St, Rm 3-101  
Baltimore, MD 21287-8985

Sylvester, Nancy  
University of OK  
920 SL Young Blvd WP2010  
Oklahoma City, OK 73104

Welborne, Karen  
University of Chicago  
5841 S Maryland Ave  
Chicago, IL 60637

# "Data Management 101"

'Embassy Suites Hotel, Milwaukee

November 1-3, 1998

## Arrivals Saturday October 31

---

- ◆ Attendees arriving early for that Saturday-night stay (to appreciate lower airline fares) may enjoy the day relaxing around the pool at Embassy Suites Hotel or shopping at nearby Brookfield Square Shopping Center or Loehmann's Plaza on Bluemound Road, or any number of other activities in the Milwaukee area.

## Day One Sunday November 1

---

- ◆ Enjoy cooked-to-order breakfast, compliments of Embassy Suites Hotel

8:00 am - 9:00 am	Registration	
9:00 am - 9:15 am	Welcome	Barbara McGary
9:15 am - 10:00 am	Basics of BMT	J. Douglas Rizzo, MD
10:00 am - 11:00 am	Registration Database/Forms	Barbara McGary
11:00 am - 11:15 am	break	
11:15 am - 11:30 am	StemSoft Product Demonstration	Jacki Hatfield
11:30 am - 12:30 pm	Core Forms 101	Diane Knutson
12:30 pm - 1:30 pm	luncheon	
1:30 pm - 3:00 pm	Core Forms 102	Diane Knutson
3:00 pm - 3:15 pm	break	
3:15 pm - 5:00 pm	Graft Inserts & Theory	Carolyn Taylor, PhD

- ◆ evening free—enjoy a complimentary cocktail reception at Embassy Suites 5:30-7:30 pm

## Day Two Monday November 2

---

- ◆ Enjoy cooked-to-order breakfast, compliments of Embassy Suites Hotel

8:00 am - 9:00 am	Registration	
9:00 am - 10:30 am	Disease-Specific Forms	Diane Knutson,
10:30 am - 10:45 am	break	
10:45 am - 12:00noon	Disease-Specific Forms continued	Diane Knutson
12:00noon- 1:15 pm	luncheon	

- ◆ Concurrent Afternoon Sessions

1:30 pm - 2:30 pm	Efficient Data Abstracting	Roundtable facilitators
2:30 pm - 3:00 pm	Audit Update	Kathy Kovatovic, RPH
3:00 pm - 3:15 pm	break	
3:15 pm - 5:00 pm	Basic Statistics	IBMTR Biostatisticians

*StemSoft is offering the following sessions free of charge, facilitated by Jacki Hatfield and Geoff Brown:*

1:30 pm - 3:00 pm	Managing Your Electronic Environment with <i>BMTbase</i>
3:00 pm - 3:15 pm	break
3:15 pm - 5:00 pm	Managing Your Electronic Environment with <i>BMTbase</i>

- ◆ evening free—enjoy a complimentary cocktail reception at Embassy Suites 5:30-7:30 pm

## Day Three Tuesday November 3

---

- ◆ Enjoy cooked-to-order breakfast, compliments of Embassy Suites Hotel

*Tuesday sessions require \$400 fee & preregistration; contact Jacki Hatfield at StemSoft in Vancouver: 602-668-0838.*

8:00 am - 12:00noon	<i>BMTbase</i> (O95 Registration, O95 Reports, BMTmerge, BMTtransfer)
12:00 noon- 1:00 pm	luncheon sponsored by StemSoft
1:00 pm - 5:00 pm	<i>BMTstats</i>

- ◆ evening free—enjoy a complimentary cocktail reception at Embassy Suites 5:30-7:30 pm

# F A S T F A C T S



## "Data Management 101"

A Workshop for First Time Attendees

Embassy Suites Hotel, Milwaukee, WI

November 1-3, 1998



**EDUCATIONAL OBJECTIVES**

- \* Provide training in data management and analysis for data managers, nurses and other allied health professionals in BMT
- \* Provide a forum for discussion of IBMTR/ABMTR guidelines for completing registration and reporting forms. (refer to enclosed Provisional Agenda)

**MEETING REGISTRATION**

There is no charge for attending "Data Management 101" for Sunday and Monday sessions, if you register before October 9th. After October 9th, a \$50 late fee will be assessed, payable in cash or by check at on-site registration. Please fax the Registration Form (below) to the Workshop Registration office: 414-827-4997. Call D'Etta at 414-456-8377 if you have questions.

There is a \$400 fee for attending the StemSoft Workshop on Tuesday. Contact Jacki Hatfield at 602-668-0838 at StemSoft in Vancouver, BC (Canada) to register for Tuesday's sessions.

**HOUSING**  
\$99 singles  
\$109 doubles

Embassy Suites Hotel is located at 1200 South Moorland Road, Brookfield, Wisconsin, 53008-1463. The hotel offers two-room suites with galley kitchen and private bedroom. Each morning guests of Embassy Suites enjoy a complimentary cooked-to-order breakfast, and each evening complimentary cocktails are available at a two-hour reception.

Call Embassy Suites Reservations BEFORE OCTOBER 9th at: 800-444-6404, refer to "G1273"

**ATTIRE**

Casual and comfortable—temperatures in Milwaukee are variable in November, but mostly cool to cold.

**ARRIVAL**

Upon arrival at Milwaukee's General Mitchell International Airport, proceed to the baggage claim area #4 and use the house phone to call Embassy Suites to send the complimentary shuttle. Rental cars are also available in the same area. Alternatively, one-way cab fare from the Airport to Embassy Suites is approximately \$30.

**EDUCATION CREDITS**

The Medical College of Wisconsin (MCW) is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. MCW designates this activity for up to 12 contact hours of continuing education for allied health professionals.

### REGISTRATION FORM

FAX to Workshop Registration Office at: 414-827-4997

or mail to IBMTR/ABMTR, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI, 53226, USA

Name: \_\_\_\_\_

Title: \_\_\_\_\_

Institution: \_\_\_\_\_

Address: \_\_\_\_\_

City: \_\_\_\_\_ State/Province: \_\_\_\_\_ Country: \_\_\_\_\_

Zip/Postal Code: \_\_\_\_\_ Telephone: \_\_\_\_\_

FAX: \_\_\_\_\_ E-mail: \_\_\_\_\_

US Social Security/Canadian Social Insurance Number (required for education credits): \_\_\_\_\_-\_\_\_\_\_-\_\_\_\_\_

IBMTR Team Number: \_\_\_\_\_ ABMTR Team Number: \_\_\_\_\_ Team Leader: \_\_\_\_\_

Anticipated arrival date: \_\_\_\_\_ Anticipated departure date: \_\_\_\_\_

*Please indicate below which sessions you plan to attend (you are not obligated):*

Sunday, November 1:  morning sessions  afternoon sessions

Monday, November 2:  morning sessions

pm concurrent sessions:  Data Abstracting  Audit Update  Basic Statistics  
 Managing Your Electronic Environment With BMTbase (repeated twice)

Tuesday, November 3:  BMTbase  BMTstats (\$400 + pre-registration required for these sessions, contact Jacki Hatfield at StemSoft-see above)

Sorry — Travel Grants are not available for this program

# “DATA MANAGEMENT 101” PROGRAM EVALUATION SUMMARY

Embassy Suites Hotel, Milwaukee, WI \* November 1-3, 1998

## Embassy Suites Hotel

poor 0%    fair 10%    good 16%    very good 55%    excellent 19%

### Hotel Comments:

- Excellent except exercise room too hot and need new equipment.
- Better exercise equipment
- In the middle of nowhere! Green velour couches?! Cracked tile... but helpful staff who would drive us around if we asked.
- Too warm in meeting rooms
- Had to change rooms 3 times. Had to check out 12:00 when conference wasn't over until 5:00. Was not aware of this until day of arrival

### Overall Program

Poor 0%    fair 0%    good 7%    very good 60%    excellent 33%

### Topics

Poor 0%    fair 0%    good 18%    very good 42%    excellent 40%

### Audio-visuals

Poor 0%    fair 12%    good 18%    very good 45%    excellent 25%

### Hand-outs

Poor 0%    fair 0%    good 7%    very good 52%    excellent 41%

### Meeting Rooms

Poor 0%    fair 0%    good 9%    very good 59%    excellent 32%

### Food & Beverage

Poor 0%    fair 3%    good 3%    very good 47%    excellent 47%

### Overall Program Comments:

- You may wish to clump the clinical background and allow the clinicians to opt out of that particular portion.
- Very impressed, did not think it would be so informative & valuable to me.
- Notebook very helpful.
- Good folder. Noise from next door-too warm on first day-have break earlier 11:30 break/12:30 lunch too close.

### Sessions (Overall)

Poor 0%    fair 0%    good 12%    very good 56%    excellent 32%

### Basics of BMT

Poor 0%    fair 6%    good 21%    very good 29%    excellent 44%

### Registration Database/Form

Poor 0%    fair 11%    good 21%    very good 24%    excellent 44%

### Core Forms 101/102

Poor 0%    fair 0%    good 9%    very good 38%    excellent 53%

### Graft Inserts & Theory

Poor 0%    fair 13%    good 27%    very good 37%    excellent 23%

**Disease-Specific Forms**

Poor 0%    fair 0%    good 6%    very good 42%    excellent 52%

**Efficient Data Abstracting**

Poor 0%    fair 10%    good 20%    very good 40%    excellent 30%

**Audit Update**

Poor 0%    fair 0%    good 24%    very good 52%    excellent 24%

**Basic Statistics**

Poor 0%    fair 4%    good 17%    very good 48%    excellent 31%

**Stem Cell Demonstration**

Poor 0%    fair 16%    good 50%    very good 17%    excellent 17%

**Managing Your Electronic Environment w/BMTbase**

poor 8%    fair 0%    good 23%    very good 38%    excellent 31%

**Overall Session Comments:**

- Disease-specific forms very good.
- Good info-a handout would be good too.
- Core Forms-most thorough, especially for the novice. It wa good to have some vision Wh-4 this is imp..how about the title "Why endure"
- Basics of BMT: could be shorter. Efficient Data Abstracting: needed larger room. Difficult to hear individual sections. Stem Cell Demonstration: could be very short or just an explanation in form of handout-not slides.
- Basics/Registration/Core Forms: very good opportunity to ask all those questions that have been bothering me for some time. Very informative & interesting, need booklet with definitions! Audit Update: Very good information. Stem Cell Demo: misleading if you did not have the program. No training involved and was not apparant at this demonstration.
- Need more clinical information.
- Core Forms: needed more time for Q&A.
- Basics of BMT: very basic. Registration Database: very basic & repitive. Core Forms: lots of info we need! Graft Inserts: we don't need info on labeling, we need info on filling out the forms. Hematopetics covered by Dr Rizzo. Basic Stats: handouts would have really helped! Stem Cell Demo: poorly coordinated.
- Great presentations although seemed a bit rushed. Could have used more time for questions. Basic Stats: great presentation but it should have been earlier in session.
- Efficient Data: somewhat loud-also hated to choose 2 wanted to go to all of them.
- Basic BMT: good presentation, but a little "too basic". Info on cell processing a little technical: no coverage of graft inserts.
- Diane Knutson did an excellent job.
- Graft Inserts: Good overview of stem cell processing, however, no review of graft insert.
- Disease Specific Forms: would have liked more time allotted for Q&A. Efficient Data: some very good ideas.
- Stem Cell: too technical.
- Graft Inserts: didn't go thru inserts (graft)
- Diane Knutson is very knowledgable and a very good teacher.
- Core Forms: could always use more time. Attended cause of Death-good tools-excellent. The most useful topic/info I received this conference.
- Efficient Data: roundtables were too loud-could not hear at table.
- Stem Cell: not enough time.
- Graft Inserts: nice job. Disease-specific: Very good overview of Multiple Myeloma.

-Could have used more time for Registration & Core. There seemed to be a lot of questions. Graft Inserts: a bit too technical. Disease-Specific: again, a little quick for me.

### **Meeting Participants**

Poor 0%    fair 4%    good 22%    very good 48%    excellent 26%

### **Attention**

Poor 0%    fair 0%    good 20%    very good 47%    excellent 33%

### **Enthusiasm**

Poor 0%    fair 0%    good 27%    very good 43%    excellent 30%

### **Involvement in Discussion**

Poor 0%    fair 0%    good 30%    very good 33%    excellent 37%

### **Comments & Suggestions for Future Programs:**

-I really enjoyed the sessions-maybe break up day one sessions a bit with roundtables, otherwise very good.

-Would like to have been able to attend all 4 roundtables. A bulleted handout & examples for the cause of death discussion was needed. Didn't take advantage of D'Ettas picks but was a very nice touch. This was good information for an out-of-towner.

-Excellent and informative conference. Thank you. Well coordinated.

-Participants: of course we were wonderful! We are doing this stuff...that alone makes us special! Please hold it in the city (ie downtown) even though I won't get to appreciate it!! In general-thanks for the opportunity to "train".

-Could start meetings earlier and finish earlier in day for a little sight seeing. People are more alert in morning and loose concentration in late PM.

-Would have been even better if some from Europe had attended. Need more discussion time. I think the centers should be encouraged to send their teams to these meetings and to be aware of all the changes that occur frequently need to be updated.

-Better or more info about cytogenetics & HLA time typing.

-Great technical details! Break up each day with discussion roundtables.

-These sessions were very interesting for me. I am very appreciative to Diane Knutson for all information and help which she is giving to me.

-Possibly more time on actual forms.

-Except stemsoft software visuals, was too small!

-I particularly liked the sessions presented by Diane Knutson. This was exactly the kind of information and help that I was looking for in this workshop. Thanks for a great job!

-Have a few pictures of BMTx, harvest, etc on the basics talk-maybe some pictures of this lab for lab talk. Why a Sunday??

-Round table discussions could have taken place on the first day of the workshop.

-Thanks for providing this-it was extremely helpful.

-This was really helpful. Thank you very much.

-Have enough time to answer questions along with topic discussions, preferably after speaker is finished with topic. This allows speaker and participants to get good feed back. Round table should not be question and answer-should be a discussion.

Operational definitions for data entry needed. Question the ability to retrieve reliable DX/TRA information from database (registry). Guidelines for research/reporting resources needed: # hours/form type/pt

-Round table discussions were very helpful in getting tips and ideas from other participants. The whole program was very helpful.

-Would suggest re-organizing Monday afternoon. I think Audit important but unable to attend; attended Stem Soft. Time could be reorganized to get Audit Statistics & Stem Soft perhaps by shortening time slightly for each. Many times Diane referred to data "just ask your transplant MD" some data is very specific & there is no variance. If everyone does their own thing, data won't mean anything. It would be beneficial to have a clinical statistician here to answer clinical questions she is unfamiliar with or doesn't know.

-Overall, would have liked more time in those topics dealing directly with the forms. The other topics, while interesting, I can get info on at home. Round table topics very good-but needed more time. Overall, a very worthwhile few days.

-This was very helpful!

-Graft Inserts & Theory was too deep in theory for what I needed to know.

## Appendix 4. Publications/Analyses in Progress

- 4.1 Klein JP, Pelz C, Zhang MJ. Technical Report #28: Modeling random effects for censored data by a multivariate normal regression model. Division of Biostatistics, Medical College of Wisconsin, 1998. (*Biometrics 1999, In press*)
- 4.2 Park HC, Klein JP. Technical Report #27: Joint modeling of death times and counts using a random effects model. Division of Biostatistics, Medical College of Wisconsin, 1997. (*Paper submitted to Biometrics*)
- 4.3 Anderson PK, Klein JP, Zhang MJ. Technical Report #23: Testing for center effects in multicenter survival studies: A Monte Carlo comparison of fixed and random effects tests. Division of Biostatistics, Medical College of Wisconsin, 1997. (*Statistics in Medicine 1999, In press*)
- 4.4 Andersen PK, Horowitz MM, Klein JP, Socie G, Stone JV, Zhang MJ. Technical Report #30: Modeling covariate adjusted mortality relative to a standard population: Does bone marrow transplantation provide a cure? Division of Biostatistics, Medical College of Wisconsin, 1998. (*Statistics in Medicine 1999, In press*)
- 4.5 Klein JP, Zhang MJ. Technical Report #21: Determining when the survival rates of two treatments are the same based on a censored data regression model. Division of Biostatistics, Medical College of Wisconsin, 1996. (*J Planning and Inference, 1999, In press*)
- 4.6 Klein JP, Zhang MJ. Technical Report #29: Confidence bands for the difference of two survival curves under proportional hazards model. Division of Biostatistics, Medical College of Wisconsin, 1998. (*Submitted*)
- 4.7 Klein JP, Qian C. Technical Report #15: Modeling multistate survival illustrated in bone marrow transplantation. Division of Biostatistics, Medical College of Wisconsin, 1996. (*1996 Proc ASA Conf 93-102, 1996*).
- 4.8 Zhang MJ. Technical Report #24: Grouped failure times, tied failure times: Two contributions to the Encyclopedia of Biostatistics. Division of Biostatistics, Medical College of Wisconsin, 1997.
- 4.9 Klein JP. Survival distributions and their characteristics: A contribution to the Encyclopedia of Biostatistics. Division of Biostatistics, Medical College of Wisconsin, 1997.
- 4.10 Johnson RA, Klein JP. Technical Report #26: Regression models for survival data. Department of Statistics, University of Wisconsin-Madison and Division of Biostatistics, Medical College of Wisconsin, 1997.



#### Appendix 4, continued.

4.11 Antman KH, Rowlings PA, Vaughan WP, Pelz CJ, Fay JW, Fields KK, Freytes CO, Gale RP, Hillner BE, Holland HK, Kennedy MJ, Klein JP, Lazarus HM, McCarthy PL Jr, Saez R, Spitzer G, Stadtmauer EA, Williams SF, Wolff S, Sobocinski KA, Armitage JO, Horowitz MM. High-dose chemotherapy with autologous hematopoietic stem cell support for breast cancer in North America. *J Clin Oncol* 15:1870-1879, 1997.

4.12 Rowlings PA, Williams SF, Antman KH, Fields KK, Fay JW, Reed E, Pelz CJ, Klein JP, Sobocinski KA, Kennedy MJ, Freytes CO, McCarthy PL Jr., Herzig RH, Stadtmauer EA, Lazarus HM, Pecora AL, Bitran JD, Wolff SN, Gale RP, Armitage JO, Vaughan WP, Spitzer G, Horowitz MM. Factors correlated with progression-free survival after high-dose therapy and hematopoietic stem cell transplantation for metastatic breast cancer. *JAMA*, 1999. In press.

4.13 Berry DA, Broadwater G, Perry MC, Aisner J, Costanza M, Parnes H, Henderson IC, Norton L, Antman K, Klein JP, Horowitz MM. Conventional vs. high-dose therapy for metastatic breast cancer: comparison of Cancer and Leukemia Group B (CALGB) and Blood and Marrow Transplant Registry (ABMTR) patients. Abstract submitted for 1999 Annual Meeting of the American Society of Clinical Oncology.

4.14 ABMTR study #BC98-03. Preliminary results: Autotransplants for stage 2/3 breast cancer.

4.15 McCarthy PL, Jr., Hurd DD, Rowlings PA, Murphy SC, Antman KH, Armitage JO, Cirenza E, Crump M, Doroshower J, Freytes CO, Gale RP, Kalman LA, Lazarus HM, Vaughan WP, Weinberger B, Wiemann MC, Horowitz MM. Autotransplants in thirteen men with breast cancer (submitted).

4.16 Bennett CL, Waters TM, Stinson TJ, Almagor O, Sobocinski KA, Klein JP, Rowlings PA, Horowitz MM. Analysis of short-term costs of allogeneic transplantation: results from the International Bone Marrow Transplant Registry/Northwestern University economic data base project. *Blood* 92 (Suppl 1): 137a, 1998.

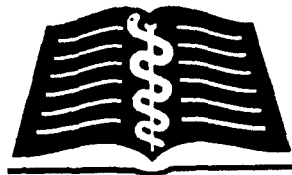
4.17 Chen CS, Seidel K, Armitage JO, Fay JW, Appelbaum FR, Horowitz MM, Shpall EJ, Weiden PL, Antman KS, Champlin RE, Kersey JH, Sullivan KM. Safeguarding the administration of high-dose chemotherapy: A national practice survey by the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant* 3 (6):331-340, 1997.

JOHN P KLEIN  
COREY PELZ  
MEI-JIE ZHANG

BY

DIVISION OF BIOSTATISTICS

DIVISION OF BIOSTATISTICS



MEDICAL  
COLLEGE  
OF WISCONSIN

MILWAUKEE, WISCONSIN

**MODELING RANDOM EFFECTS FOR CENSORED DATA BY A  
MULTIVARIATE NORMAL REGRESSION MODEL**

**BY**

**JOHN P KLEIN  
COREY PELZ  
MEI-JIE ZHANG**

**BY**

**DIVISION OF BIostatISTICS  
THE MEDICAL COLLEGE OF WISCONSIN**

TECHNICAL REPORT 28

**Abstract**

A normal regression model with a frailty factor to account for statistical dependence between the observed survival times is introduced. This model, as opposed to other frailty models, has survival times which, conditional on the frailty, have an accelerated failure time representation. The dependence properties of this model are discussed and maximum likelihood estimation of model's parameters is considered. A number of examples are considered to illustrate the approach.

## 1. Introduction

In the analysis of survival data a common assumption that is made is that the life histories for individuals under study are all statistically independent (at least conditionally on the observed fixed time covariates). In some cases, when individuals within some subgroup share common unmeasured traits, this assumption may not be valid. For example, the survival times of siblings or married couples in human studies or litter mates in animal studies may be associated.

Recently, a number of authors have proposed using the so called shared frailty model to account for the dependence between the event times. In this model all individuals within a group share a common unobservable random effect, the frailty, which acts multiplicatively on each individual's hazard rate. That is, for the  $i$ th individual, with covariates  $Z_i$ , in a group of size  $M$ , we model the hazard rate of the event time,  $X_i$ , by

$$h(t | Z_i, W) = W h(t | Z_i), \quad i = 1, \dots, M.$$

The individual hazard rates, given the frailty, are modeled by assuming a proportional hazards regression model with either a known (typically Weibull or piecewise constant) baseline hazard rate or by an arbitrary baseline hazard rate which yields an extension to the Cox (1972) regression model (See Klein and Moeschberger 1997 for examples). Conditional on the unobserved frailty, individuals within a group are assumed to be independent.

Common models for the frailty are the gamma distribution (c.f. Clayton (1991), Klein (1992) or Nielsen et al (1992)), the positive stable distribution (See Hougaard (1986a), Wang et al (1995)), the inverse Gaussian (c.f. Hougaard (1986b), Klein et al (1992)), and the log normal distribution (McGilchrist and Aisbett (1991) or Yau and McGilchrist (1997)).

In this note we take an alternative approach to modeling dependence between the survival times of group members. We model survival within a group, given an unobserved frailty, by an accelerated failure time model, or more equivalently we model the logarithm of the event time as a linear function of the covariates. That is, for the  $j$ th individual in a group, we model  $Y_j = \log(X_j)$ , by

$$Y_j = \mu + \beta^t Z_j + E_j, \quad j=1, \dots, M.$$

Here  $E_j$  are mean 0 random variables. Under the usual accelerated failure model the  $E_j$ 's are assumed to be an independent and identically distributed sample from some distribution such as the extreme value distribution (Weibull Regression model), the logistic (Log logistic Regression) or the normal distribution (log normal regression). Estimation for these models is available in most

packages such as SAS and BMDP. To model association within a group we shall assume that the  $E_j$ 's can be decomposed into a sum of an individual specific error,  $W_i$  and a group specific error,  $W_0$ . That is,

$$E_j = \omega^{1/2}W_j + \theta^{1/2}W_0.$$

Assuming the variance of  $W_j$  and  $W_0$  are equal to 1, then  $\omega$  is the within subject variance and  $\theta$  the between subject variation. In this model  $W_i$  can be thought of as the measurement error specific to the  $i$ th individual and  $W_0$  as the unmeasured uncertainty common to all individuals within a group. The correlation between the lifetimes within a group is  $\theta/(\theta+\omega)$  and the model reduces to the usual accelerated failure time model when  $\theta=0$ .

In the sequel we consider this model when the  $W$ 's follow a standard normal distribution. This leads to a, conditional on  $W_0$ , log normal regression model for the survival times  $X_i$ . Unconditionally, the joint distribution of the  $X_i$ 's has a multivariate log normal distribution. The log normal distribution has a hazard rate which is initially increasing and then decreasing. The Log normal has been suggested as a model for the survival times of several chronic diseases such as Hodgkin's disease (Osgood 1958), chronic leukemia (Feinleib and MacMahon 1960), and onset times of Alzheimer's disease (Horner 1987). The multivariate log normal model after a quadratic transformation (with no censoring) was used by Herskind et al (1996) to model the longevity of Danish twins. The "hump-shaped" hazard rate is often used in modeling survival after successful surgery where there is an initial increase in risk due to infection, hemorrhaging, or other complications just after the procedure, followed by a steady decline in risk as the patient recovers. We have found the log normal distribution gives a good fit when modeling the bone marrow transplant recovery process where patients are at high risk initially after transplant when their immune systems are depleted but have a decreased risk once the new cells engraft. The model is not appropriate, however, when the conditional hazard rates are monotone as is commonly the case in modeling the onset times of solid organ cancers.

In the next section we investigate the dependence properties of this model. In Section 3 we derive maximum likelihood estimators for the parameters of the model when the data is right censored. In Section 4 we show several examples of the use of this model and in Section 5 we present a crude graphical method checking the modeling assumptions.

## 2. The Multivariate Normal Regression Model

For each of the  $M$  individuals in a group we assume that the logarithm of their survival times  $Y_j = \ln[X_j]$  is

$$Y_j = \mu + \beta^t Z_j + \theta^{1/2} W_j + \omega^{1/2} W_0, j=1, \dots, M. \quad (2.1)$$

Suppose that  $W_0, W_1, \dots, W_M$  are an independent and identically distributed sample from a standard normal distribution. Then the joint distribution of  $(Y_1, \dots, Y_M)$  is M-variate normal with  $E[Y_j] = \mu + \beta^t Z_j$ ,  $\text{Var}[Y_j] = \omega + \theta$  and  $\text{Cov}[Y_j, Y_k] = \theta$ ,  $j \neq k$ . For this model the correlation between the log survival times of any two members of the group is  $\rho = \theta/(\theta + \omega)$  and Kendall's  $\tau$  is  $2\text{Sin}^{-1}(\rho)/\pi$ . Note that the correlation and Kendall's  $\tau$  are both zero when  $\theta$  is equal to 0 and tend to 1 as  $\theta$  tends to infinity.

On the original time scale  $(X_1, \dots, X_M)$  has a M-variate log normal distribution (See Jones and Miller 1966). We have

$$E[X_j] = \exp\{\mu + \beta^t Z_j + (\omega + \theta)/2\}, j=1, \dots, M;$$

$$\text{Var}[X_j] = \exp\{2(\mu + \beta^t Z_j) + \omega + \theta\} [\exp\{\omega + \theta\} - 1], j=1, \dots, M;$$

$$\text{Cov}[X_j, X_k] = [\exp\{\theta\} - 1] \exp\{(\mu + \beta^t Z_j) + (\mu + \beta^t Z_k) + \omega + \theta\}, j \neq k;$$

and

$$\text{Corr}[X_j, X_k] = \frac{[\exp\{\theta\} - 1]}{[\exp\{\omega + \theta\} - 1]}, j \neq k.$$

Note that the correlation between  $X_j$  and  $X_k$  is a monotone increasing function of  $\theta$  with a correlation of zero when  $\theta$  equals zero and a limit of  $\exp\{-\omega\}$  as  $\theta$  tends to infinity. Since the marginal distributions of the X's have a log normal distribution, the correlation coefficient may not be the best parameter to measure association. However, Kendall's tau is unaffected by a common monotone transformation applied to the each margin so that the value of  $\tau$  is the same as for the log survival times. Note that  $\tau$  is also monotone in  $\theta$ , but the upper limit of the range of  $\tau$  is 1 which corresponds to the maximal association one can have.

### 3. ESTIMATION OF MODEL PARAMETERS

Suppose we have data on G subgroups each following the model (2.1). Let  $M_i$  be the number of subjects in the  $i$ th group. While it is permissible for  $M_i$  to be one we require that at least one subgroup have more than one member, otherwise  $\theta$  and  $\omega$  are not identifiable from the data. For the  $j$ th subject in the  $i$ th group let  $T_{ij}$  be their on study time;  $\delta_{ij}$  be the indicator of whether they died ( $\delta_{ij} = 1$ ) or were censored ( $\delta_{ij} = 0$ ); and let  $Z_{ij}$  be their  $(p+1)$  - vector of covariate values,

$j=1, \dots, M_i, i=1, \dots, G$ . For convenience we take the first element of  $Z_{ij}$  to be 1 to account for the intercept term in the model.

To construct the contribution to the likelihood for the  $i$ th group let  $d_i = \sum_{j=1}^{M_i} \delta_{ij}$  be the number of deaths in the  $i$ th group. If all members of the group die ( $d_i = M_i$ ) then the contribution to the likelihood is the joint density function of  $Y_i = (Y_{i1}, \dots, Y_{iM_i})^t$  evaluated at  $\ln[T_{ij}]$ ,  $j=1, \dots, M_i$ . If there is any censored observation between the  $M_i$  individuals then rewrite  $Y_i = (Y_i^C, Y_i^D)^t$ , where  $Y_i^D$  is the  $d_i$  vector of death times and  $Y_i^C$  is the  $(M_i - d_i)$  vector of censored observations. Using standard results on the multivariate normal distribution given in Andersen (1958) it is easy to show that the conditional distribution of  $Y_i^C$  given  $Y_i^D$  is  $(M_i - d_i)$ -variate normal with

$$E[Y_{ik}^C | Y_i^D] = \beta^t Z_{ik} + \frac{\theta}{d_i \theta + \omega} \sum_{j=M_i - d_i + 1}^{M_i} [Y_{ij} - \beta^t Z_{ij}], \text{ for } k=1, \dots, (M_i - d_i); \quad (3.1)$$

$$\text{Var}[Y_{ik}^C | Y_i^D] = \omega + \frac{\theta \omega}{d_i \theta + \omega}, \text{ for } k=1, \dots, (M_i - d_i); \quad (3.2)$$

and

$$\text{Cov}[Y_{ik}^C, Y_{ik'}^C | Y_i^D] = \frac{\theta \omega}{d_i \theta + \omega}, \text{ for } k', k=1, \dots, (M_i - d_i), k' \neq k. \quad (3.3)$$

The contribution to the likelihood for the  $i$ th group is the product of the density function for  $Y_i^D$  times the conditional survival function of  $Y_i^C$  given  $Y_i^D$  evaluated at  $Y_{ij} = \ln[T_{ij}]$ . The conditional survival function of  $Y_i^C$  given  $Y_i^D$  involves evaluation of a  $(M_i - d_i)$  dimensional integral. To reduce the dimensionality of this integral, which must be evaluated numerically, we use the following lemma which is motivated by results in Chapter 35, Section 4 of Johnson and Kotz (1972), to reduce the dimensionality of the integral to be evaluated.

*Lemma* Let  $X$  have a  $k$ -variate normal distribution with mean 0 and correlations equal to  $\rho \geq 0$ . Then

$$P[X_1 \geq x_1, \dots, X_k \geq x_k] = \int_{-\infty}^{\infty} \phi(u) \prod_{j=1}^k \left\{ 1 - \Phi \left[ \frac{x_j - u \rho^{1/2}}{(1-\rho)^{1/2}} \right] \right\} du, \quad (3.4)$$

where  $\phi(u) = \frac{1}{(2\pi)^{1/2}} \exp\{-u^2/2\}$  and  $\Phi(u) = \int_{-\infty}^u \phi(v)dv$  are the standard normal density and distribution functions.

Proof:

Let  $U_0, U_1, \dots, U_k$  be independent standard normal random variables then

$$X_j = \rho^{1/2} U_0 + (1-\rho)^{1/2} U_j, \quad j=1, \dots, k.$$

The inequality  $\{X_j \geq x_j\}$  is equivalent to  $U_j \geq \frac{X_j - \rho^{1/2}U_0}{(1-\rho)^{1/2}}$  which leads to the representation (3.4).

■

Applying the above lemma and 3.1-3.3 gives a contribution to the log likelihood for the  $i$ th group,  $i=1, \dots, G$ , of  $L_i = L_i^D + L_i^C$ , where  $L_i^D$  is the contribution of the  $d_i$  deaths given by

$$L_i^D = -\frac{d_i}{2} \ln[2\pi] - \left(\frac{1}{2}\right) \{ (d_i-1)\ln[\omega] + \ln[d_i \theta + \omega] \} - \frac{S_{2i}(\beta)}{2\omega} + \frac{\theta S_{1i}(\beta)^2}{2\omega (d_i \theta + \omega)} \quad (3.5)$$

with  $S_{1i}(\beta) = \sum_{j=1}^{M_i} \delta_{ij} \{\ln[T_{ij}] - \beta^t Z_{ij}\}$  and  $S_{2i}(\beta) = \sum_{j=1}^{M_i} \delta_{ij} \{\ln[T_{ij}] - \beta^t Z_{ij}\}^2$ ; and

$$L_i^C = \ln \int_{-\infty}^{\infty} \phi(u) \prod_{k=1}^{M_i - d_i} \left\{ 1 - \Phi \left[ \frac{\ln[T_{ik}] - \beta^t Z_{ik} - \frac{\theta}{d_i \theta + \omega} S_{1i}(\beta)}{\omega^{1/2}} - \frac{\theta^{1/2}}{(d_i \theta + \omega)^{1/2}} u \right] \right\} du. \quad (3.6)$$

The overall log likelihood is the sum of the log likelihoods for the individual groups. In the Appendix we give the first and second partial derivatives of the likelihood with respect to the parameters.

To maximize the log likelihood we use the following procedure. First, we find the maximum likelihood estimates and the value of the log likelihood under an assumption of independence using a Newton-Raphson algorithm. This is equivalent to maximizing the likelihood under the constraint that  $\theta$  is equal to zero. The derivatives in the appendix can be used to



implement this step of the algorithm or a statistical package such as SAS or BMDP can be used to find these estimates. In using our representation (3.6) or one of the derivatives of this integral there is still a univariate integral to evaluate. In our examples we used a 20 point Gauss-Hermite formula (See Abramowitz and Stegun, 1970) for this integration. We found in all our examples that the approximations we use give us excellent agreement with the estimates and likelihoods when  $\theta=0$  obtained from both SAS and BMDP.

The second step of the procedure is a crude examination of the profile log likelihood as a function of  $\theta$ . This is done to find starting values for the implementation of a full Newton-Raphson maximization routine. The likelihood is maximized with respect to  $\omega$  and  $\beta$  for a fixed value of  $\theta$ . The profile likelihood is computed for a number of values of  $\theta$ . The value of  $\theta$  which gives the maximum in this search is used in the third step of the procedure which is a full implementation of the Newton-Raphson algorithm. Using the estimates of  $\omega$  and  $\beta$  found when  $\theta = 0$  as starting points in a Newton-Raphson algorithm is not possible since the likelihood has a stationary point at 0. Once the estimates of  $(\theta, \omega, \beta)$  are found the negative of the final Hessian matrix is inverted to find the observed information matrix which yields standard errors of the maximum likelihood estimators.

#### 4. Examples

To illustrate this technique we shall consider three examples. The first example is based on a tumorigenesis study of fifty litters of male rats reported in Mantel et al. (1977). For each litter one rat was selected to receive the drug and the other two rats were placebo treated controls. One might expect that the times to tumor formation for rats in a given litter would be correlated due to shared genetic or environmental effects. Time to tumor was measured in weeks and death before tumor occurrence yields a right-censored observation. There is a single covariate in the model reflecting the drug effect. The results are in Table 1 for the Multivariate Normal Regression Model and for the model assuming independence between litter mates.

**Table 1**  
**Results of Fitting Multivariate Normal Model to the Litter-Matched Rats**

Effect	Multivariate Normal Model		Independence Model	
	Estimate	Standard Error	Estimate	Standard Error
Intercept	4.9654	0.0960	4.9692	0.0926
Drug	-0.2365	0.0972	-0.2464	0.1083
Within Subject Variance( $\omega$ )	0.1658	0.0486	0.2333	0.0583
Frailty ( $\theta$ )	0.0691	0.0435		
Ln Likelihood	-70.1020		-72.0130	

The likelihood ratio test of hypothesis of no association between litter mates ( $\theta=0$ ) has a chi-square of 3.82 with one degree of freedom. The p-value is 0.05 which suggests that there is some evidence of a litter effect. To measure the strength of the association between litter mates one can use any one of three measures. The first is the correlation between the log survival times estimated by

$$\hat{\rho}_1 = \frac{\hat{\theta}}{(\hat{\theta} + \hat{\omega})}, \quad (4.1)$$

which has an estimated variance of

$$\hat{V}[\hat{\rho}_1] = \frac{\hat{\omega}^2 V[\hat{\theta}] + \hat{\theta}^2 V[\hat{\omega}] + 2 \hat{\omega} \hat{\theta} \text{Cov}[\hat{\theta}, \hat{\omega}]}{(\hat{\theta} + \hat{\omega})^4}. \quad (4.2)$$

The second is the correlation between the survival times which is estimated by

$$\hat{\rho}_2 = \frac{\exp[\hat{\theta}] - 1}{\exp[\hat{\theta} + \hat{\omega}] - 1}, \quad (4.3)$$

which has an estimated variance of

$$\hat{V}[\hat{\rho}_2] = \frac{\exp[\hat{\theta}]}{(\exp[\hat{\theta} + \hat{\omega}] - 1)^4} \times \{ \exp[2\hat{\omega}] (1 - \exp[\hat{\theta}])^2 V[\hat{\theta}] + (\exp[\hat{\omega}] - 1)^2 V[\hat{\omega}] + 2 \exp[\hat{\omega}] (1 - \exp[\hat{\theta}]) (\exp[\hat{\omega}] - 1) \text{Cov}[\hat{\theta}, \hat{\omega}] \} \quad (4.4)$$

The final measure of association is Kendall's  $\tau$  which is estimated by

$$\hat{\tau} = \frac{2 \text{Sin}^{-1}[\hat{\rho}_1]}{\pi} \quad (4.5)$$

which has an estimated variance of

$$\hat{V}[\hat{\tau}] = \frac{4 \hat{V}[\hat{\rho}_1]}{\pi(1-\hat{\rho}_1^2)} \quad (4.6)$$

Estimates of the asymptotic variance of  $\hat{\theta}$  and  $\hat{\omega}$  are available from the observed information matrix. In this example we have the following estimates of the strength of association.

Parameter	Estimate	Standard Error	95% Confidence Interval
$\rho_1$	0.2942	0.0443	(0.2074,0.3810)
$\rho_2$	0.2702	0.0472	(0.1778,0.3627)
$\tau$	0.1901	0.0361	(0.1193,0.2609)

This data was previously analyzed by Andersen et al (1996) using a multiplicative frailty model. For this model, conditional on a gamma distributed frailty,  $W$ , the life times of litter mates were assumed to be independent with a hazard rate  $W\lambda_o(t)\exp[\beta Z_j]$ ,  $j=1,\dots,M$ .  $\lambda_o(t)$  was either treated non-parametrically or was modeled using a Weibull or piecewise constant hazard rate. Using this model the likelihood ratio statistics for testing the hypothesis of independence were found to be 1.52 for the semi-parametric model; 1.62 for a Weibull model; and 1.58 and 1.52 for piecewise constant models with 6 or 31 intervals, respectively. All models give an estimate of Kendall's tau of about 0.19 in close agreement with the estimates obtained from the multivariate normal model. The standard error of these estimates, however, was about 0.15 which is considerably larger than that obtained from the log normal model.

The log normal distribution is not typically used for cancer incidence data since its hazard rate is decreasing after some point in time. In this example, however, the hazard rate has yet to start to decline at 4 years which is well past the expected lifetime of rats used in the study. This may explain why this model appears to fit the data reasonably well.

A second example is based on data found in Batchelor and Hackett (1970) who report the results of a study of 16 acutely burned patients treated with skin allografts. Patients received from one to four grafts. There were a total of 34 grafts among the 16 patients of which 30 failed. For each graft the time in days to rejection of the graft was recorded as well as an indicator variable  $Z$  which had a value of 1 if the graft was a good match of HLA skin type and 0 if it was a poor match. Thirty of the thirty-four grafts were rejected. The survival times of some grafts were censored by the death of the patient. It is reasonable to assume that grafts on a given patient may

have rejection times which are correlated. The results of fitting the multivariate normal and independence model to this data are found in Table 2.

**Table 2**  
**Results of Fitting Multivariate Normal Model to the Skin-Graft Data**

Effect	Multivariate Normal Model		Independence Model	
	Estimate	Standard Error	Estimate	Standard Error
Intercept	3.050	0.129	3.060	0.121
HLA Match	0.501	0.140	0.556	0.183
Within Subject Variance( $\omega$ )	0.129	0.046	0.271	0.0732
Frailty ( $\theta$ )	0.140	0.077	-	
Ln Likelihood	-24.05		-27.10	

The likelihood ratio test of hypothesis of no association between the survival of grafts on the same person has a chi-square of 6.1 which has a p-value of 0.014, which suggests that there is somewhat strong evidence of a correlation between the graft rejection times on a given patient. The strength of this association, as measured by  $\rho_1$ ,  $\rho_2$  and  $\tau$  is as follows:

Parameter	Estimate	Standard Error	95% Confidence Interval
$\rho_1$	0.521	0.058	(0.407, 0.635)
$\rho_2$	0.487	0.140	(0.357, 0.618)
$\tau$	0.349	0.197	(0.251, 0.447)

Here we see 95% confidence intervals for all three measures are bounded away from zero and that for all three parameters the point estimate suggests a strong association of rejection times within a given patient.

This model was also fit by Andersen et al (1996) using a semi parametric multiplicative gamma frailty model. They found that the likelihood ratio chi square for testing the hypothesis of no association was 1.34 which, as opposed to the multivariate normal model, is not significant. Their estimate of  $\tau$  was 0.217 with a standard error of 0.178 (95% confidence interval: (-0.13,0.566)). A gamma frailty Weibull model found a likelihood ratio chi square for the test of no association of 11.4 which is highly significant. The estimate of  $\tau$  for the Weibull model is 0.49 with a 95% confidence interval of (0.257,0.727) which is in agreement with the log normal model. In this case the sample size is quite small and the number of distinct event times (7) is very small

which suggests that a semi parametric model may not have sufficient power to detect the association between skin graft survival on the same person.

For the third example we consider a set of 1571 selected from the Framingham Heart Study (See Dawber 1980 for details). Subjects were included in the sample if they reach age 45 with no prior evidence of coronary heart disease. Patients were followed to first evidence of coronary heart disease (250 cases) or until their 10th cycle of Framingham exams. Covariates, measured at the exam closest to age 45, included in the model are body mass index (BMI) measured in  $\text{kg/m}^2$ , cholesterol level (CHOL) measured in  $\text{mg/dL}$ , sex (male -1, female-0), smoking status (smoker-1) and hypertension status (HYP) (normal -0, hypertensive or borderline hypertensive-1). The time variable used was the patients onstudy time measured from age 45 and event of interest is the occurrence of coronary heart disease.

In this example, siblings who share a common genetic code and a common environment in childhood may have event times which are correlated. In the study there were 1401 sib groups with 1-4 members per group. The results of the fit of the log normal distribution are as follows:

**Table 3**  
**Results of Fitting Multivariate Normal Model to the Framingham Heart Study Data**

Effect	Multivariate Normal Model		Independence Model	
	Estimate	Standard Error	Estimate	Standard Error
Intercept	4.6168	0.0766	4.6149	0.0765
BMI	-0.0434	0.0238	-0.0435	0.0238
CHOL	-0.0493	0.0195	-0.0484	0.0194
SMOKE	-0.0451	0.0190	-0.0707	0.0181
SEX	-0.0404	0.0181	-0.0872	0.0173
HYP	-0.0443	0.0172	-0.0451	0.0190
Within Subject Variance( $\omega$ )	0.0405	0.0070	0.0437	0.0044
Frailty ( $\theta$ )	0.0032	0.0058		
Ln Likelihood	-338.14		-338.29	

In this example the likelihood ratio chi-square test of the hypothesis is 0.31. In this example, as in the other examples, the interpretation of the risk coefficients in the independence and dependence model are different. In the independence model the effect of a risk factor is compared between subjects in the study with different values of the covariate, while in the multivariate normal model the comparison is within a given group. For the above example we see that the effect of smoking is larger in the independence model than in the multivariate normal

model. Since smoking behavior tends to be similar between siblings, perhaps determined in childhood, this is not too surprising. In the independence model, part of the magnitude of the  $\beta$  is reflecting the family effect, while in the multivariate normal model the comparison between smokers and non smokers is on siblings. Similarly, the effect of sex is larger in the independence model which might be expected since in most sibships of size two or larger the members were of the same sex. For the other factors there is relatively little difference between the effects of the covariates under the two models. The total variance in the independence model of 0.0437 which is approximately equal to the within sibship variance of 0.0032 and the between group variance of 0.0405, so that the multivariate normal model allows one to examine in more detail the various contributions to the variance.

## 5. Checking For Model Fit

The problem of checking for the fit of the multivariate normal model is difficult. A crude method of checking the fit of the model is to use the fact that marginally each log survival time follows a normal distribution with mean  $\beta^t \mathbf{Z}_j$  and variance  $\omega + \theta$ . To check the model we randomly select one observation from each group and define the generalized residual (See Klein and Moeschberger (1997)) by

$$R_k = \frac{Y_k - \beta^t \mathbf{Z}_k}{[\omega + \theta]^{1/2}}, \quad (4.1)$$

where  $Y_k$  is the randomly selected log survival time from the  $k$ th group,  $k=1, \dots, G$ . The  $Y_k$ 's are independent since only one observation comes from each group. If the multivariate normal model holds then the sample  $(R_k, \delta_k)$  should be a censored sample from a standard normal distribution. This can be checked by a normal hazard plot. That is, we plot  $\Phi^{-1}[1 - \exp[-\hat{\Lambda}(R_k)]]$  versus  $\log R_k$ , where  $\hat{\Lambda}()$  is the Nelson-Aalen estimator of the cumulative hazard rate of the generalized residuals.

If the normal model holds marginally then each hazard plot should be close to the 45° line.

Figure 1 shows the hazard plots for 10 samples from the fitted model for the Framingham Heart Study example. Here we see that the hazard plots are all clustered close to the 45° line and there is no evidence of a lack of fit of the model.

Figures 2 and 3 show the plots of ten samples of residuals from the litter matched tumorigenesis study and the skin graft study respectively. Here the sample sizes for each residual curve are small (size 50 and 16, respectively) so there is a high degree of uncertainty in these graphs. For the tumorigenesis study it appears that the multivariate normal provides a reasonable fit to the data. The log normal distribution is not typically used for cancer incidence data since its hazard rate is decreasing after some point in time. In this example, however, the hazard rate has yet to start to decline at 4 years which is well past the expected lifetime of rats used in the study.

This may explain why this model appears to fit the data reasonably well. For the skin graft data most of the replicates lie above the 45° line, particularly around a log residual value of zero suggesting that the multivariate normal model is suspect.

One may try to make a normal hazard plot using all the residuals or make separate log normal hazard plots at each level of the covariates. Such plots are difficult to interpret when there is a significant association between individuals within groups since the residuals no longer are an independent sample from the log normal distribution.

## 6. Discussion

In this note we have presented an alternative to the multiplicative frailty model which allows an investigator to access the strength of association between event times and to adjust regression coefficients for possible random effects. Here the effect of the common group effect is additive on the log failure times within a group. On the original time scale the effect of the shared random effect is to change the time scale for all members of the group by a factor  $\exp\{\theta^{1/2}W_0\}$ . This should be contrasted to the usual random effects model where the frailty acts multiplicatively on the hazard rate of each group member.

In this paper we have based estimation on a log normal model for the frailties. This model was used, primarily, since the joint distribution of the log event times within a group is well known. Other distributions, such as the standard extreme value distribution or the logistic distribution could be used as models for the  $W$ 's. These would lead to multivariate generalizations of the Weibull and log logistic distributions on the original time scale. Of course the Weibull generalization of the accelerated failure model will yield a model equivalent to a multiplicative frailty model.

This model is of use when there are some groups that have at least two members. When the frailty is used to describe heterogeneity due to omitting covariates in a univariate regression model (See Keiding et al. 1997) this approach is not feasible since it is impossible to separate the random effect,  $W_0$ , from the error distribution,  $W_1$ , when there is a single observation in each group.

The multivariate log normal model can be extended in a natural way to allow for two independent random effects acting on each individual. For example, one may wish to model simultaneously the association of death times between siblings who share a common genetic code and between married couples who share a common environmental effect.

## Acknowledgments

We wish to thank the associate editor and the referees for their insightful comments on an earlier draft of the paper. This research was supported by Grant R01-CA54706-04 from the National Cancer Institute.

## Bibliography

- Aalen, O.O. And Husebye, E. (1991) Statistical Analysis Of Repeated Events Forming Renewal Processes, *Statistics In Medicine* 10, 1227-1240.
- Abramowitz, M. and Stegun, I.A. (1972) *Handbook Of Mathematical Functions With Formulas, Graphs And Mathematical Tables*, National Bureau of Standards Washington D.C.
- Andersen, P. K., Klein, J. P., Knudsen, K. M., and Tabanera-Palacios, R. (1997). Estimation Of Variance In Cox's Regression Model With Frailties, *Biometrics* 53, 1475-1484.
- Andersen, T.W. (1958) *An Introduction to Multivariate Statistical Analysis* John Wiley & Sons, Inc. New York.
- Batchelor, J. R. and Hackett, M. (1970). HLA Matching In The Treatment Of Burned Patients With Skin Allografts. *Lancet*, 2, 581-583.
- Clayton, D.G. (1991). A monte carlo method for bayesian inference in frailty models. *Biometrics* 47, 467-485.
- Cox, D. R. (1972). Regression Models And Life-Tables (With Discussion). *Journal Of The Royal Statistical Society B*, 34, 187-220.
- Dawber, T.R. (1980) *The Framingham Study: Epidemiology of Atherosclerotic Disease* Cambridge, Massachusetts: Harvard University Press.
- Feinlieb, M. and MacMahon, B. (1960) Variation In The Duration Of Survival Of Patients With Chronic Leukemia. *Blood* 17, 332-349.
- Herskind et al (1996). The Heritability Of Human Longevity: A Population Based Study Of 2872 Danish Twins Born 1870-1900. *Human Genetics* 97, 467-475.
- Horner, R.D. (1987). Age At Onset Of Alzheimer's Disease: Cue To The Relative Importance Of Etiologic Factors? *American Journal of Epidemiology* 126, 409-414.
- Hougaard, P. (1986a). A Class Of Multivariate Failure Time Distributions. *Biometrika*, 73, 671-678.
- Hougaard, P. (1986b). Survival Models For Heterogeneous Populations Derived From Stable Distributions. *Biometrika*, 73, 387-396.
- Johnson, N. L. and Kotz, S. (1972) *Distributions in Statistics: Continuous Multivariate Distributions* John Wiley & Sons, Inc. New York.
- Jones, R.M. and Miller, K.S. (1966) On the multivariate lognormal distribution. *Journal of Industrial Mathematics* ,16, 63-76.



- Keiding, N., Andersen, P. K. and Klein, J.P. The Role Of Frailty Models And Accelerated Failure Time Models In Describing Heterogeneity Due To Omitted Covariates. *Statistics in Medicine* 16, 215-224, 1997.
- Klein, J. P. (1992). Semiparametric Estimation Of Random Effects Using The Cox Model Based On The EM Algorithm. *Biometrics*, 48, 795-806.
- Klein, J. P., Moeschberger, M. L., Li, Y. H. and Wang S.T. (1992). Estimating Random Effects In The Framingham Heart Study. In J. P. Klein and P. Goel, Editors, *Survival Analysis: State Of The Art*, pp. 99-120. Kluwer Academic Publishers, Boston.
- Klein, J.P. and Moeschberger, M.L. (1997) *Survival Analysis: Techniques For Censored And Truncated Data*, Springer-Verlag, New York.
- Mantel, N., Bohidar, N. R., and Ciminera, J. L. (1977). Mantel-Haenszel Analysis Of Litter-Matched Time-To-Response Data, With Modifications For Recovery Of Interlitter Information. *Cancer Research*, 37, 3863-3868.
- McGilchrist, C. A. and Aisbett, C. W. (1991). Regression With Frailty In Survival Analysis. *Biometrics*, 47, 461-466.
- Nielsen, G. G., Gill, R. D., Andersen, P. K., and Sørensen, T. I. A. (1992). A Counting Process Approach To Maximum Likelihood Estimation In Frailty Models. *Scandinavian Journal Of Statistics*, 19, 25-43.
- Osgood, E.W. (1958) Methods for Analyzing Survival Data, Illustrated by Hodgkin's disease. *American Journal of Medicine* 24, 40-47.
- Wang, S. T., Klein, J. P., and Moeschberger, M. L. (1995). Semi-Parametric Estimation Of Covariate Effects Using The Positive Stable Frailty Model. *Applied Stochastic Models And Data Analysis*, 11, 121-133.
- Yau, K.K.W and McGilchrist, C.A. (1997). Use Of Generalized Linear Mixed Models For The Analysis Of Clustered Survival Data. *Biomedical Journal* 39, 3-11.

## Appendix

The partial derivatives of  $L_i^D$  with respect to the parameters are

$$\frac{\partial L_i^D}{\partial \theta} = -\frac{d_i}{2[d_i \theta + \omega]} + \frac{S_{1i}(\beta)^2}{2[d_i \theta + \omega]^2} \quad (\text{A.1})$$

$$\frac{\partial L_i^D}{\partial \omega} = -\frac{d_i-1}{2\omega} - \frac{\omega}{2[d_i \theta + \omega]} + \frac{S_{2i}(\beta)}{2\omega^2} - \frac{\theta S_{1i}(\beta)^2 (d_i \theta + 2\omega)}{2\omega^2 [d_i \theta + \omega]^2} \quad (\text{A.2})$$

$$\frac{\partial L_i^D}{\partial \beta_k} = \frac{S_i^{(k)}(\beta)}{\omega} - \frac{M_i \theta S_{1i}(\beta) [\sum_{j=1}^{M_i} \delta_{ij} Z_{ijk}]}{\omega [d_i \theta + \omega]}, \quad k=0, \dots, p \quad (\text{A.3})$$

$$\frac{\partial^2 L_i^D}{\partial \theta^2} = \frac{d_i^2}{2[d_i \theta + \omega]^2} - S_{1i}(\beta)^2 \frac{d_i}{[d_i \theta + \omega]^3} \quad (\text{A.4})$$

$$\frac{\partial^2 L_i^D}{\partial \theta \partial \omega} = \frac{d_i}{2[d_i \theta + \omega]^2} - \frac{S_{1i}(\beta)^2}{[d_i \theta + \omega]^3} \quad (\text{A.5})$$

$$\frac{\partial^2 L_i^D}{\partial \theta \partial \beta_k} = -\frac{M_i S_{1i}(\beta) [\sum_{j=1}^{M_i} \delta_{ij} Z_{ijk}]}{[d_i \theta + \omega]^2}, \quad k=0, \dots, p \quad (\text{A.6})$$

$$\frac{\partial^2 L_i^D}{\partial \omega^2} = \frac{d_i-1}{2\omega^2} + \frac{1}{2[d_i \theta + \omega]^2} - \frac{S_{2i}(\beta)}{\omega^3} + \frac{\theta S_{1i}(\beta)^2 [(d_i \theta)^2 + 3 d_i \theta \omega + 3\omega^2]}{\omega^3 [d_i \theta + \omega]^3} \quad (\text{A.7})$$

$$\frac{\partial^2 L_i^D}{\partial \omega \partial \beta_k} = -\frac{S_i^{(k)}(\beta)}{\omega^2} + \frac{M_i S_{1i}(\beta) [\sum_{j=1}^{M_i} \delta_{ij} Z_{ijk}] \theta (d_i \theta + 2\omega)}{\omega^2 [d_i \theta + \omega]^2}, \quad k=0, \dots, p \quad (\text{A.8})$$

$$\frac{\partial^2 L_i^D}{\partial \beta_k \partial \beta_{k'}} = -\frac{\sum_{j=1}^{M_i} \delta_{ij} Z_{ijk} Z_{ijk'}}{\omega} + \frac{\theta [\sum_{j=1}^{M_i} \delta_{ij} Z_{ijk}] [\sum_{j=1}^{M_i} \delta_{ij} Z_{ijk}]}{\omega [d_i \theta + \omega]}, \quad k, k'=0, \dots, p \quad (\text{A.9})$$

Where  $S_i^{(k)} = \sum_{j=1}^{M_i} \delta_{ij} \{ \ln[T_{ij}] - \beta^t Z_{ij} \} Z_{ijk}$ .

To express the partial derivatives of  $L_1^C$  let

$$i_i(\theta, \omega, \beta) = \int_{-\infty}^{\infty} \phi(u) P(u; \theta, \omega, \beta) du,$$

$$P(u; \theta, \omega, \beta) = \prod_{k=1}^{M_i-d_i} \left\{ 1 - \Phi \left[ \frac{\ln[T_{ik}] - \beta^t Z_{ik}}{\omega^{1/2}} - \frac{S_{1i}(\beta)\theta}{\omega^{1/2}[d_i\theta + \omega]} - \frac{\theta^{1/2}}{[d_i\theta + \omega]^{1/2}} u \right] \right\},$$

$$h_{ij}[u; \theta, \omega, \beta] = \frac{-d \log[1 - \Phi(x)]}{dx} \quad \text{and} \quad h'_{ij}[u; \theta, \omega, \beta] = \frac{d^2 \log[1 - \Phi(x)]}{dx^2}$$

$$\text{evaluated at } x = \frac{\ln[T_{ij}] - \beta^t Z_{ij}}{\omega^{1/2}} - \frac{S_{1i}(\beta)\theta}{\omega^{1/2}(d_i\theta + \omega)} - \frac{\theta^{1/2}}{(d_i\theta + \omega)^{1/2}} u.$$

The partial derivatives of  $i_i(\theta, \omega, \beta)$  with respect to the parameters are

$$\frac{\partial i_i(\theta, \omega, \beta)}{\partial \theta} = \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta + \omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta + \omega)^{3/2}} \right] h_{ij}[u; \theta, \omega, \beta] P(u; \theta, \omega, \beta) du; \quad (\text{A.12})$$

$$\begin{aligned} \frac{\partial i_i(\theta, \omega, \beta)}{\partial \omega} &= \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\omega\theta + d_i\theta^2)}{2\omega^{3/2}(d_i\theta + \omega)^2} - u \frac{\theta^{1/2}}{2(d_i\theta + \omega)^{3/2}} \right] \\ &\quad \times h_{ij}[u; \theta, \omega, \beta] P(u; \theta, \omega, \beta) du; \end{aligned} \quad (\text{A.13})$$

$$\begin{aligned} \frac{\partial i_i(\theta, \omega, \beta)}{\partial \beta_k} &= \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{Z_{iik}}{\omega^{1/2}} - \frac{\theta \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk} \right]}{\omega^{1/2}(d_i\theta + \omega)} \right] h_{ij}[u; \theta, \omega, \beta] P(u; \theta, \omega, \beta) du; \quad k=0, \dots, p \\ &\quad (\text{A.14}) \end{aligned}$$

$$\begin{aligned} \frac{\partial^2 i_i(\theta, \omega, \beta)}{\partial \theta^2} &= - \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{2d_i\omega^{1/2} S_{1i}(\beta)}{(d_i\theta + \omega)^3} + u \frac{4d_i\theta\omega + \omega^2}{4\theta^{3/2}(d_i\theta + \omega)^{5/2}} \right] h_{ij}[u; \theta, \omega, \beta] P(u; \theta, \omega, \beta) du \\ &\quad - \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta + \omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta + \omega)^{3/2}} \right]^2 h'_{ij}[u; \theta, \omega, \beta] P(u; \theta, \omega, \beta) du \end{aligned}$$

$$+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{\infty} \int \phi(u) \left[ \frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta+\omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta+\omega)^{3/2}} \right]^2 h_{ij}[u:\theta,\omega,\beta] h_{ig}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du$$

(A.15)

$$\begin{aligned} \frac{\partial^2 i_i(\theta,\omega,\beta)}{\partial\theta\partial\omega} &= \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{S_{1i}(\beta)(d_i\theta-3\omega)}{2\omega^{1/2}(d_i\theta+\omega)^3} + u \frac{2d_i\theta-\omega}{4\theta^{1/2}(d_i\theta+\omega)^{5/2}} \right] h_{ij}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du \\ &- \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta+\omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta+\omega)^{3/2}} \right] \\ &\quad \times \left[ \frac{\ln[T_{ij}] - \beta' Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega+d_i\theta^2)}{2\omega^{3/2}(d_i\theta+\omega)^2} - u \frac{\theta^{1/2}}{2(d_i\theta+\omega)^{3/2}} \right] h_{ij}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du \\ &+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{\infty} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{\ln[T_{ij}] - \beta' Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega+d_i\theta^2)}{2\omega^{3/2}(d_i\theta+\omega)^2} - u \frac{\theta^{1/2}}{2(d_i\theta+\omega)^{3/2}} \right] \\ &\quad \times \left[ \frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta+\omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta+\omega)^{3/2}} \right] h_{ij}[u:\theta,\omega,\beta] h_{ig}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du \end{aligned}$$

(A.16)

$$\begin{aligned} \frac{\partial^2 i_i(\theta,\omega,\beta)}{\partial\theta\partial\beta_k} &= - \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{\omega^{1/2} \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk} \right]}{(d_i\theta+\omega)^2} \right] h_{ij}[\theta,\omega,\beta] P(u:\theta,\omega,\beta) du \\ &- \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{Z_{ijk}}{\omega^{1/2}} - \frac{\theta \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk} \right]}{\omega^{1/2}(d_i\theta+\omega)} \right] \left[ \frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta+\omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta+\omega)^{3/2}} \right] h_{ij}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du \\ &+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{\infty} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{\omega^{1/2} S_{1i}(\beta)}{(d_i\theta+\omega)^2} + u \frac{\omega}{2\theta^{1/2}(d_i\theta+\omega)^{3/2}} \right] \left[ \frac{Z_{ijk}}{\omega^{1/2}} - \frac{\theta \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk} \right]}{\omega^{1/2}(d_i\theta+\omega)} \right] h_{ij}[u:\theta,\omega,\beta] \\ &\quad \times h_{ig}[u:\theta,\omega,\beta] P(u:\theta,\omega,\beta) du, \quad k=0,\dots,p \end{aligned}$$

(A.17)

$$\begin{aligned}
\frac{\partial^2 i_i(\theta, \omega, \beta)}{\partial \omega^2} &= \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{S_{1i}(\beta)(3d_i^2\theta^3 + 10d_i\theta^2\omega + 15\theta\omega^2)}{4\omega^{5/2}(d_i\theta + \omega)^3} - \frac{3(\ln[T_{ij}] - \beta^t Z_{ij})}{4\omega^{5/2}} \right. \\
&\quad \left. + u \frac{3\theta^{1/2}}{4(d_i\theta + \omega)^{5/2}} \right] h_{ij}[u: \theta, \omega, \beta] P(u: \theta, \omega, \beta) du \\
&- \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega + d_i\theta^2)}{2\omega^{3/2}(d_i\theta + \omega)^2} - u \frac{\theta^{1/2}}{2(d_i\theta + \omega)^{3/2}} \right]^2 h'_{ij}[u: \theta, \omega, \beta] P(u: \theta, \omega, \beta) du \\
&+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega + d_i\theta^2)}{2\omega^{3/2}(d_i\theta + \omega)^2} - u \frac{\theta^{1/2}}{2(d_i\theta + \omega)^{3/2}} \right] \\
&\times \left[ \frac{\ln[T_{ig}] - \beta^t Z_{ig}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega + d_i\theta^2)}{2\omega^{3/2}(d_i\theta + \omega)^2} - u \frac{\theta^{1/2}}{2(d_i\theta + \omega)^{3/2}} \right] h_{ij}[u: \theta, \omega, \beta] h_{ig}[u: \theta, \omega, \beta] P(u: \theta, \omega, \beta) du
\end{aligned} \tag{A.18}$$

$$\begin{aligned}
\frac{\partial^2 i_i(\theta, \omega, \beta)}{\partial \omega \partial \beta_k} &= \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ -\frac{Z_{ijk}}{2\omega^{3/2}} + \frac{(3\theta\omega + d_i\theta^2) \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk} \right]}{2\omega^{3/2}(d_i\theta + \omega)^2} \right] h_{ij}[u: \theta, \omega, \beta] P(u: \theta, \omega, \beta) du \\
&- \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{Z_{ijk}}{\omega^{1/2}} - \frac{\theta \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk} \right]}{\omega^{1/2}(d_i\theta + \omega)} \right] \left[ \frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega + d_i\theta^2)}{2\omega^{3/2}(d_i\theta + \omega)^2} - u \frac{\theta^{1/2}}{2(d_i\theta + \omega)^{3/2}} \right] \\
&\times h'_{ij}[u: \theta, \omega, \beta] P(u: \theta, \omega, \beta) du \\
&+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{\ln[T_{ij}] - \beta^t Z_{ij}}{2\omega^{3/2}} - \frac{S_{1i}(\beta)(3\theta\omega + d_i\theta^2)}{2\omega^{3/2}(d_i\theta + \omega)^2} - u \frac{\theta^{1/2}}{2(d_i\theta + \omega)^{3/2}} \right] \\
&\times \left[ \frac{Z_{igk}}{\omega^{1/2}} - \frac{\theta \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk} \right]}{\omega^{1/2}(d_i\theta + \omega)} \right] h_{ij}[u: \theta, \omega, \beta] h_{ig}[u: \theta, \omega, \beta] P(u: \theta, \omega, \beta) du
\end{aligned} \tag{A.19}$$

$$\begin{aligned}
\frac{\partial^2 i_i(\theta, \omega, \beta)}{\partial \beta_k \partial \beta_{k'}} &= - \sum_{j=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) \left[ \frac{Z_{ijk}}{\omega^{1/2}} - \frac{\theta \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk} \right]}{\omega^{1/2}(d_i \theta + \omega)} \right] \left[ \frac{Z_{ijk'}}{\omega^{1/2}} - \frac{\theta \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk'} \right]}{\omega^{1/2}(d_i \theta + \omega)} \right] \\
&\quad \times h'_{ij}[u: \theta, \omega, \beta] P(u: \theta, \omega, \beta) du \\
+ \sum_{j=1}^{M_i-d_i} \sum_{g=1}^{M_i-d_i} \int_{-\infty}^{\infty} \phi(u) &\left[ \frac{Z_{ijk}}{\omega^{1/2}} - \frac{\theta \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk} \right]}{\omega^{1/2}(d_i \theta + \omega)} \right] \left[ \frac{Z_{igk'}}{\omega^{1/2}} - \frac{\theta \left[ \sum_{j=1}^{M_i} \delta_{ij} Z_{ijk'} \right]}{\omega^{1/2}(d_i \theta + \omega)} \right] \\
&\times h_{ij}[u: \theta, \omega, \beta] h_{ig}[u: \theta, \omega, \beta] P(u: \theta, \omega, \beta) du, \quad k, k'=0, \dots, p
\end{aligned} \tag{A.20}$$

Figure 1  
Check Of Fit Of Multivariate Normal Model  
Framingham Data

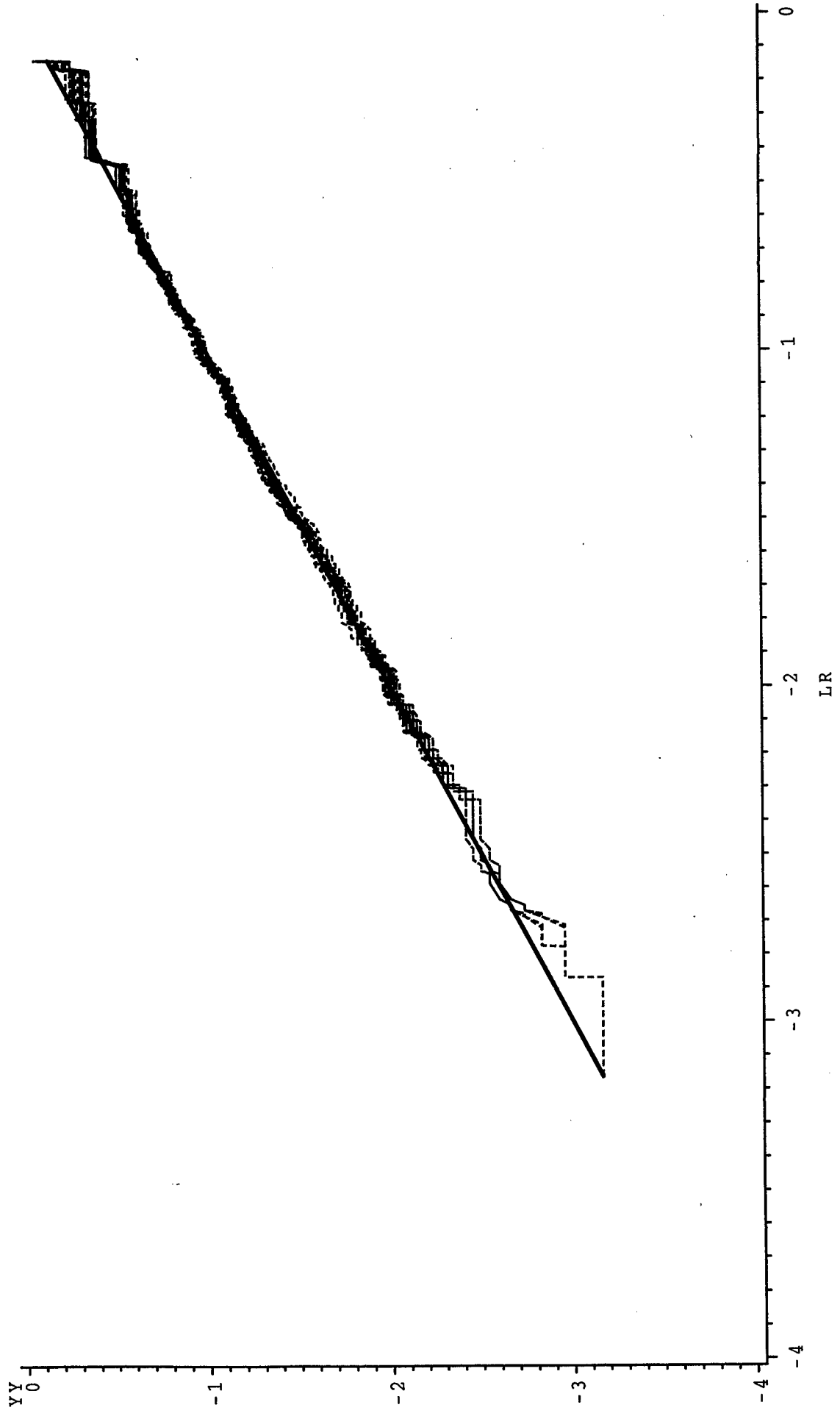


Figure 2  
Check Of Fit Of Multivariate Normal Model  
Litter-Matched Rats Data Set

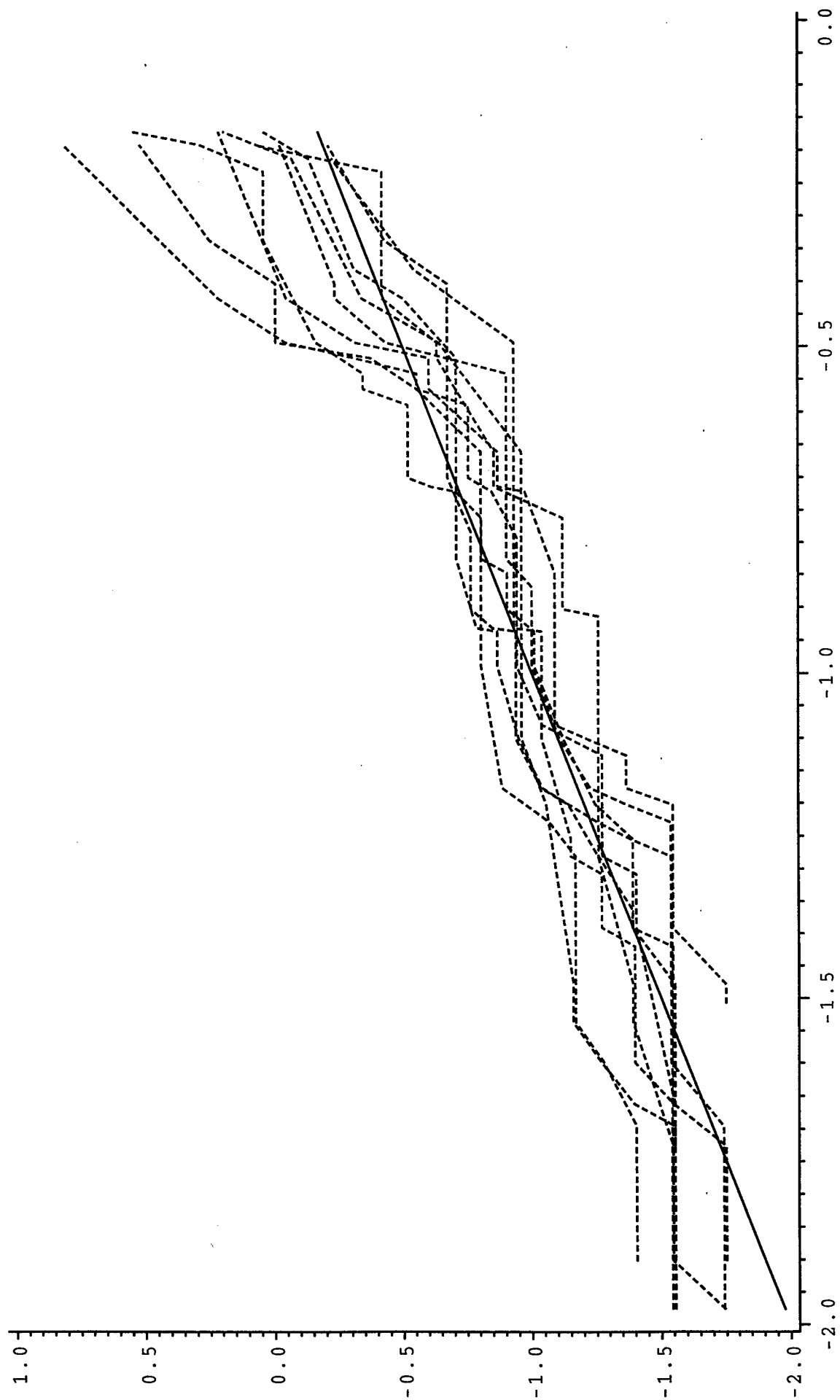
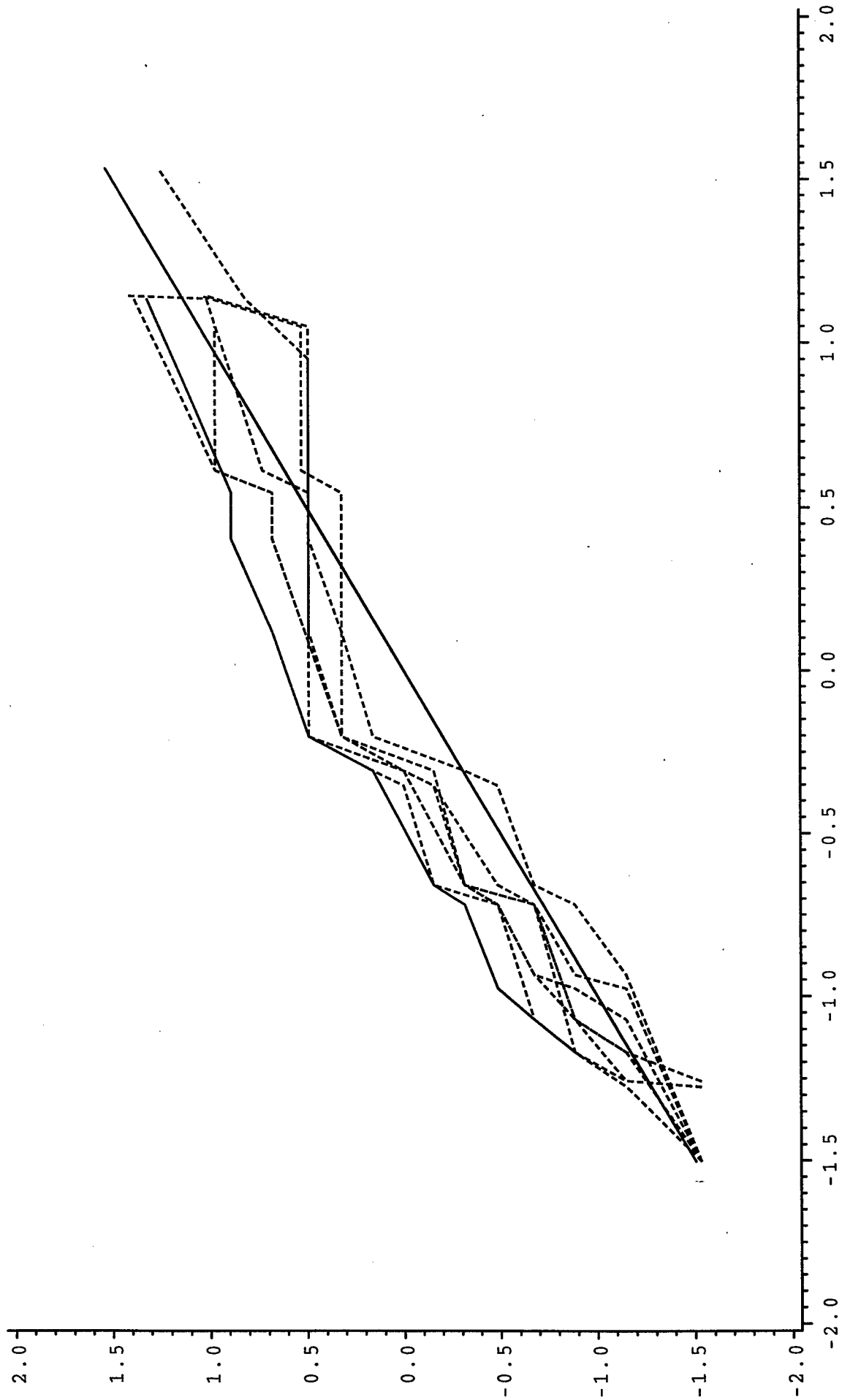




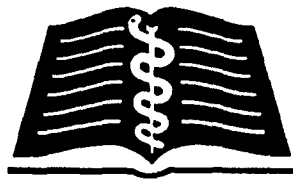
Figure 3  
Check Of Fit Of Multivariate Normal Model  
Skin-Graft Data Set



**Joint Modeling of Death Times  
and  
Counts Using a Random Effects Model**

Hee-Chang Park  
Department of Statistics  
Changwon National University

**DIVISION OF BIOSTATISTICS**



**MEDICAL  
COLLEGE  
OF WISCONSIN**

**MILWAUKEE, WISCONSIN**

**Joint Modeling of Death Times  
and  
Counts Using a Random Effects Model**

Hee-Chang Park  
Department of Statistics  
Changwon National University  
Korea

and

John P. Klein  
Division of Biostatistics  
The Medical College of Wisconsin

Technical Report 27

August 1997

Division of Biostatistics  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee WI 53226  
Phone: (414)456-8280

# Joint Modeling Of Death Times And Counts Using A Random Effects Model

**Hee-Chang Park**

**Department of Statistics  
Changwon National University  
Korea**

**and**

**John P Klein  
Division of Biostatistics  
The Medical College of Wisconsin**

## **Abstract**

We consider the problem of modeling count data where the observation period is determined by the survival time of the individual under study. We assume a random effects or frailty model to allow for a possible association between the death times and the counts. We assume that, given a random effect, the death times follow a Weibull distribution with a rate that depends on some covariates. For the counts, given the random effect, a Poisson process is assumed with the intensity depending on time and the covariates. A gamma model is assumed for the random effect. Maximum likelihood estimators of the model parameters are obtained. The model is applied to data set of patients with breast cancer who received a bone marrow transplant. A model for the time to death and the number of supportive transfusions a patient received is constructed and consequences of the model are examined.

## 1. INTRODUCTION

A common problem that arises in longitudinal studies is to model the effects of some explanatory factors on the number of occurrences of a given event that have occur in some time interval. For example, one may wish to model the number of transfusions given to a bone marrow transplant patient in the course of their recovery, the number of admissions to the hospital of a patient with a serious illness, or the number of doses of a drug given to a patient with a heart attack in the emergency room. We shall denote by  $N(t)$  denote the cumulative number of events that have occurred up to time  $t$ .

Data on  $N(t)$  is available only as long as the patient is under observation. Patients can be removed from the study in one of two ways. They can be removed alive or censored at either a random lost-to-follow-up time or at the end of the study, or, observation on the patient can stop due to the death of the patient. We shall let  $X$  denote the time to death and  $(T, \delta)$  denote the on study time and censoring indicator ( $\delta=1$  if  $T=X$ ,  $\delta=0$  if  $T>X$ ). We assume that the censoring mechanism is independent of the time to death and the number of events that have occurred at a given time.

In most cases it is not reasonable to assume that  $N(t)$  and  $T$  are independent. In the bone marrow examples, patients who require more frequent blood transfusions are often having problems in maintaining their graft and as such are at higher risk for death than patients requiring fewer transfusions. Thus  $N(t)$  and  $X$  should be positively associated. We shall induce an association between the counts and the survival times by using a so called shared frailty or random effect model. Frailty models have been used to model association in survival studies by a number of authors (See, for example Clayton 1978, Nielsen et al 1992, Klein 1992). Lawless (1987) has used random effects models to model count data. Here we shall introduce a common random effect in the model for  $T$  and  $N(t)$  which induces a positive association between these two random quantities. The random effect represents the unmeasured factors that are acting simultaneously on both the number of events and the time to death. The variance of this random factor represents a measure of the strength of this positive association between the two random quantities.

In the next Section we will describe how a model using a common gamma frailty can be applied in this problem. We shall assume that, conditional on a set of potential risk factors, the time to death follows a Weibull distribution and the counts follow a Poisson process. We develop some properties of the model which help in the interpretation of the effects of the covariates on both the time to death and the number of events. In Section 3 we discuss the problem of estimating model parameters.

In Section 4 we apply these procedures to data from the Autologous Blood and Marrow Transplant Registry (ABMTR) on 701 patients with high risk breast cancer given high dose

chemotherapy followed by autologous hematopoietic stem-cell support (an autologous bone marrow transplant). Patients were transplanted between 1990-1994 and followed until 1996. The median follow up time was 16.5 months with a range of 0.1 to 66 months. Three hundred and sixty-one (51.5%) of the patients died during the course of the study. Patients had median of 5 transfusions from the same donor. One hundred and forty-four requiring no transfusions and the maximum number of transfusions was 172. Table 1 summarizes the number of transfusions.

**Table 1**  
**Frequency of transfusions**

Number of Transfusions	Number of patients
0	144
1	30
2	63
3	53
4	45
5	34
6	31
7	24
8	22
9	21
10	19
11	8
12	16
13	13
14	10
15	9
16	11
17	9
18	13
19	8
≥20	118

Five potential risk factors were considered in the study. Two factors were treated as continuous covariates: patient's age at transplant (median 44 years range 24.5-64.4) and the waiting time from diagnosis to transplant ( median 626 days range 92 to 4811 days). One factor, year of transplant was coded as a binary covariate (90-92 (44%) and 93-94 (56%)). Two factors were categorical and coded as a series of binary covariates: Stage of disease at transplant (primary stage 2-3 disease (32.2%), metastatic disease in complete remission (18.7%), partial remission (28.0%) or resistant disease (21.1 %)) and the graft source (bone marrow (49.4%), peripheral blood stem cell (39.5%), or both (11.1%)). Additional details of the study can be found in Antman et al (1997).

## 2. The Model

In this Section we present a model for the joint distribution of the time to death,  $X$ , and the number of events which occur up to time  $t$ ,  $N(t)$ . We let  $W$  denote a shared random effect which has a common multiplicative effect on both the rate at which death is occurring and the rate at which the events are occurring. This random effect, which is allowed to vary from person to person, is analogous to a frailty in the usual multivariate survival modeling (See Klein et al (1992)) and as a memodel for unobserved heterogeneity in modeling count data (See Lawless (1987)). It represents common genetic, disease specific or environmental factors that were not measured on the patient which are affecting both the number of events and the time to death. Here we assume that  $W$  has a gamma distribution with a mean of 1 and a variance  $\theta$ . That is ,

$$f(w) = \frac{w^{1/\theta-1} \exp[-w/\theta]}{\Gamma[1/\theta] \theta^{1/\theta}}, \theta \geq 0 \quad (2.1)$$

For a given patient we have two sets of covariates which are potential explanatory factors for either the time to death or for the count (or both). Suppose that there are  $p_d$  covariates which are explanatory for death and  $p_c$  covariates which are explanatory for the number of events. We define the  $p_d+1$  vector  $\mathbf{Z}_d$  whose first component is equal to 1 and whose remaining  $p_d$  columns are set equal to the  $p_d$  explanatory covariates for death. Similarly let  $\mathbf{Z}_c$  be the  $p_c+1$  vector of risk factor for the number of events. Again for convenience the first component of  $\mathbf{Z}_c$  is set to 1 for an intercept term. Note that the same factor can be included in both  $\mathbf{Z}_p$  and  $\mathbf{Z}_c$ .

Given the value of  $W=w$  (and  $\mathbf{Z}_d$ ) we assume that the time to death follows a Weibull distribution with hazard rate

$$h(t | \mathbf{Z}_d) = w \alpha t^{\alpha-1} \exp\{\beta \mathbf{Z}_d\}, t \geq 0, \alpha > 0. \quad (2.2)$$

This is a standard Weibull regression model as discussed in Klein and Moeschberger (1997) with the inclusion of the random effect,  $w$ .

For the number of events we assume, given  $W=w$  (and  $\mathbf{Z}_c$ ), that  $N(t)$  follows a Poisson process with a rate

$$\lambda(t | \mathbf{Z}_c) = w t^\phi \exp\{\gamma \mathbf{Z}_c\}, t \geq 0, \phi > 0. \quad (2.3)$$

Given  $W$  we assume that  $N(t)$  and  $X$  are independent.

To study properties of this model we first need to note that  $N(t)$  is only observable as long as  $t \leq X$ , and that  $N(t)=N(X)$  when  $X>t$ . Thus we have, given  $W=w$ , that, with some abuse of notation,

$$\begin{aligned} P[X=t, N(s)=k|w] &= P[X=t, N(\min(s,t))=k|w] \\ &= w\alpha t^{\alpha-1} \exp\{\beta Z_d\} \exp[-wt^\alpha \exp\{\beta Z_d\}] \\ &\quad \times \frac{[w\min(s,t)^\phi \exp\{\gamma Z_c\}]^k \exp[-w\min(s,t)^\phi \exp\{\gamma Z_c\}]}{k!} \end{aligned} \quad (2.4)$$

Also

$$\begin{aligned} P[X \geq t, N[s]=k |w] &= \int_t^\infty P[X = t, N[s]=k |w] dt \text{ for } t \geq s \\ &= \int_t^s P[X = t, N[t]=k |w] dt + P[X \geq s, N[s]=k |w] \text{ for } t < s. \end{aligned} \quad (2.5)$$

To find the unconditional distribution of  $X$  and  $N(\cdot)$  we take the expectation of (2.4) with respect  $W$ . For  $\theta > 0$ , this yields,

$$\begin{aligned} P[X=t, N(s)=k] &= \int_0^\infty P[X=t, N(s)=k|w] \frac{w^{1/\theta-1} \exp[-w/\theta]}{\Gamma[1/\theta] \theta^{1/\theta}} dw \\ &= \frac{\Gamma(1/\theta+k+1)}{k! \Gamma(1/\theta)} [\alpha \theta t^{\alpha-1} \exp\{\beta Z_d\}] [\theta \min(s,t)^\phi \exp\{\gamma Z_c\}]^k \\ &\quad \times [1 + \theta t^\alpha \exp\{\beta Z_d\} + \theta \min(s,t)^\phi \exp\{\gamma Z_c\}]^{-(1/\theta+k+1)}. \end{aligned} \quad (2.6)$$

When  $\theta$  is equal to zero then  $W$  is equal to one almost surely and  $X$  and  $N(\cdot)$  are independent Weibull and Poisson random variables, respectively.

From (2.5) we have

$$P[X \geq t, N(s)=k] = \frac{\Gamma(1/\theta+k)}{k! \Gamma(1/\theta)} [\theta s^\phi \exp\{\gamma Z_c\}]^k [1 + \theta t^\alpha \exp\{\beta Z_d\} + \theta s^\phi \exp\{\gamma Z_c\}]^{-(1/\theta+k)}, \quad (2.7)$$

when  $t \geq s$  and

$$\begin{aligned} P[X \geq t, N(s)=k] &= \frac{\Gamma(1/\theta+k+1)}{k! \Gamma(1/\theta)} [\alpha \theta^{k+1} \exp\{\beta Z_d + k\gamma Z_c\}] \\ &\quad \times \int_t^s u^{k\phi + \alpha - 1} \{1 + \theta u^\alpha \exp\{\beta Z_d\} + \theta u^\phi \exp\{\gamma Z_c\}\}^{-(1/\theta+k+1)} du \end{aligned} \quad (2.8)$$



$$+ \frac{\Gamma(1/\theta+k)}{k! \Gamma(1/\theta)} [\theta s^\phi \exp\{\gamma Z_c\}]^k [1+\theta s^\alpha \exp\{\beta Z_d\} + \theta s^\phi \exp\{\gamma Z_c\}]^{-(1/\theta+k)},$$

when  $s > t$ .

For this model one can show that the marginal distribution of  $X$  is a univariate Burr distribution with survival function

$$S(t) = [1+\theta t^\alpha \exp\{\beta Z_d\}]^{-1/\theta}. \quad (2.9)$$

For  $s \leq t$  the conditional distribution of  $N(s)$  given  $X > t$  follows a Pascal distribution with parameters  $1/\theta$  and  $q$  with

$$q = \frac{\theta s^\phi \exp\{\gamma Z_c\}}{1+\theta t^\alpha \exp\{\beta Z_d\} + \theta s^\phi \exp\{\gamma Z_c\}}. \quad (2.10)$$

That is

$$P[N(s)=k | T > t] = \binom{1/\theta+k-1}{k} q^k p^{1/\theta}, \quad (2.11)$$

where  $p=1-q$ . The mean number of transfusions at time  $s$  for a patient alive at time  $t \geq s$  is  $E[N(s)=k | T > t] = q/(\theta p)$  and the conditional variance is  $V[N(s)=k | T > t] = q/(\theta p^2)$ .

To find the marginal distribution of  $N(s)$  we need to compute  $P[X \geq 0, N(s)=k]$ . From (2.8) we see that

$$P[N(s)=k] = \frac{\Gamma(1/\theta+k+1)}{k! \Gamma(1/\theta)} [\alpha \theta^{k+1} \exp\{\beta Z_d + k \gamma Z_c\}] \\ \times \int_0^s u^{k\phi+\alpha-1} \{1+\theta u^\alpha \exp\{\beta Z_d\} + \theta u^\phi \exp\{\gamma Z_c\}\}^{-(1/\theta+k+1)} du \quad (2.12) \\ + \frac{\Gamma(1/\theta+k)}{k! \Gamma(1/\theta)} [\theta s^\phi \exp\{\gamma Z_c\}]^k [1+\theta s^\alpha \exp\{\beta Z_d\} + \theta s^\phi \exp\{\gamma Z_c\}]^{-(1/\theta+k)}.$$

This quantity needs to be evaluated numerically.

### 3. Estimation of model parameters

Estimation of model parameters is based on the total number of transfusions a patient received during their period of observation. Let  $T_i$  be the on study time for the  $i$ th person and  $\delta_i$  be the death indicator ( $\delta_i = 1$  if dead,  $\delta_i = 0$  if censored). Let  $N_i = N_i(T_i)$  be the total number of transfusion given to the patient. Note that, as opposed to Lawless (1987), we only know the total number of events an individual has experienced not the exact times at which these events have occurred. Let  $Z_{di}$  and  $Z_{ci}$  be the covariate vectors for the  $i$ th person. For individuals who die, their contribution to the likelihood is  $P[X=T_i, N(T_i)=N_i]$  which is given by (2.6). For individuals

who are censored, their contribution to the likelihood is  $P[X > T_i, N(T_i) = N_i]$ , which is given by (2.7). Based on a sample of size  $n$ , the log likelihood is (up to an additive constant) given by

$$LL = \sum_{i=1}^n \left\{ \ln[\Gamma(1/\theta + N_i + \delta_i)] + \delta_i \ln[\alpha] + [\delta_i(\alpha - 1) + N_i \phi] \ln[T_i] + \delta_i \beta Z_{di} + N_i \gamma Z_{ci} + (N_i + \delta_i) \ln[\theta] - (1/\theta + N_i + \delta_i) \ln[1 + \theta T_i^\alpha \exp\{\beta Z_{di}\} + \theta T_i^\phi \exp\{\gamma Z_{ci}\}] \right\} - n \ln[\Gamma(1/\theta)], \quad (3.1)$$

when  $\theta > 0$ . For  $\theta = 0$  the log likelihood is the sum of two likelihoods,  $L_1(\alpha, \beta)$  and  $L_2(\phi, \gamma)$ , the first the usual likelihood from a Weibull regression model,

$$L_1(\alpha, \beta) = \sum_{i=1}^n \delta_i [(\alpha - 1) \ln[T_i] + \ln[\alpha] + \beta Z_{di}] - T_i^\alpha \exp\{\beta Z_{di}\}$$

and the second Poisson likelihood,

$$L_2(\phi, \gamma) = \sum_{i=1}^n N_i [\phi \ln[T_i] + \gamma Z_{ci}] - T_i^\phi \exp\{\gamma Z_{ci}\}.$$

Estimates of  $\theta$ ,  $\alpha$ ,  $\phi$ ,  $\beta$  and  $\gamma$  are found by maximizing the log likelihood numerically. In the appendix we provide the score statistics, which are the first partial derivatives of  $LL$  with respect to the parameters, and the observed information matrix,  $\mathbf{I}$ , which is the negative of the matrix of second partial derivatives. The inverse of the observed information matrix is the estimated covariance matrix of the maximum likelihood estimators. Wald, score and likelihood ratio tests for the parameters of the model can be performed using standard constructions (See Appendix B of Klein and Moeschberger (1997) for details.)

#### 4. Example

We shall illustrate inference for this model using the data discussed in Section 1. To estimate model parameters we used Marquart's (1963) method to numerically maximize the likelihood (3.1). This method, which is a compromise between the method of steepest descent and the Newton-Raphson technique, was used since it is difficult to obtain initial estimates of the model parameters, and the number of parameters is quite large. Details of the technique are found in Appendix A of Klein and Moeschberger (1997). A FORTRAN program was written to perform the estimation procedures.

We first fit the model with all 5 factors for both the time to death and the number of transfusions. In Table 2 we report the parameter estimates, standard errors and the Wald chi-square test of the hypothesis the parameter is equal to zero. We then use a backward stepwise procedure

to eliminate factors one at time to find a final model in which all factors are significant at the 5% level.

The final model is reported in Table 3. Here we see that the risk factors for death are the stage of disease with patients transplanted with resistant disease or in partial remission having higher death rates; the source of the graft, with patients transplanted with both bone marrow and peripheral blood stem cells having a worst prognosis; and the lag time between diagnosis and transplant with patients being transplanted soon after diagnosis doing more poorly. For the number of transfusions, all five factors are significant. Here younger patients transplanted later than 1992 with a long time from diagnosis to transplant tend to have fewer transfusions. For stage of disease patients transplanted in complete remission or with resistant disease tend to have more transfusions, while patients given only peripheral blood stem cells tend to have fewer transfusions.

The Wald test of the hypothesis of no association between the death times and the number of transfusions (i.e.  $H_0: \theta=0$ ) is strongly rejected in both models. Since this is a test about a parameter on the boundary of the parameter space, the likelihood ratio test may be more appropriate. When  $\theta=0$ ,  $X$  and  $N[\cdot]$  are independent, so the likelihood is the product of the typical Weibull likelihood and a Poisson likelihood. Maximum likelihood estimates can be found by maximizing these two likelihoods separately. The total log likelihood is the sum of two individual likelihoods. Table 4 shows the results of fitting the two separate models, using the covariates in the final model. Here the total likelihood is -8049.86 which yields a likelihood ratio chi-square of 7,879.20 with 1 degree of freedom, which is highly significant.

A comparison of Tables 3 and 4 shows that effect of ignoring the significant association between the death times and the number of transfusions. In the models for the death times, the factor graft source is not significant in the independence model, but is highly significant in the dependence model. In the models for the number of transfusions the two models are also different. First, the baseline intensity,  $t^{\phi} \exp\{\beta_0\}$  is decreasing in the independence model ( $\phi = -0.18$ ), but increasing in time in the dependence model ( $\phi = 0.40$ ). Second, the sign of the regression coefficient for "partial remission" is different in the two model.

There are several implications of the model which can be deduced from the results in Section 2. First we can estimate the mean number of transfusions at time  $t$  for a patient who is alive at this time with a given set of covariates by  $\hat{q}/(\hat{\theta} \hat{p})$ , with  $q$  given by (2.10). A routine use of the delta method gives an estimate of the standard error of the estimate. Using (2.11) we can estimate the probability that a patient will have  $k$  transfusions by time  $s$  given they are alive at this time. Again, standard errors can be found by a simple application of the delta method. Table 5 show the point estimates and standard errors of these two quantities for a 44 year old patient transplanted after 1992 with a 626 day waiting time from diagnosis to transplant. Estimates at 6,

12, 18 and 24 months are given for all twelve combinations of disease status and cell source. Here we see that for patients not having resistant disease the expected number of transfusions varies from about 3.5-4 for patients given peripheral blood stem cells only, from about 5-6 for patients given bone marrow only, and from about 5-8 for patients given both types of cells. Patients with resistant disease are expected to have substantially more transfusions. Similar patterns hold for the estimated probabilities of at least one transfusion. Note that for a fixed set of covariates the expected number of transfusions is not necessarily increasing in time since this is the expected number of transfusions for a survivor and patients with more transfusions in most cases tend to have a lower survival rate.

The model can also be used to examine how the number of transfusions a patient has effects their survival rates. Using the parameter estimates and (2.11) one can estimate the marginal probability, given the covariates, that  $N(s)=k$ . The integral in (2.11) needs to be evaluated numerically, which we do in the sequel using a 24 point Gauss Legendre formula. Using this estimate and (2.7) we can estimate the conditional survival function for an individual alive at time  $s$  who has had a given number of transfusions. That is we estimate  $P[X>t | N[s]=k, X\geq s, \mathbf{Z}_d, \mathbf{Z}_c]$ . Figure 1 shows the effect of the number of transplants on survival for a 44 year old patient with primary disease transplanted using bone marrow after 1992 with a 626 day waiting time from diagnosis to transplant who was alive with 0, 1, 2, 5, 10, or 15 transfusions at 6 months. We see that after 3 years from this time the estimated survival ranges from about 98% for a patient give no transfusions to about 32% for a patient given 15 transfusions. To study the effect of the risk factors on survival we plot in Figure 2 the conditional survival curves for the twelve combinations of graft source and disease status for a 44 year old patient transplanted after 1992 with a 626 day waiting time from diagnosis to transplant who was alive with 5 transfusions at 6 months.

### Acknowledgments

We wish to thank Corey Peltz and Mei-Jie Zhang for their helpful comments on this paper and the ABMTR for providing the data used in this paper. Professor Klein's research was supported by grant R01 CA54706-06 from the National Cancer Institute. Prof. Park was supported by a grant from the Korean Science Foundation.

### References

- Antman, K. H. et al (1997). High-Dose Chemotherapy With Autologous Hematopoietic Stem-Cell Support For Breast Cancer in North America. *Journal of Clinical Oncology* **15**, 1870-1879.

- Clayton, D. G. (1978). A Model For Association In Bivariate Life Tables And Its Application In Epidemiological Studies Of Familial Tendency In Chronic Disease Incidence. *Biometrika*, 5, 141-151.
- Klein, J. P. (1992). Semiparametric Estimation Of Random Effects Using The Cox Model Based On The EM Algorithm. *Biometrics*, 48, 795-806.
- Klein, J. P. and Moeschberger, M.L. (1997) *Survival Analysis: Techniques For Censored And Truncated Data*. Springer-Verlag, New York.
- Klein, J. P., Moeschberger, M. L., Li, Y. H. and Wang S.T. (1992). Estimating Random Effects In The Framingham Heart Study. In J. P. Klein and P. Goel, Editors, *Survival Analysis: State Of The Art*, pp. 99-120. Kluwer Academic Publishers, Boston.
- Lawless, J.F. (1987) Regression Methods For Poisson Process Data *JASA* **82**, 808-815.
- Marquardt, D. (1963). An Algorithm For Least-Squares Estimation Of Non-Linear Parameters. *SIAM Journal Of Applied Mathematics*, 11, 431-441.
- Nielsen, G. G., Gill, R. D., Andersen, P. K., and Sørensen, T. I. A. (1992). A Counting Process Approach To Maximum Likelihood Estimation In Frailty Models. *Scandinavian Journal Of Statistics*, 19, 25-43.

**Table 2**

**Maximum Likelihood Estimates Of Model Parameters In Initial Model**

<b>Factor</b>	<b>Estimate</b>	<b>SE</b>	<b>D.F.</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
<b>Time to Death</b>					
Intercept	-5.94	0.50			
<u>Stage Of Disease</u>			3	121.52	<0.0001
Complete Remission	0.63	0.24	1	6.89	0.0087
Partial Remission	2.10	0.22	1	91.12	<0.0001
Resistant Disease	2.15	0.24	1	80.25	<0.0001
<u>Graft Source</u>			2	10.59	0.0050
Peripheral Blood Stem Cell	-0.01	0.18	1	0.03	0.8625
Marrow And Peripheral Blood	0.78	0.26	1	9.00	0.0027
<u>Year Of Transplant (90-92)</u>	0.15	0.17	1	0.77	0.3807
<u>Age</u>	0.01	0.01	1	2.09	0.1481
<u>Waiting Time To Transplant</u>	-2.3x10 <sup>-4</sup>	6.8x10 <sup>-5</sup>	1	11.12	0.0009
<b>Number of Transfusions</b>					
Intercept	0.47	0.35			
<u>Stage Of Disease</u>			3	53.21	<0.0001
Complete Remission	3.2x10 <sup>-3</sup>	0.15	1	4.6x10 <sup>-4</sup>	0.9829
Partial Remission	0.26	0.14	1	3.45	0.0633
Resistant Disease	1.03	0.15	1	47.15	<0.0001
<u>Graft Source</u>			2	20.72	<0.0001
Peripheral Blood Stem Cell	-0.35	0.12	1	8.51	0.0035
Marrow And Peripheral Blood	0.37	0.19	1	3.79	0.0515
<u>Year Of Transplant (90-92)</u>	-0.26	0.12	1	4.73	0.0296
<u>Age</u>	0.02	0.01	1	11.72	0.0006
<u>Waiting Time To Transplant</u>	-7.6x10 <sup>-5</sup>	3.2x10 <sup>-5</sup>	1	5.78	0.0162
θ	1.58	0.10	1	263.01	<0.0001
α	1.31	0.06			
φ	0.41	0.05			
Log Likelihood	-4108.86				

**Table 3**  
**Maximum Likelihood Estimates Of Model Parameters In Final Model**

<b>Factor</b>	<b>Estimate</b>	<b>SE</b>	<b>D.F.</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
<b>Time to Death</b>					
Intercept	-5.23	0.245			
<u>Stage Of Disease</u>					
Complete Remission	0.65	0.240	3	125.27	<0.0001
Partial Remission	2.09	0.220	1	7.34	0.0068
Resistant Disease	2.21	0.234	1	90.25	<0.0001
<u>Graft Source</u>					
Peripheral Blood Stem Cell	-0.05	0.168	2	9.91	0.0070
Marrow And Peripheral Blood	0.71	0.249	1	0.09	0.7660
			1	8.13	0.0044
<u>Waiting Time To Transplant</u>	-2.2x10 <sup>-4</sup>	6.8x10 <sup>5</sup>	1	10.31	0.0013
<b>Number of Transfusions</b>					
Intercept	0.79	0.286			
<u>Stage Of Disease</u>					
Complete Remission	0.02	0.146	3	57.41	<0.0001
Partial Remission	0.25	0.141	1	0.02	0.8875
Resistant Disease	1.05	0.152	1	3.14	0.0762
<u>Graft Source</u>					
Peripheral Blood Stem Cell	-0.38	0.118	2	21.82	<0.0001
Marrow And Peripheral Blood	0.35	0.182	1	10.37	0.0013
			1	3.70	0.0545
<u>Year Of Transplant (90-92)</u>	-0.32	0.088	1	13.69	0.0002
<u>Age</u>	.02	0.005	1	10.58	0.0011
<u>Waiting Time To Transplant</u>	-7.2x10 <sup>-5</sup>	3.2x10 <sup>-5</sup>	1	5.11	0.0238
θ	1.57	0.097	1	267.46	<0.0001
α	1.31	0.057	1		
φ	0.40	0.050			
Log Likelihood	-4110.26				

**Table 4**  
**Model Based On Independence Between The Death Times And Number Of Transfusions**

	<b>Estimate</b>	<b>SE</b>	<b>D.F.</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
<b>Time to Death</b>					
Intercept	-4.54	0.21			
<u>Stage Of Disease</u>					
Complete Remission	0.67	0.19	1	12.06	0.0005
Partial Remission	1.53	0.17	1	79.73	<0.0001
Resistant Disease	1.76	0.18	1	100.06	<0.0001
<u>Graft Source</u>					
Peripheral Blood Stem Cell	-0.17	0.12	1	2.17	0.1407
Marrow And Peripheral Blood	0.30	0.17	1	3.03	0.0820
<u>Waiting Time To Transplant</u>	-1.84x10 <sup>-4</sup>	5.94x10 <sup>-5</sup>	1	9.61	0.0019
$\alpha$	1.04	0.05			
Weibull Log Likelihood	-1599.32				
<b>Number of Transfusions</b>					
Intercept	2.39	0.08			
<u>Stage Of Disease</u>					
Complete Remission	-0.04	0.04	1	1.42	0.2338
Partial Remission	-0.27	0.04	1	55.87	<0.0001
Resistant Disease	0.58	0.03	1	304.15	<0.0001
<u>Graft Source</u>					
Peripheral Blood Stem Cell	-0.37	0.03	1	180.97	<0.0001
Marrow And Peripheral Blood	0.05	0.03	1	1.70	0.1924
<u>Year Of Transplant (90-92)</u>	-0.12	0.02	1	23.73	<0.0001
<u>Age</u>	0.01	1.51E-03	1	83.61	<0.0001
<u>Waiting Time To Transplant</u>	-3.23E-05	1.20E-05	1	7.20	0.0073
$\phi$	-0.18	0.01			
Poisson Log Likelihood	-6450.54				
Total Log Likelihood	-8049.86				



**Table 5**  
**Estimated Mean Number Of Transfusions And The Probability Of At Least One Transfusion For A 44 Year Old Patient Transplanted After 1992 With A 626 Day Waiting Time To Transplant For A Patient Alive at 6, 12, 18 or 24 Months**

Disease Status <sup>1</sup>	Cell Source <sup>2</sup>	Expected Number Of Transfusions /SE				Probability Of At Least One Transfusion/SE			
		6 months	12 months	18 months	24 months	6 months	12 months	18 months	24 months
Primary	BM	5.946	7.087	7.486	7.546	0.774	0.795	0.802	0.803
		0.628	0.647	0.649	0.650	0.024	0.021	0.021	0.021
		CR	5.671	6.281	6.216	5.929	0.767	0.781	0.779
PR	BM	0.688	0.654	0.615	0.588	0.026	0.024	0.025	0.026
		5.082	4.266	3.513	2.956	0.752	0.727	0.696	0.667
		0.480	0.410	0.365	0.329	0.026	0.031	0.036	0.041
Resistant	BM	10.780	8.810	7.157	5.975	0.840	0.820	0.797	0.774
Primary	PBSC	1.150	0.948	0.830	0.739	0.023	0.028	0.034	0.039
		4.085	4.890	5.188	5.250	0.720	0.747	0.755	0.757
		0.555	0.607	0.618	0.616	0.029	0.025	0.025	0.025
CR	PBSC	3.907	4.358	4.338	4.158	0.713	0.730	0.729	0.723
		0.537	0.537	0.520	0.506	0.030	0.027	0.028	0.029
		PR	3.547	3.012	2.496	2.108	0.698	0.671	0.637
Resistant	PBSC	0.375	0.323	0.286	0.257	0.028	0.033	0.038	0.042
		7.536	6.230	5.091	4.265	0.803	0.780	0.753	0.727
		0.759	0.638	0.562	0.504	0.024	0.030	0.035	0.040
Primary	Both	7.851	8.617	8.462	8.023	0.807	0.818	0.816	0.810
		1.278	1.306	1.259	1.210	0.025	0.024	0.025	0.027
		CR	7.099	6.975	6.308	5.632	0.796	0.793	0.781
PR	Both	1.201	1.106	1.025	0.959	0.027	0.028	0.031	0.035
		5.153	3.710	2.843	2.299	0.754	0.705	0.660	0.622
		0.800	0.629	0.515	0.435	0.033	0.043	0.052	0.058
Resistant	Both	10.703	7.528	5.714	4.598	0.840	0.802	0.768	0.738
		1.513	1.160	0.939	0.790	0.027	0.037	0.046	0.053

<sup>1</sup> Primary - Primary Stage 2-3 disease; CR-Complete Remission; PR-Partial Remission; Resistant-Resistant disease.

<sup>2</sup> BM-Bone Marrow; PBSC- Peripheral Blood Stem Cells; Both- Both sources

## Appendix

From (3.1) we have a log likelihood given by

$$LL = \sum_{i=1}^n \log[\Gamma(1/\theta + \delta_i + N_i)] + \ln[\alpha] D + (\alpha - 1) S_{DLT} + \sum_{i=1}^n \delta_i \beta Z_{di} \\ + \phi S_{NLT} + \sum_{i=1}^n N_i \gamma Z_{ci} - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \ln[Y_i] - (n/\theta) \ln[\theta] - n \ln[\Gamma(1/\theta)] \quad (A.1)$$

where  $D$  is the number of deaths,  $S_{DLT} = \sum_{i=1}^n \delta_i \ln[T_i]$ ,  $S_{NLT} = \sum_{i=1}^n N_i \ln[T_i]$ , and

$$Y_i = 1/\theta + T_i^\alpha \exp\{\beta Z_{di}\} + T_i^\phi \exp\{\gamma Z_{ci}\}.$$

The score statistics are:

$$\frac{\partial LL}{\partial \alpha} = D/\alpha + S_{DLT} - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{\ln[T_i] T_i^\alpha \exp\{\beta Z_{di}\}}{Y_i}, \quad (A.2)$$

$$\frac{\partial LL}{\partial \phi} = S_{NLT} - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{\ln[T_i] T_i^\phi \exp\{\gamma Z_{ci}\}}{Y_i}, \quad (A.3)$$

$$\frac{\partial LL}{\partial \theta} = -\frac{1}{\theta^2} \sum_{i=1}^n \Psi(1/\theta + \delta_i + N_i) + \frac{1}{\theta^2} \sum_{i=1}^n \ln[Y_i] + \frac{1}{\theta^2} \sum_{i=1}^n \frac{1/\theta + \delta_i + N_i}{Y_i} + \frac{n}{\theta^2} [\ln[\theta] - 1 + \Psi(1/\theta)]; \quad (A.4)$$

$$\frac{\partial LL}{\partial \beta_j} = \sum_{i=1}^n \delta_i Z_{dij} - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{Z_{dij} T_i^\alpha \exp\{\beta Z_{di}\}}{Y_i}, \quad j = 0, \dots, p_d; \quad (A.5)$$

$$\frac{\partial LL}{\partial \gamma_j} = \sum_{i=1}^n N_i Z_{cij} - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{Z_{cij} T_i^\phi \exp\{\gamma Z_{ci}\}}{Y_i}, \quad j = 0, \dots, p_c, \quad (A.6)$$

where  $\Psi(\cdot)$  is the digamma function.

The second partial derivatives of the log likelihood are:

$$\frac{\partial^2 LL}{\partial \alpha^2} = -D/\alpha^2 - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{(\ln[T_i])^2 T_i^\alpha \exp\{\beta Z_{di}\} [1/\theta + T_i^\phi \exp\{\gamma Z_{ci}\}]}{Y_i^2}, \quad (A.7)$$

$$\frac{\partial^2 LL}{\partial \alpha \partial \phi} = \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{(\ln[T_i])^2 T_i^\alpha \exp\{\beta Z_{di}\} T_i^\phi \exp\{\gamma Z_{ci}\}}{Y_i^2}, \quad (A.8)$$

$$\frac{\partial^2 LL}{\partial \alpha \partial \theta} = \frac{1}{\theta^2} \sum_{i=1}^n \frac{\ln[T_i] T_i^\alpha \exp\{\beta Z_{di}\}}{Y_i} - \frac{1}{\theta^2} \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{\ln[T_i] T_i^\alpha \exp\{\beta Z_{di}\}}{Y_i^2}, \quad (\text{A.9})$$

$$\frac{\partial^2 LL}{\partial \alpha \partial \beta_j} = - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{\ln[T_i] Z_{dij} T_i^\alpha \exp\{\beta Z_{di}\} [1/\theta + T_i^\phi \exp\{\gamma Z_{ci}\}]}{Y_i^2}, \quad j = 0, \dots, p_d; \quad (\text{A.10})$$

$$\frac{\partial^2 LL}{\partial \alpha \partial \gamma_j} = \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{\ln[T_i] Z_{cij} T_i^\alpha \exp\{\beta Z_{di}\} T_i^\phi \exp\{\gamma Z_{ci}\}}{Y_i^2}, \quad j = 0, \dots, p_c; \quad (\text{A.11})$$

$$\frac{\partial^2 LL}{\partial \phi^2} = - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{(\ln[T_i])^2 T_i^\phi \exp\{\gamma Z_{ci}\} [1/\theta + T_i^\alpha \exp\{\beta Z_{ci}\}]}{Y_i^2}, \quad (\text{A.12})$$

$$\frac{\partial^2 LL}{\partial \phi \partial \theta} = \frac{1}{\theta^2} \sum_{i=1}^n \frac{\ln[T_i] T_i^\phi \exp\{\gamma Z_{ci}\}}{Y_i} - \frac{1}{\theta^2} \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{\ln[T_i] T_i^\phi \exp\{\gamma Z_{ci}\}}{Y_i^2}, \quad (\text{A.13})$$

$$\frac{\partial^2 LL}{\partial \phi \partial \beta_j} = \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{\ln[T_i] Z_{dij} T_i^\alpha \exp\{\beta Z_{di}\} T_i^\phi \exp\{\gamma Z_{ci}\}}{Y_i^2}, \quad j = 0, \dots, p_d; \quad (\text{A.14})$$

$$\frac{\partial^2 LL}{\partial \phi \partial \gamma_j} = - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{\ln[T_i] Z_{cij} T_i^\phi \exp\{\gamma Z_{ci}\} [1/\theta + T_i^\alpha \exp\{\beta Z_{di}\}]}{Y_i^2}, \quad j = 0, \dots, p_c; \quad (\text{A.15})$$

$$\begin{aligned} \frac{\partial^2 LL}{\partial \theta^2} &= \frac{2}{\theta^3} \sum_{i=1}^n \Psi(1/\theta + \delta_i + N_i) - \frac{2}{\theta^3} \sum_{i=1}^n \ln[Y_i] - \frac{2}{\theta^3} \sum_{i=1}^n \frac{1/\theta + \delta_i + N_i}{Y_i} \\ &+ \frac{1}{\theta^4} \sum_{i=1}^n \left\{ \Psi'(1/\theta + \delta_i + N_i) - \frac{1}{Y_i} \left[ 2 - \frac{1/\theta + \delta_i + N_i}{Y_i} \right] \right\} + \frac{n}{\theta^3} \left[ 3 - 2 \ln[\theta] - 2\Psi(1/\theta) - \frac{1}{\theta} \Psi'(1/\theta) \right]; \end{aligned} \quad (\text{A.16})$$

$$\frac{\partial^2 LL}{\partial \theta \partial \beta_j} = \frac{1}{\theta^2} \sum_{i=1}^n \frac{Z_{dij} T_i^\alpha \exp\{\beta Z_{di}\}}{Y_i} - \frac{1}{\theta^2} \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{Z_{dij} T_i^\alpha \exp\{\beta Z_{di}\}}{Y_i^2}, \quad j=0, \dots, p_d; \quad (\text{A.17})$$

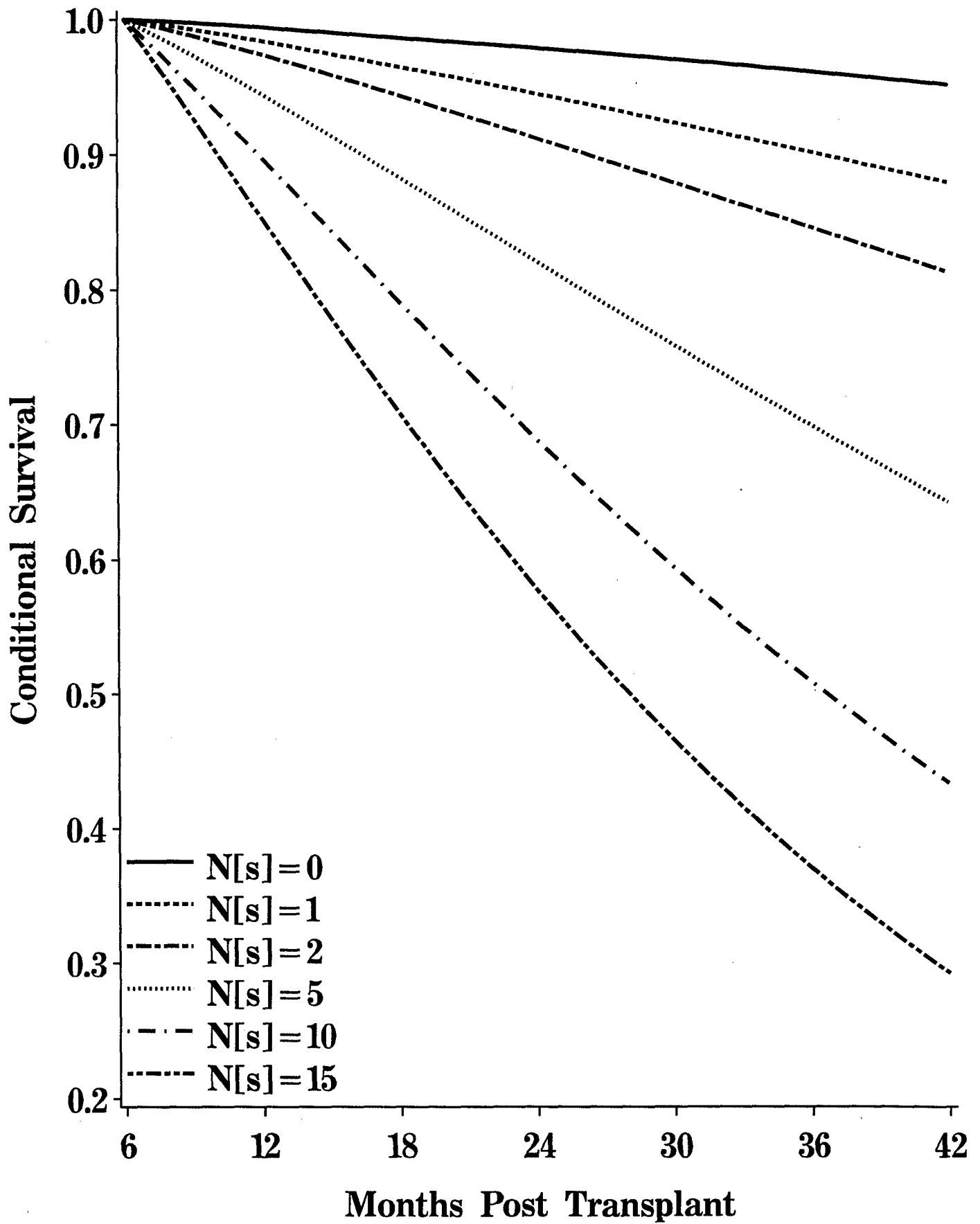
$$\frac{\partial^2 LL}{\partial \theta \partial \gamma_j} = \frac{1}{\theta^2} \sum_{i=1}^n \frac{Z_{cij} T_i^\phi \exp\{\gamma Z_{ci}\}}{Y_i} - \frac{1}{\theta^2} \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{Z_{cij} T_i^\phi \exp\{\gamma Z_{ci}\}}{Y_i^2}, \quad j=0, \dots, p_c; \quad (\text{A.18})$$

$$\frac{\partial^2 LL}{\partial \beta_j \partial \beta_k} = - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{Z_{dij} Z_{dik} T_i^\alpha \exp\{\beta Z_{di}\} [1/\theta + T_i^\phi \exp\{\gamma Z_{ci}\}]}{Y_i^2}, \quad j, k = 0, \dots, p_d; \quad (\text{A.19})$$

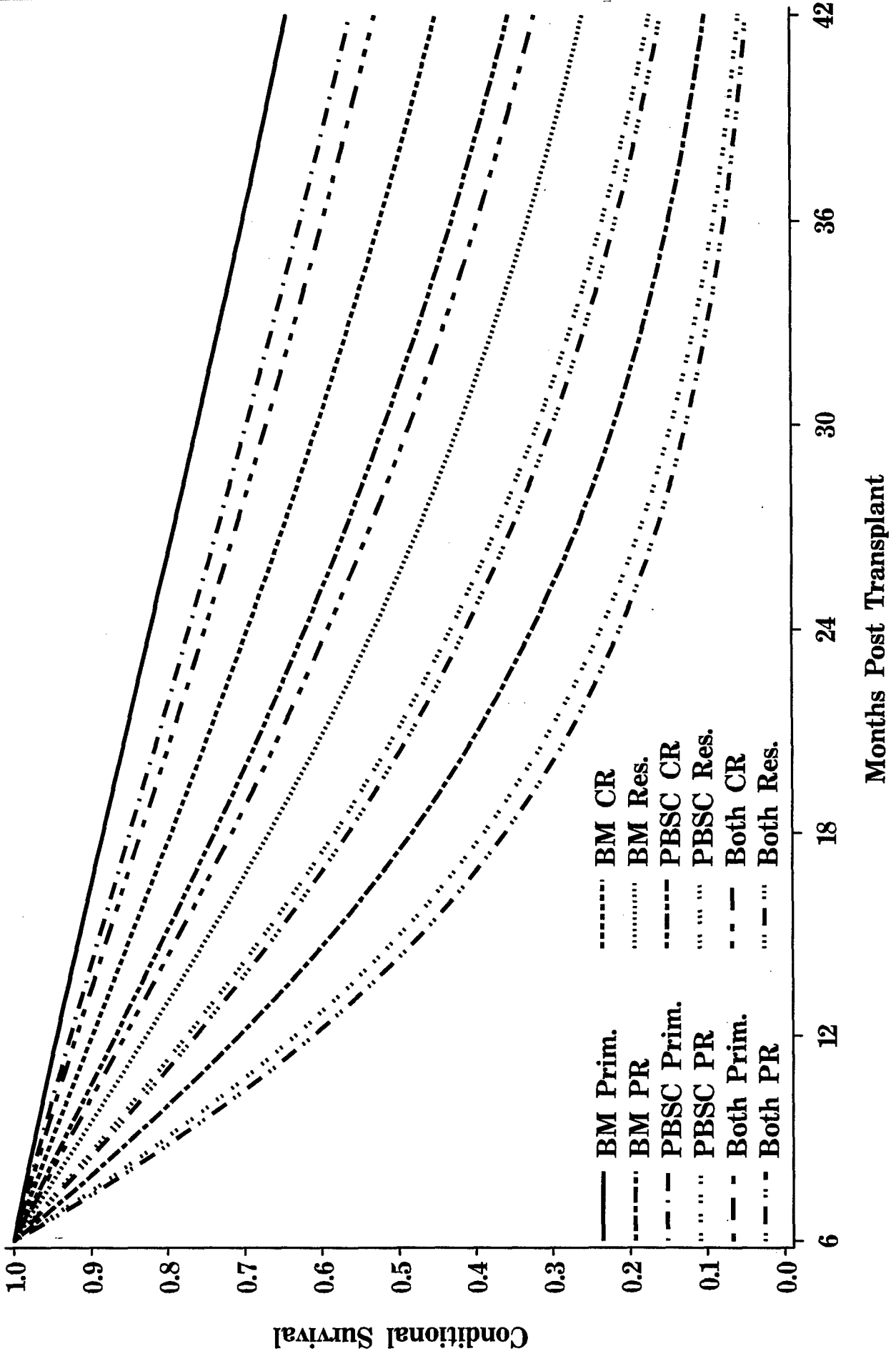
$$\frac{\partial^2 LL}{\partial \beta_j \partial \gamma_k} = \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{Z_{dij} Z_{cik} T_i^\alpha \exp\{\beta Z_{di}\} T_i^\phi \exp\{\gamma Z_{ci}\}}{Y_i^2}, \quad j = 0, \dots, p_d, \quad k=0, \dots, p_c; \quad (\text{A.20})$$

$$\frac{\partial^2 LL}{\partial \gamma_j \partial \gamma_k} = - \sum_{i=1}^n (1/\theta + \delta_i + N_i) \frac{Z_{cij} Z_{cik} T_i^\phi \exp\{\gamma Z_{ci}\} [1/\theta + T_i^\alpha \exp\{\beta Z_{di}\}]}{Y_i^2}, \quad j, k = 0, \dots, p_c. \quad (\text{A.21})$$

Figure 1  
Conditional Survival Function



**Figure 2**  
**Conditional Survival Function Given 5 Transfusions at 6 Months**



**Testing For Center Effects In  
Multicenter Survival Studies:  
A Monte Carlo Comparison Of  
Fixed And Random Effects Tests**

Per Kragh Andersen  
University of Copenhagen and Danish Epidemiology Centre  
John P. Klein and Mei-Jie Zhang  
Medical College of Wisconsin

**DIVISION OF BIOSTATISTICS**



**MEDICAL  
COLLEGE  
OF WISCONSIN**

**MILWAUKEE, WISCONSIN**

**Testing For Center Effects In  
Multicenter Survival Studies:  
A Monte Carlo Comparison Of  
Fixed And Random Effects Tests**

Per Kragh Andersen  
University of Copenhagen and Danish Epidemiology Centre  
John P. Klein and Mei-Jie Zhang  
Medical College of Wisconsin

Technical Report 23

January 1997

Division of Biostatistics  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee WI 53226  
Phone: (414)456-8280



# Testing For Center Effects In Multicenter Survival Studies: A Monte Carlo Comparison Of Fixed And Random Effects Tests

Per Kragh Andersen

University of Copenhagen and Danish Epidemiology Centre

And

John P. Klein and Mie-Jie Zhang  
Medical College of Wisconsin

## SUMMARY

The problem of testing for a center effect following a proportional hazards regression is considered. Two approaches to the problem can be used. One approach fits a proportional hazards model with a fixed covariate included for each center. The need for a center specific adjustment is evaluated using either a score, Wald or likelihood ratio test of the hypothesis that all the center specific covariates are equal to zero. An alternative approach is to introduce a random effect or frailty for each center into the model. Recently, Commenges and Andersen [1], have proposed a score test for this random effects model.

By a Monte Carlo study we compare the performance of these two approaches when either the fixed or random effects model holds true. The study shows that for moderate samples the fixed effects tests have nominal levels much higher than specified, but the random effect test performs as expected under the null hypothesis. Under the alternative hypothesis the random effect test has good power to detect relatively small fixed or random center effects. Also if the center effect is ignored the estimator of the main effect may be quite biased and the estimator is inconsistent. The tests are illustrated on a retrospective multicenter study of the recovery from bone marrow transplantation.

## 1. Introduction

A common question arising in multi-center prospective clinical trials and in retrospective studies from collaborative registry studies is whether some statistical adjustment is needed to account for effects specific to the individual centers contributing patients to the trial. Such an adjustment may be needed to account for factors, related to the outcome, which vary from center to center but are not adjusted for in the analysis. These factors may involve measurable quantities like a center's protocol for supportive therapy, the number of similar cases treated by the center, etc., or they be unmeasurable factors like the quality of the center's medical staff or differences in a center's catchment population.

In this paper we study two methods for testing the hypothesis of no center specific effect when the outcome measure is the time to some event. In such studies, typically, data is

analyzed using the Cox [2] proportional hazards regression model. The typical analysis includes covariates for the main effect of interest in the study as well as patient specific covariates which are related to the outcome of interest. The patient specific covariates are included in the final model in a partial attempt to make an adjustment for differences in patient demographics between institutions (See Klein and Moeschberger [3] for details on model building in this situation.)

The first method used to test for the presence of a center effect in such studies is the use of a fixed effect proportional hazards model. In this approach one institution is picked as a baseline institution and a set of indicator covariates are included for all other institutions. If we let  $\mathbf{Z}$  denote the treatment and patient specific covariates and  $X_i = \{1 \text{ if the patient is from institution } i; 0 \text{ otherwise}\}$ , for  $i = 1, \dots, K$ , where  $K$  is the number of institutions contributing to the study, then the hazard rate for the  $j$ th patient from institution  $i$  is

$$\lambda_{ij}(t|\mathbf{Z}_{ij}) = \lambda_0(t) \exp\{\beta' \mathbf{Z}_{ij} + \theta' \mathbf{X}\} \quad (1)$$

where  $\mathbf{X} = (X_1, \dots, X_{K-1})$ . If there is no center specific effect in the study then  $\theta_1 = \theta_2 = \dots = \theta_{K-1} = 0$ . To test the hypothesis of no center effect one can use a standard Wald, likelihood ratio or score test available in many statistical packages (See Andersen et al [4] or Klein and Moeschberger [3] for details).

An alternate approach to testing for a center effect is to use a random effects or frailty model. Such models were introduced by Clayton [5] and Vaupel et al. [6] and further discussed by, among others, Klein [7], Nielsen et al [8], Andersen et al. [4] and Klein and Moeschberger [3]. Here one assumes that the center specific effect for the  $i$ th center is represented by a mean 0, variance 1, unobservable random variable,  $\epsilon_i$ , which acts multiplicatively on the hazard rate for all individuals within the center. That is

$$\begin{aligned} \lambda_{ij}(t|\mathbf{Z}_{ij}) &= \lambda_0(t) \exp\{\beta' \mathbf{Z}_{ij} + \sigma \epsilon_i\} \\ &= \lambda_0(t) u_i \exp\{\beta' \mathbf{Z}_{ij}\} \end{aligned} \quad (2)$$

where  $u_i = \exp\{\sigma \epsilon_i\}$ . The  $\epsilon_i$ 's are an *i.i.d.* sample from the unknown frailty distribution. In this model, the test of no center effect reduces to a test of the hypothesis that  $\sigma$  is equal to 0. Commenges and Andersen [1] have recently developed a score test of this hypothesis that does not require specification of the unknown frailty distribution. Computational details of this test are given in the Appendix.

In this paper we examine the relative performance of these two procedures by a Monte Carlo study. Details of the study are given in Section 2. In Section 3 we examine the performance of the two approaches when the null hypothesis is true. In Section 4 we examine the power of the two approaches when either the fixed or random effect model is true. In Section 5 we illustrate the use of the two statistics on a data set of allogeneic bone marrow transplants based on data from a collaborative bone marrow transplant registry. Finally, in Section 6 we summarize our conclusions and make some suggestions of how to proceed when the hypothesis of no center effect is rejected.

## 2. The Monte Carlo Study

To study the two approaches to testing for a potential center effect a Monte Carlo study was performed. In the study a single fixed time covariate,  $Z$ , was used. The covariate  $Z$  was taken to be +1 for half of the patients at each center and -1 for the remaining half. The value of the regression coefficient was taken to be either zero or  $\ln(2)$ . The baseline hazard rate was assumed to be one for all  $t$ . A random censoring time was generated for each subject from an exponential population with hazard rate equal to either 1/9 or 3/7. This leads to approximately 10% or 30% of the observations being censored, respectively.

To investigate the relationship between the number of centers and the number of observations per center on the power of the tests we generated data coming from 5, 10 or 20 centers with a total of 100, 200, or 400 observations in the total sample. Data was generated from one of five models for the center effect. For the first case all observations were independent and no center effect was generated. This corresponds to the null case. For the other four cases data was generated either from a model with fixed center effects (1) or from the random effects model (2) with either a gamma, positive stable or inverse Gaussian frailty model. To make the model comparable for the random effects models the parameters of the frailty model were chosen to give a Kendall's  $\tau$  of either 0.1, 0.3, or 0.5 between individuals within a center. Note since the inverse Gaussian model has a  $\tau$  of less than 0.5 only the  $\tau = 0.1$  and 0.3 cases were available.

For the gamma frailty model the  $u_i$  were simulated from a gamma distribution with mean 1 and variance  $\alpha$  using the IMSL routine `rngam`. This model has a value of  $\tau = \alpha/(\alpha + 1)$ . For the inverse Gaussian distribution with probability density function  $f(u) = (\eta\pi)^{-1/2} \exp\{2/\eta\} \exp\{-u/\eta - 1/(\eta u)\}$ , the  $u_i$  were generated using the routine in Micheal et al [9]. For this model Kendall's  $\tau$  is  $0.5 - 2/\eta + (8/\eta^2) \exp\{4/\eta\} \int_{4/\eta}^{\infty} \exp(-u)/u du$ . For the positive stable distribution with Laplace transform  $\exp(-u^\rho)$ ,  $0 \leq \rho \leq 1$ , the  $u_i$ 's were generated using results in Chambers et al [10]. Here Kendall's  $\tau$  is  $1 - \rho$ . For the fixed center effects model we model the center effect as  $\theta_i = c(i - 3)$ , for  $i = 1, \dots, 5$  when  $K = 5$  and as  $\theta_i = c[-K - 2 + 2i]/2$ ,  $i = 1, \dots, K/2$  and  $\theta_i = c[i - K/2]$  for  $i = K/2, \dots, K$  when  $K = 10$  or  $K = 20$ . To determine the value of  $c$  we treat the  $\theta_i$  as arising from a discrete distribution,  $E$ , with mass  $1/K$  at each  $\theta_i$ . Then the expected value of  $E$  is zero as is the expected value of  $\epsilon_i$  in (2). To find  $c$  we match the variance of  $\exp\{E\}$  with that of the variance of the gamma frailty distribution. This gives a "association" in the fixed effects model of roughly the same strength as in the gamma frailty model. Note that while we treated the center effect in a random manner to get a value of  $c$ , in the simulation the values of  $c$  are fixed. Table 1 summarizes the parameters used in our study.

**Table 1**  
**Parameters used in The Monte Carlo Study**

Center Effect	$\tau=0.1$	$\tau = 0.3$	$\tau = 0.5$
Gamma	$\alpha = 2/9$	$\alpha = 6/7$	$\alpha = 2$
Positive Stable	$\rho = 0.9$	$\rho = 0.7$	$\rho = 0.5$
Inverse Gaussian	$\eta = 0.551$	$\eta = 4.070$	Not Possible
Constant	K=5	c=0.311	c=0.534
	K=10	c=0.132	c=0.230
	K=20	c=0.007	c=0.122
		c=0.709	c=0.305
			c=0.161

For each sample we compute the Wald, likelihood ratio and score test for the fixed effects model, the score test for the random effects model and the estimate of the  $\beta$  based on a proportional hazards model which does not adjust for center effects and for the model which makes a fixed effect adjustment for the center effects. This is done in each run for 5,000 samples. We estimate the power of the four test of center effects at a 0.05 significance level and the bias and mean squared error of the two estimates of  $\beta$ .

### 3. Significance levels of the tests

Table 2 shows the estimated null power of the likelihood ratio fixed effects test and the random effects score test, at a 0.05 significance level, based on 5,000 replicates for each combination of  $\beta$ ,  $K$  and total sample size. Here we have reported only the likelihood ratio test for the fixed effects model since its performance was in all cases the best of the three possible fixed effects test statistics. From this table we first see that the test based on a fixed center effects model requires a very large sample size before it achieves the desired level. When the number of subjects at each center is small the test is anti-conservative. This fact appears to be true even when there are ten or more groups with 400 total observations and the results suggest that unless the number of subjects in each group is very large the fixed effect test should not be used because it rejects the hypothesis of no center effect too often when the null hypothesis is true.

For the random effects score test, with only a few exceptions, the nominal level of the test is achieved. When  $K = 5$  and the total sample is 100 the test may be slightly anti-conservative, but the estimated power achieved is closer to 0.05 than for any of the fixed effects tests.

### 4. Behavior When There Is A Group Effect

As seen in the previous section the fixed effects test for a group effect tends to reject the null hypothesis of no group effect too often when the number of subjects per group is small. The random effects test does, however, appear to maintain the correct significance level for these small sample cases. In our examination of the power of these tests we found that the power of the fixed effects test was higher in all cases than the random effects test. However,

due to the problem with the fixed effects test when the null hypothesis is true these higher powers give a false impression that this test is performing better than the random effects test. Higher power is to be expected since the nominal significance levels of the fixed effects tests are higher than those of the random effects test.

To examine the power of the random effects tests we report in Table 3 the estimated power of the random effects tests for  $\tau = 0.1$  and  $0.3$  for the gamma, inverse Gaussian, and positive stable frailty models and the fixed effects models. When  $\tau = 0.5$  for the gamma, positive stable random effects models and for the fixed effects model, all tests essentially have a power of 1. From this table we see that the random effects test has good power to detect fixed group effects. The power is quite high for all types of group effects for small associations between individuals within a group when the total sample size is large or the number per group is large. For a given number of groups and a given total sample size the power decreases as the censoring fraction increases.

While the random effects test for group effects has reasonable power to detect these effects a natural question is whether the presence of a group effect has an effect on the estimate of treatment efficacy. To examine this question we studied the relative excess bias in estimating  $\beta$  in a model that ignores the center effect when such an effect exists. We computed for each combination of the total sample size  $N$ , number of groups  $K$ , the degree of association,  $\tau$ , and group effect  $\beta$  the quantity

$$r = \frac{B(0) - B(\tau)}{|B(0)|}, \quad (3)$$

where  $B(\tau)$  is the estimator of the bias of the estimator of  $\beta$  based on a model which ignores the center effect. Here  $B(0)$  is from data simulated from a model with no center effect.

We analysed these data using ANOVA techniques as in Andersen et al. [11]. Separate analyses were made for  $\beta = 0$  and  $\beta = \ln(2)$  and we included the factors  $N * K$ ,  $\tau$ , percent CENSoring, and DISTribution of the center effects since inclusion of more interactions did not improve the fit of the model. That is, the model used for both values of  $\beta$  was

$$E(r) = \alpha + \beta_{N*K} + \gamma_{\tau} + \delta_{\text{CENS}} + \varepsilon_{\text{DIST}}.$$

For  $\beta = 0$  none of these factors had any significant effect on  $r$  which, as one would expect, was small in all cases. For  $\beta = \ln(2)$ ,  $E(r)$  was everywhere larger than for  $\beta = 0$ . That is because under the random effects models and apparently under the constant effects models as well the estimates computed without adjustment for center effects tend to shrink towards zero. Furthermore,  $E(r)$  increased in absolute value as the strength of association,  $\tau$ , increases. Thus the averages over the other factors in the model were  $-17.2$ ,  $-45.2$ , and  $-70.9$  for  $\tau = 0.1$ ,  $0.3$ , and  $0.5$ , respectively. The amount of censoring had no effect and the type of distribution and the number of groups,  $K$ , had little effect on  $r$  whereas  $E(r)$  increased in absolute value when the total sample size,  $N$ , increases, the averages over the other factors in the model being  $-19.3$ ,  $-41.7$ , and  $-72.7$  for  $N = 100$ ,  $200$  and  $400$ , respectively.

This suggests that the estimators computed by ignoring either a fixed or random effect are inconsistent. It implies that the so called marginal approach of Lee et al [12] or Wei et al [13] which computes the estimate of  $\beta$  under an independent working model and uses a robust variance estimator is not appropriate in this problem.

## 5. Example

To illustrate the tests we consider a sample of 609 Acute Myelogenous Leukemia (AML) patients reported to the International Bone Marrow Transplant registry (IBMTR). All patients were given an HLA-identical sibling transplant for the leukemia which was in their first complete remission at the time of transplant. The IBMTR is an international cooperative group which collects data on allogenic transplants conducted world wide. The sample here consists of data reported by the 60 largest reporting centers over the period 1988-1994. Each center contributed at least 5 transplants to the study and had at least one patient relapsing or dying. Table 4 shows the distribution of the number of cases per center.

The goal of the study was to model the relationship between the patient's age (dichotomized as  $\leq 30$  versus  $> 30$ ) and Karnofski score ( $< 90$  versus  $\geq 90$ ) at the time of transplant and treatment failure. The treatment is said to fail if the patient dies or relapses. Ignoring any possible center effects the estimates of the risk coefficients were 0.26 ( $se=0.13$ ,  $p=0.05$ ) for the effect of being over thirty at transplant and 0.32 ( $se=0.17$ ,  $p=0.07$ ) for having a Karnofski score under 90. The four tests for a possible group effect give the following results:

Fixed Effects	
Likelihood ratio Test	$p=0.228$
Score Test	$p=0.008$
Wald Test	$p=0.104$
Random Effects	$p=0.996$

Note that the fixed effects score test suggests the presence of a center effect while the other tests do not show evidence of a center effect. In light of our simulation results which show that the score test rejects too often we conclude that there is no need here to adjust for a center effect. Note that if we had chosen to adjust for a fixed center effect then the estimates for the risk coefficients would be 0.33 ( $se=0.15$ ,  $p=0.024$ ) for age and 0.25 ( $se=0.22$ ,  $p=0.249$ ) for Karnofski score which would lead to somewhat different conclusions than the model without a group effect.

## 6. Discussion

Our Monte Carlo study has shown that the use of a fixed effects model to test for a center effect in a small to moderate size multi-center trial tells us too often that an adjustment for such an effect is needed when in fact there is no such effect. This test requires a large number

of subjects in each center to give significance levels close to the nominal level. The sample sizes needed in each center are much larger than what is commonly encountered in practice. The random effects test of Commenges and Andersen [1] seems to behave quite well under the null hypothesis of center effect even when the number of observations in each group is fairly small and it seems to have reasonable power to detect either a fixed or random group effect.

The random effects test has a few additional advantages over the fixed effects test. First, the estimates of the center effect in the fixed effects proportional regression model requires at least one event for each center. When this does not hold the estimates do not exist. This restriction is not required for the random effects model. Second, when all the events in one center occur before (or after) all the events at an other center then the estimates of that center's fixed effect is at minus infinity (or plus infinity). Again this is not a problem for the random effects test. Finally, the Wald and likelihood ratio tests for fixed effects test requires the maximization of a log likelihood which is a function of  $p + (K - 1)$  parameters, where  $p$  is the number of patient specific covariates. When there is a large number of centers this may be a large number of parameters and numerical problems may occur if good starting values are not used. Note that the random effects test requires maximization with respect to only  $p$  covariates.

When the presence of a center effect is detected then the natural question arises as to how adjust for this effect. As noted earlier some adjustment is needed since the presence of a center effect, either fixed or random, makes the estimators of the risk coefficients computed under an assumption of no center effect inconsistent. The suggestion of Liang et al. [14] to use an independence working model in this case and a robust estimator of the variance of the estimator is not appropriate since the estimators do not seem to be consistent in these cases.

Some model which incorporates the center effect is needed. One possibility is to use the fixed effects model for this adjustment. This model can be fit using standard statistical software. We looked at the relative excess bias (3) of this main effect adjusted for a fixed center effect as compared to the bias under the independence model (data not shown) and in this case, as opposed to the unadjusted relative bias studied above, the relative bias decreased as the sample size increases. This was true, not only when the fixed effects model is correct, but is also true when the random effect model is true. This suggests that this model may provide a quick means of making a crude adjustment for a center effect when the sample sizes are large. A second possibility would be to estimate the treatment effect in a Cox regression model *stratified* by center but then centers with no events would contribute no information to the estimate.

An alternative to using fixed effect models to adjust for a center effect would be to use a frailty model. The technology for fitting a proportional hazards model with a fixed effect can be found in Nielsen et al [8], Klein [6] and Andersen et al [15], for the gamma frailty model and Klein et al [16] for the inverse Gaussian model and Wang et al [17] for the positive stable model.

## Acknowledgements

This research was supported by Grant 5 R01 CA54706-05 from the National Cancer Institute. The activities of the Danish Epidemiology Society are supported by a grant from the Danish National Research Foundation.

## REFERENCES

1. Commenges, D. and Andersen, P. K. (1995). Score Test Of Homogeneity For Survival Data. *Lifetime Data Analysis*, **1**, 145-160.
2. Cox, D. R. (1972). Regression Models And Life-Tables (With Discussion). *Journal Of The Royal Statistical Society B*, **34**, 187-220.
3. Klein, J. P. and Moeschberger, M. L. (1997) *Survival Analysis: Techniques For Censored And Truncated Data*, Springer-Verlag, New York.
4. Andersen, P. K., Borgan, Ø., and Gill, R. D. and Keiding, N. (1993). *Statistical Models Based On Counting Processes*. Springer-Verlag, New York.
5. Clayton, D. G. (1978). A Model For Association In Bivariate Life Tables And Its Application In Epidemiological Studies Of Familial Tendency In Chronic Disease Incidence. *Biometrika*, **65**, 141-151.
6. Vaupel, J. W. , Manton, K.G. and Stallard, E. (1979) The Impact Of Hetrogeneity In Individual Frailty And The Demographics Of Mortality. *Demography* , **16**, 439-454.
7. Klein, J. P. (1992). Semiparametric Estimation Of Random Effects Using The Cox Model Based On The EM Algorithm. *Biometrics*, **48**, 795-806.
8. Nielsen, G. G., Gill, R. D., Andersen, P. K., and Sørensen, T. I. A. (1992). A Counting Process Approach To Maximum Likelihood Estimation In Frailty Models. *Scandinavian Journal Of Statistics* , **19**, 25-43.
9. Micheal, J.R., Schucany, W.R. and Hass, R.W. (1976) Generating Random Variates Using Transformations With Multiple Roots, *The American Statistician* , **30**, 88-90.
10. Chambers, J.M., Mallows, C. L. and Stuck, B.W. (1976) A Method For Simulating Positive Stable Random Variates. *Journal of the American Statistical Association* , **71**, 340-350.
11. Andersen, P.K., Bentzon, M.W., and Klein, J.P. (1996) Estimating The Survival Function In the Proportional Hazards Regression Model: A Study Of The Small Sample Size Properties. *Scandinavian Journal Of Statistics*, **23**, 1-12.
12. Lee, E. W., Wei, L. J., and Amato, D. A. (1992). Cox-Type Regression Analysis For Large Numbers Of Small Groups Of Correlated Failure Time Observations. In J. P. Klein and P. Goel, Editors, *Survival Analysis: State Of The Art*, pp. 237-248. Kluwer Academic Publishers, Boston.
13. Wei, L. J., Lin, D. Y., and Weissfeld, L. (1989). Regression Analysis Of Multivariate Incomplete Failure Time Data By Modeling Marginal Distributions. *Journal Of The American Statistical Association*, **84**, 1065-1073.



14. Liang, K-Y. Self, S.G. and Chang, Y-C (1993) Modelling Marginal Hazards in Multivariate Failure Time Data. *Journal of the Royal Statistical Society* ,B55, 441-453.
15. Andersen, P.K., Klein, J.P., Kunudnsen, K.M. and Tabanera y Palacios, R. Estimation Of Variance In Cox's Regression Model With Gamma Frailties. Technical Report #10, Division of Biostatistics, The Medical College of Wisconsin, 1995.
16. Klein, J. P., Moeschberger, M. L., Li, Y. H. and Wang S.T. (1992). Estimating Random Effects In The Framingham Heart Study. In J. P. Klein and P. Goel, Editors, *Survival Analysis: State Of The Art*, pp. 99-120. Kluwer Academic Publishers, Boston.
17. Wang, S.T., Klein, J. P. and Moeschberger, M. L. (1995). Semi-Parametric Estimation of Covariate Effects Using The Positive Stable Frailty Model. *Applied Stochastic Models and Data Analysis*, 11, 121-133.

**Table 2. Estimated Null Power Of The Fixed and Random Effects Tests**

Total Sample Size	Number of Groups	Percent Deaths	$\beta$	Likelihood Ratio	Random Effects Test
100	5	0.7	0.00	0.0674**	0.0588*
100	5	0.7	0.69	0.0540	0.0538
100	5	0.9	0.00	0.0670**	0.0626**
100	5	0.9	0.69	0.0590*	0.0582*
100	10	0.7	0.00	0.0802**	0.0610**
100	10	0.7	0.69	0.0774**	0.0532
100	10	0.9	0.00	0.0860**	0.0592*
100	10	0.9	0.69	0.0816**	0.0498
100	20	0.7	0.00	0.1592**	0.0590*
100	20	0.7	0.69	0.1486**	0.0526
100	20	0.9	0.00	0.1996**	0.0556
100	20	0.9	0.69	0.1494**	0.0552
200	5	0.7	0.00	0.0590*	0.0608**
200	5	0.7	0.69	0.0566*	0.0564*
200	5	0.9	0.00	0.0640**	0.0556
200	5	0.9	0.69	0.0520	0.0530
200	10	0.7	0.00	0.0704**	0.0572*
200	10	0.7	0.69	0.0600**	0.0568*
200	10	0.9	0.00	0.0690**	0.0508
200	10	0.9	0.69	0.0652**	0.0564*
200	20	0.7	0.00	0.0948**	0.0556
200	20	0.7	0.69	0.0956**	0.0544
200	20	0.9	0.00	0.1032**	0.0578*
200	20	0.9	0.69	0.0926**	0.0508
400	5	0.7	0.00	0.0550	0.0528
400	5	0.7	0.69	0.0508	0.0566*
400	5	0.9	0.00	0.0564*	0.0566*
400	5	0.9	0.69	0.0556	0.0626**
400	10	0.7	0.00	0.0542	0.0556
400	10	0.7	0.69	0.0604**	0.0580*
400	10	0.9	0.00	0.0584*	0.0490
400	10	0.9	0.69	0.0562*	0.0500
400	20	0.7	0.00	0.0670**	0.0462
400	20	0.7	0.69	0.0690**	0.0534
400	20	0.9	0.00	0.0736**	0.0506
400	20	0.9	0.69	0.0668**	0.0470

\*\* - more than 3 SE larger than the nominal level

\* - 2-3 SE larger than the nominal level.

**Table 3. Power Of The Random Effects Test For Group Effects**

<i>N</i>	<i>K</i>	$\beta$	$\tau$	Constant		Gamma		Inverse Gaussian		Positive Stable	
				70% Dead	90% Dead	70% Dead	90% Dead	70% Dead	90% Dead	70% Dead	90% Dead
100	5	0.00	0.1	0.659	0.784	0.538	0.618	0.555	0.644	0.446	0.486
100	5	0.00	0.3	0.995	1.000	0.909	0.942	0.903	0.952	0.891	0.921
100	5	0.69	0.1	0.638	0.767	0.541	0.620	0.542	0.630	0.444	0.477
100	5	0.69	0.3	0.994	1.000	0.903	0.944	0.902	0.953	0.890	0.911
100	10	0.00	0.1	0.495	0.619	0.502	0.619	0.485	0.608	0.454	0.466
100	10	0.00	0.3	0.979	0.996	0.944	0.984	0.948	0.986	0.947	0.963
100	10	0.69	0.1	0.470	0.612	0.495	0.608	0.481	0.598	0.440	0.454
100	10	0.69	0.3	0.972	0.996	0.939	0.979	0.944	0.983	0.943	0.964
100	20	0.00	0.1	0.278	0.386	0.301	0.501	0.297	0.451	0.289	0.303
100	20	0.00	0.3	0.850	0.937	0.839	0.978	0.871	0.977	0.923	0.948
100	20	0.69	0.1	0.271	0.381	0.313	0.492	0.299	0.431	0.272	0.278
100	20	0.69	0.3	0.841	0.938	0.861	0.980	0.881	0.978	0.924	0.942
200	5	0.00	0.1	0.967	0.994	0.784	0.846	0.790	0.853	0.624	0.680
200	5	0.00	0.3	1.000	1.000	0.975	0.986	0.969	0.986	0.960	0.977
200	5	0.69	0.1	0.954	0.987	0.777	0.842	0.778	0.845	0.610	0.661
200	5	0.69	0.3	1.000	1.000	0.971	0.979	0.971	0.987	0.955	0.974
200	10	0.00	0.1	0.902	0.973	0.827	0.894	0.824	0.901	0.689	0.730
200	10	0.00	0.3	1.000	1.000	0.996	0.999	0.995	0.999	0.990	0.997
200	10	0.69	0.1	0.897	0.964	0.814	0.886	0.826	0.895	0.672	0.717
200	10	0.69	0.3	1.000	1.000	0.995	0.998	0.997	0.999	0.991	0.995
200	20	0.00	0.1	0.767	0.875	0.767	0.877	0.776	0.876	0.659	0.696
200	20	0.00	0.3	1.000	1.000	0.997	1.000	0.999	1.000	0.998	0.999
200	20	0.69	0.1	0.741	0.866	0.757	0.871	0.746	0.867	0.651	0.671
200	20	0.69	0.3	1.000	1.000	0.998	1.000	0.998	1.000	0.997	1.000
400	5	0.00	0.1	1.000	1.000	0.920	0.942	0.927	0.952	0.766	0.814
400	5	0.00	0.3	1.000	1.000	0.993	0.996	0.992	0.995	0.987	0.993
400	5	0.69	0.1	1.000	1.000	0.924	0.947	0.920	0.949	0.765	0.809
400	5	0.69	0.3	1.000	1.000	0.993	0.997	0.991	0.996	0.985	0.993
400	10	0.00	0.1	0.999	1.000	0.974	0.990	0.974	0.990	0.861	0.891
400	10	0.00	0.3	1.000	1.000	1.000	1.000	1.000	1.000	0.999	1.000
400	10	0.69	0.1	0.999	1.000	0.964	0.983	0.972	0.988	0.854	0.895
400	10	0.69	0.3	1.000	1.000	1.000	1.000	1.000	1.000	0.999	1.000
400	20	0.00	0.1	0.995	1.000	0.983	0.992	0.983	0.994	0.900	0.924
400	20	0.00	0.3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
400	20	0.69	0.1	0.993	0.999	0.979	0.992	0.979	0.993	0.895	0.921
400	20	0.69	0.3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 4. The Distribution Of The Number Of Cases Per Center

<u>Number Of Cases</u>	<u>Number Of Centers</u>
5	11
6	13
7	7
8	6
10	2
11	5
12	2
13	1
14	1
15	2
17	1
18	1
19	2
20	2
22	1
26	1
28	1
34	1

## Appendix

For the  $j$ th subject  $j = 1, \dots, S_i$  in the  $i$ th group  $i = 1, \dots, n$  let  $T_{ij}$  be the observation time of subject and  $D_{ij} = 1$  if subject died and 0 otherwise. The frailty model (2) proposed in Section 1 can be specified as a counting process  $N_{ij} = I(T_{ij} \leq t, D_{ij} = 1)$  with

$$dN_{ij}(s) = dM_{ij}(s) + Y_{ij}(s) \exp\{\sigma \varepsilon_i + \beta' z_{ij}\} \lambda_0(s) ds,$$

where  $Y_{ij}(s) = I(T_{ij} > s)$ ,  $M_{ij}(\cdot)$  is a martingale,  $\varepsilon_i$ 's are *iid* random variables with an unspecified distribution  $G$  which has mean 0 and variance 1.

Let  $\bar{N} = \sum_{i,j} N_{ij}$ ,  $S^{(0)}(\beta, s) = \sum_{i,j} Y_{ij}(s) \exp(\beta' z_{ij})$ , and  $\hat{\beta}$  be the maximum partial likelihood estimate of  $\beta$  under the null hypothesis of  $\sigma = 0$ . The cumulative baseline hazard function  $\Lambda_0(t) = \int_0^t \lambda_0(s) ds$  can be estimated by

$$\hat{\Lambda}_0(t) = \int_0^t \frac{d\bar{N}(s)}{S^{(0)}(\hat{\beta}, s)}.$$

Then the martingale  $M_{ij}(t)$  can be estimated as

$$\hat{M}_{ij}(t) = N_{ij}(t) - \hat{\Lambda}_{ij}(\hat{\beta}, t),$$

where  $\hat{\Lambda}_{ij}(\beta, t) = \exp(\beta' z_{ij}) \hat{\Lambda}_0(t)$ .

Let  $p_{ij}(\beta, s) = Y_{ij}(s) \exp(\beta' z_{ij}) / S^{(0)}(\beta, s)$  and  $p_i(\beta, s) = \sum_j p_{ij}(\beta, s)$ . To test the hypothesis of homogeneity of  $\sigma = 0$ , the score test statistic is given by

$$T(\hat{\beta}) = \sum_{i=1}^n \left( \sum_{j=1}^{S_i} \hat{M}_{ij}(t) \right)^2 - \bar{N}(\infty) + \int_0^\infty \sum_{i=1}^n p_i^2(\hat{\beta}, s) d\bar{N}(s).$$

Let  $H_i(\beta, s) = 2 \left\{ \hat{M}_i(s) - \sum_{l=1}^n \hat{M}_l(s-) p_l(\beta, s) - p_i(\beta, s) + \sum_{l=1}^n p_l^2(\beta, s) \right\}$ , where  $\hat{M}_i(s) = \sum_j \hat{M}_{ij}(s)$ . The variance of  $T(\hat{\beta})$  can be consistently estimated by

$$\hat{I}_c = \hat{I}(\hat{\beta}) - \hat{J}(\hat{\beta}) I_{\hat{\beta}}^{-1} \hat{J}(\hat{\beta})',$$

where  $I_{\hat{\beta}}^{-1}$  is the information matrix relative to  $\hat{\beta}$ ,

$$\hat{I}(\beta) = \sum_{i=1}^n \int_0^\infty H_i^2(\beta, s) p_i(\beta, s) d\bar{N}(s), \text{ and}$$

$$\hat{J}(\beta) = \sum_{i=1}^n \int_0^\infty H_i(\beta, s) \sum_{j=1}^{S_i} z_{ij} p_{ij}(\beta, s) d\bar{N}(s).$$

Then the test statistic for homogeneity is  $H = T(\hat{\beta}) / \sqrt{\hat{I}_c}$  which has an asymptotic standard normal distribution under the null hypothesis.

**MODELING COVARIATE ADJUSTED  
MORTALITY RELATIVE TO A STANDARD  
POPULATION: DOES BONE MARROW  
TRANSPLANTATION PROVIDE A CURE?**

Per Kragh Andersen, Mary M. Horowitz,  
John P. Klein, Gerard Socie,  
Judith Veum Stone and Mei-Jie Zhang

**DIVISION OF BIostatISTICS**



**MEDICAL  
COLLEGE  
OF WISCONSIN**

**MILWAUKEE, WISCONSIN**

**MODELING COVARIATE ADJUSTED  
MORTALITY RELATIVE TO A STANDARD  
POPULATION: DOES BONE MARROW  
TRANSPLANTATION PROVIDE A CURE?**

Per Kragh Andersen, Mary M. Horowitz,  
John P. Klein, Gerard Socie,  
Judith Veum Stone and Mei-Jie Zhang

Technical Report 30

June 1998

Division of Biostatistics  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee WI 53226  
Phone: (414)456-8280

# MODELING COVARIATE ADJUSTED MORTALITY RELATIVE TO A STANDARD POPULATION: DOES BONE MARROW TRANSPLANTATION PROVIDE A CURE?

Per Kragh Andersen<sup>1</sup>, Mary M. Horowitz<sup>2</sup>, John P. Klein<sup>2,3</sup>, Gerard Socie<sup>4</sup>,  
Judith Veum Stone<sup>2</sup> and Mei-Jie Zhang<sup>2,3,\*</sup>

<sup>1</sup>Department of Biostatistics, The University of Copenhagen

<sup>2</sup>International Bone Marrow Transplant Registry, The Medical College of Wisconsin, Milwaukee, WI 53226

<sup>3</sup>Division of Biostatistics, The Medical College of Wisconsin, Milwaukee, WI 53226

<sup>4</sup>Service d'Hematologie, Greffe de Moelle, Hopital Sainte Louis, Paris France

\* The corresponding author

## SUMMARY

A study of long term survival of 1,487 patients given an allogenic bone marrow transplant for acute myelogenous leukemia and 729 patients given a transplant for severe aplastic anemia was conducted by the International Bone Marrow Transplant registry. One aim of this study is to determine if the mortality rates of these patients returns after some period of time to the same mortality rate as in the general population. To examine this question a model for the relative mortality of a bone marrow transplant patient relative to a matched individual in the general population is presented. This model allows for different relative mortality rates depending on the risk factors the patient may have. We discuss an estimation procedure for this model and construct a test that the mortality rate in the transplanted population is the same as in the reference population over a given time interval.

## 1 Introduction

Allogenic bone marrow transplantation has been a common treatment for leukemia, aplastic anemia and genetic disorders. In the past twenty years the number of patients treated by means of this therapy has greatly increased<sup>1</sup> so that now this is a standard treatment for patients with acute myelogenous leukemia (AML)<sup>2</sup> and severe aplastic anemia (SAA)<sup>3</sup>. While the short term effects of this treatment modality have been studied extensively, with few exceptions<sup>4</sup> there has been little study of the long term effects on patient survival.

Numerous studies have been conducted to determine risk factors for bone marrow transplants. These studies have focused on making comparisons between bone marrow transplantation patients or on comparisons of the effectiveness of transplantation therapy to



chemotherapy. These studies, based on a Cox regression model<sup>5</sup>, provide relative risk estimates of treatment modalities or prognostic indications. All estimates are relative to other patients with the disease.

With increasing follow-up of transplant patients it is natural to ask if bone marrow transplant in fact "cures" all patients or some subgroup of patients. Here, by "cured" we mean the patient's mortality rate has returned to the same mortality rate as one would expect in a person of the same age and gender in the general population. While it is not reasonable to expect a return to the standard mortality rate of the general population immediately after transplant, it is possible that after some time the excess mortality directly related to the therapy may have washed out. Of interest is the estimation of this time of "cure" or the testing at a fixed time point to determine if the patient has been cured. It is also highly likely that this cure time may depend on some risk factors either known at the time of transplantation or by some point in time in the patients post transplant recovery process.

Twenty-five years ago the International Bone Marrow Transplant Registry (IBMTR) was found with the goal of collecting data on consecutive allogeneic marrow transplants from member centers<sup>6</sup>. The IBMTR is a volunteer organization of 406 transplant teams worldwide that report all their consecutive cases to a central statistical center. Approximately 40% of the allogeneic transplants performed are reported to the Registry. Extensive data on patient risk factors is collected at the time of transplantation on most patients and patient follow-up information is obtained every six months.

In this note we shall present a model for the excess relative mortality due to transplantation in a group of 1,487 AML and 729 SAA patients from 14 countries. All patients included in the sample were alive and free of their primary disease at two years post transplant, so that all deaths observed in the sample are from causes not related to the short term toxicity of the transplant itself. All patients were transplanted between 1980 and 1993. This is a subsample of a larger sample previously reported<sup>4</sup> on which we were able to obtain current published life table information. Table 1 shows the distribution of the number of cases by the country where the patient was transplanted. Standard mortality tables were obtained for these countries by sex and for the US by sex and race (black versus non-black).

Of the 1,487 AML patients 160 died, while 34 of the 729 SAA patients died. For the AML patients the median follow-up was 6.2 years with a range of 2-16.7 years. For the aplastic anemia patients the median follow-up time was 6.7 years with a range of 2-16.8 years. The median age of the AML patients at the time of transplantation was 22.4 years (range 0.5-56.6 years) and was 18.8 years (range 0.2-69.4 years) for SAA patients.

There are a number of factors that have been shown to be predictive of survival following a transplant. One important factor is the development of graft-versus-host disease (GVHD). Two types of GVHD can occur, acute GVHD which occurs in the first 100 days post transplant and chronic GVHD which occurs after 100 days. We include as risk factors for survival a binary indicator of whether the patient had acute GVHD, an indicator of whether a patient had chronic GVHD prior to two years that was still active at two years, and indicator of whether a patient had chronic GVHD prior to two years that was resolved at two years. Age of the patient at the time of transplantation has been found to be associated with survival

in transplant studies using the Cox model. While we shall be making an adjustment for age by using the age specific survival rates from published life tables, it is still of interest to see if young patients have a different "cure" rate than older patients. We divided the patients into three age groups: children (age  $\leq 16$  years), young patients (16-25 years) and older patients ( $> 25$  years). A final covariate to be considered is the stage of the disease at the time of transplantation. For AML patients we classify patients as having early (transplanted in first complete remission), intermediate (transplanted in a second or later complete remission) or advanced (transplanted in relapse) disease. For SAA patients patients are classified as having earlier disease (time from diagnosis to transplant less than one year) or advanced disease (time from diagnosis to transplant more than one year). Table 2 summarizes the covariates for the two diseases.

To examine the effects of these covariates on survival the standard Cox regression model was fit to the data. For this model the hazard rate of an individual with covariate vector  $\mathbf{Z}$  is of the form

$$h(t|\mathbf{Z}) = h_0(t) \exp\{\boldsymbol{\gamma}^t \mathbf{Z}\}, \quad (1.1)$$

where  $\boldsymbol{\gamma}$  is the vector of covariates and  $h_0(t)$  is a baseline hazard rate. Here the risk coefficients,  $\boldsymbol{\gamma}$ , provide information on the relative effects of the covariates on survival among transplant patients and  $h_0(t)$  is the death rate for, in our example, a child transplant patient with early disease who has had neither type of GVHD. The results of fitting the standard Cox model are given in Table 3. These results show that for AML transplant patients, those with active chronic GVHD and intermediate or advanced disease tend to have lower survival, relative to other AML transplant patients. For SAA patients those with either acute GVHD or active chronic GVHD and advanced disease, tend to have lower survival, relative to other SAA transplant patients.

In the next section we present a model for the survival of bone marrow transplant patients relative to the survival rates in the general population. The estimated relative mortality is allowed to be effected by a patient's risk factors at the time of transplant. We develop a test of the hypothesis that the relative mortality is equal to one over a given time interval. This is a test that the mortality rate in the treated population over this interval is the same as that in the general population. In Section 3 we return to the example to determine at various times after transplant if a patient with a certain set of covariates has a mortality rate which has returned to normal.

## 2 A Model for Excess Relative Mortality

For each patient we assume that the mortality rate of a patient of the same age and sex (and possibly race) is known. At a time,  $t$ , after transplant let  $\mu_i(t)$  be the standard mortality rate of the patient in the general population. Note that if the patient were transplanted at age  $a$ , then  $\mu_i(u)$  is the mortality rate in the general population of a patient of age  $a + u$ . For the  $i$ th patient we have covariates  $\mathbf{Z}_i = (Z_{i1}, \dots, Z_{ip})^t$ .

The death rate of the  $i$ th patient at  $t$  years post transplant is modeled as:

$$\lambda_i(t|\mathbf{Z}_i) = \alpha_0(t)\mu_i(t) \exp\{\beta^t \mathbf{Z}_i\}, \quad (2.2)$$

where  $\alpha_0(t)$  is a baseline relative mortality due to transplantation and  $\beta^t = (\beta_1, \dots, \beta_p)$  is a  $p$ -vector of covariate to be estimated from the data. Note that this model is of the form of the usual proportional hazards regression model with the inclusion of a time dependent covariate,  $\ln[\mu_i(t)]$  with a regression parameter constrained to be one.

Model (2.2) was originally proposed by Andersen et al<sup>7</sup> as a model for relative mortality. When  $\alpha_0(t)$  is fixed at one this is the model of Breslow et al<sup>8</sup>. When there are no covariates this is the model of Andersen and Væth<sup>9</sup>.

To estimate parameters of the model, let  $T_i$  be the on study time and  $\delta_i$  be the death indicator ( $\delta_i = 1$  if  $T_i$  is a death, 0 otherwise) for the  $i$ th patient. Define the counting process  $N_i(t) = I\{T_i \leq t, \delta_i = 1\}$  and  $Y_i(t) = I\{T_i \geq t\}$ , where  $I\{\cdot\}$  is the indicator function. Let  $\bar{N}(t) = \sum_i N_i(u)$ ,  $S_0(t, \beta) = \sum_i Y_i(t)\mu_i(t) \exp\{\beta^t \mathbf{Z}_i\}$ . Define the  $p$ -vector  $\mathbf{S}_1(t, \beta) = \sum_i \mathbf{Z}_i Y_i(t)\mu_i(t) \exp\{\beta^t \mathbf{Z}_i\}$  and the  $p \times p$  matrix  $\mathbf{S}_2(t, \beta) = \sum_i \mathbf{Z}_i \mathbf{Z}_i^t Y_i(t)\mu_i(t) \exp\{\beta^t \mathbf{Z}_i\}$ . Using standard counting process techniques<sup>10</sup> the log partial likelihood is

$$L(\beta) = \sum_i \int_0^T \beta^t \mathbf{Z}_i dN_i(u) - \int_0^T \ln\{S_0(u, \beta)\} d\bar{N}(u), \quad (2.3)$$

where  $T$  is the maximum on study time. The maximum partial likelihood estimators of  $\beta$  are found by solving the score equations

$$\mathbf{U}(\beta, T) = \sum_i \int_0^T dN_i(u) - \int_0^T \frac{\mathbf{S}_1(u, \beta)}{S_0(u, \beta)} d\bar{N}(u) = 0, \quad (2.4)$$

and information matrix is given by

$$\mathbf{I}(\beta, T) = \int_0^T \left\{ \frac{\mathbf{S}_2(u, \beta)}{S_0(u, \beta)} - \left[ \frac{\mathbf{S}_1(u, \beta)}{S_0(u, \beta)} \right]^2 \right\} d\bar{N}(u). \quad (2.5)$$

The estimated covariance matrix of the  $\hat{\beta}$ 's is given by  $\hat{\Sigma} = \mathbf{I}(\hat{\beta}, T)^{-1}$ .

The cumulative relative mortality due to transplantation, for an individual with a covariate vector  $\mathbf{Z}_0$ , over the interval  $[s, t]$  is given by

$$A(s, t, \mathbf{Z}_0) = A_0(s, t) \exp\{\beta^t \mathbf{Z}_0\}, \quad (2.6)$$

where

$$A_0(s, t) = \int_s^t \alpha_0(u) du. \quad (2.7)$$

The quantity  $A_0(s, t)$  can be estimated consistently by

$$\hat{A}_0(s, t) = \int_s^t \frac{d\bar{N}(u)}{S_0(u, \hat{\beta})}. \quad (2.8)$$

Applying Andersen et al<sup>10</sup> Corollary VII.2.6. with  $Y_i(t)$  replaced by  $Y_i(t)\mu_i(t)$ , it can be shown that a consistent estimator for the variance of  $\hat{A}(s, t, \mathbf{Z}_0) = \hat{A}_0(s, t) \exp\{\hat{\beta}_t \mathbf{Z}_0\}$  is given by

$$Var [\hat{A}(s, t, \mathbf{Z}_0)] = \left[ \exp\{\hat{\beta}_t \mathbf{Z}_0\} \right]^2 \left\{ \int_s^t \frac{d\bar{N}(u)}{S_0(u, \hat{\beta})^2} + \hat{\mathbf{W}}^t \hat{\Sigma} \hat{\mathbf{W}} \right\}, \quad (2.9)$$

where

$$\hat{\mathbf{W}} = \int_s^t \left\{ \frac{\mathbf{S}_1(u, \hat{\beta})}{S_0(u, \hat{\beta})} - \mathbf{Z}_0 \right\} \frac{d\bar{N}(u)}{S_0(u, \hat{\beta})}. \quad (2.10)$$

Using  $\hat{A}(s, t, \mathbf{Z}_0)$  and  $Var[\hat{A}(s, t, \mathbf{Z}_0)]$  we may test the hypothesis that the mortality rate for an individual with a set of covariates,  $\mathbf{Z}_0$ , is the same as in the general population over the interval  $[s, t]$ . If the mortality rates are equal over the interval then  $\alpha_0(u)e^{\beta^t \mathbf{Z}_0} = 1$ , for all  $u \in [s, t]$  and  $A(s, t, \mathbf{Z}_0) = (t - s)$ . The test statistic is given by

$$Q(s, t) = \frac{\hat{A}(s, t, \mathbf{Z}_0) - (t - s)}{Var[\hat{A}(s, t, \mathbf{Z}_0)]^{1/2}} \quad (2.11)$$

which has a large sample standard normal distribution when the null hypothesis is true. Large positive values of  $Q(s, t)$  favor the alternative hypothesis (since relative rates lower than one are not biologically feasible) so that the null hypothesis is rejected when  $Q(s, t)$  is larger than the appropriate upper percentile of a standard normal.

### 3 Estimates of Relative Mortality for BMT Patients

To apply the inference procedure discussed in the previous Section to BMT patients with AML or SAA we first need to obtain the population mortality rates,  $\mu_i(\cdot)$ , for each patient. To obtain these rates we asked IBMTR team members in each of the countries listed in Table 1 to provide us with population mortality data. For all countries, except the United Kingdom, this information came to us in the form of a life table. For the UK population death rates, by sex, for the year 1991 were obtained directly from the Office of Population Census and Surveys. Unabridged life table estimates of the population survival probabilities by sex were obtained from government sources for the 1992 Australian, 1988 Brazilian, 1985-7 Canadian, 1986-1990 Danish, 1992 Japanese, 1985-6 Spanish, 1991 Swedish and 1989 American (by race) survival. These provide the values of the population survival rate,  $S(x)$ , for ages  $x = 0, 1, 2, \dots$ . For the Netherlands, based on the 1980-4 life table, estimates of  $S(x)$  were available at ages 0.5, 1.5, 2.5,  $\dots$  years. Estimates for other countries were from abridged tables. For the 1986-7 German (FRG) life table, estimates of  $S(x)$  were available for  $x = 0, 1, 2, 5, 10, \dots$ . For Italy (1985 table) and Portugal (1991 tables), estimates were available at  $x = 0, 1, 5, 10, \dots$ .

From these tables we compute the population mortality rate,  $\lambda(a)$ , at age  $a$  by assuming a constant mortality over the interval reported in the population life table. Under this assumption for an unabridged life table we have

$$\lambda(a) = -\ln[S(x+1)] - (-\ln[S(x)]), \quad \text{for } x \leq a < x+1,$$

while for a table with five year intervals we compute

$$\lambda(a) = -\ln[S(x+5)] - (-\ln[S(x)])/5, \quad \text{for } x \leq a < x+1.$$

Once the population mortality rates are computed the value of  $\mu_i(t)$  for a patient of age  $a_i$  at transplant is given by  $\lambda(a_i + t)$ , where  $\lambda(\cdot)$  is from the proper age (race) and sex matched population. Using these population rates we obtain the estimates of the relative mortality risk coefficients by maximizing (2.3). The estimates are given in Table 4.

An examination of Table 4 shows that there is a significant effect of age on the relative mortality rate. Patients who are younger are dying at a faster rate than older patients relative to the age matched mortality rates in the general population. Note that in the standard Cox model (Table 2), where comparisons are between transplanted patients, there is no age effect for either disease. If there is no effect of age on transplant outcomes then the finding of an age effect in the relative mortality model is not surprising since younger patients have a lower population mortality rate. For both diseases the estimates of the effects of the other covariates are similar in the Cox model and the relative mortality model.

In Figures 1 and 2 we plot a smoothed estimate of the relative mortality rate,  $\hat{\lambda}_0(t) \exp(\hat{\beta}Z_0)$  for an AML and SAA patient in each of the three age groups. The plots are for patients who had not had graft-versus-host disease and were in the early disease state. These estimates were obtained by smoothing the estimates of  $A(0, t, Z_0)$  using an Epanechnikov kernel smoothing routine with a bandwidth of 2 years (See Gasser and Müller<sup>11</sup> (1979)). From these figures it appears that for young AML patients there is little evidence of a "cure", while for older patients there is some evidence that after about 10 years after transplantation the risk of death may have returned to the baseline population mortality rate. For young SAA patients it appears that their mortality rates are similar to those in the general population after about six years, while older SAA patients appear to have the same mortality rate at two years after transplant.

The above observations can be confirmed using the test described in the previous Section. To perform the test we set  $t$  equal to 12.6 years after transplant for AML and 12.4 years for SAA patients. These values were the times at which the last event occurred in the respective samples. For AML patients we test at  $s = 8$  and 10 years if the mortality rate is the same for an AML patient as in the general population over the period  $[s, t]$  using (2.10) for selected values of the covariates. The results are in Table 5. From this table we see that with the exception of old patients with early disease or old patients with no chronic GVHD and advanced disease the test rejects the hypothesis that the mortality rate has returned to normal over the period 8-12.6 years. For all patients over the interval 10-12.6 years there is no evidence that the mortality rate is different from the reference population.

For SAA patients the results presented in Table 6 show a different pattern. Here it appears that for patients over age 16 with no adverse risk factors the mortality rate is the same as in the general population after two years post transplant. For patient over age 25 with a single risk factor (active GVHD, prior history of acute GVHD or late disease) their rate is the same as in the general population after 4 years, while if they have 2 or more risk factors the death rate is the same after 6 years. For young patients there is no difference between their mortality and the reference rates after 6 years if they have one of the risk factors present.

## 4 Discussion

The techniques discussed here for estimation of the relative mortality rate are simple extensions of the Cox proportional hazards model. They are extended to include left truncated data by a simple redefinition of the risk set. The assumption of a proportional effect of the covariates on the relative mortality can be tested by using a time dependent covariate approach as in the usual proportional hazards regression model.

The test statistic (2.11) has little power to detect a relative mortality rate which crosses one over the interval  $[s, t]$ . While it is mathematically possible that  $\int_s^t \alpha_0(u) e^{\beta^t \mathbf{Z}_0} du = (t-s)$  and  $\alpha_0(u) e^{\beta^t \mathbf{Z}_0} \neq 1$  for all  $u \in [s, t]$ , this would require that treated patients have a lower mortality rate than matched individuals in the general population. In most situations this is not biologically plausible.

As noted earlier these models have been suggested by other authors and estimates of  $A(s, t, \mathbf{Z}_0)$  are found in these papers. For this statistic the calculation of the variance of the estimator, requires some care since the estimator of  $A(s, t, \mathbf{Z}_0)$  does not have independent increments.

In looking at the results in Tables 5 and 6 there is an obvious multiple testing problem in performing tests at different time points and at multiple covariate values. One could argue that some type of a corrected significance level should be used to make the comparisons of interest. We choose not to do so since our goal is to provide the investigator with only a crude notion of when the patients mortality rate has returned to normal and the p-values computed serve as measures of evidence against this hypothesis.

The ability to determine whether and when the mortality rate of a transplant recipients returns to that of a normal population is important for several reasons. First, it can help guide strategies for long-term medical follow-up of transplant recipients. Patient groups with persistently high mortality rates relative to the general population can be targeted for more frequent or intensive surveillance and study. Second, patients whose risk is similar to that of the general population can be reassured. This reassurance can significantly improve the quality of life for the transplant survivor. Finally, the convincing demonstration of risks similar to the general population may allow transplant survivors to obtain life and health

insurance. This is currently a difficult and serious problem facing many transplant survivors.

## Acknowledgements

Professors Andersen, Klein and Zhang's research was supported by Grant R01-CA54706-04 from the National Cancer Institute. The activities of the IBMTR are supported by Public Health Service Grant P01-CA40053.

## References

1. Horowitz, MM and Rowlings PA. "An update from the International Bone Marrow Transplant Registry and The Autologous Blood and Marrow Transplant Registry on current activity in hematopoietic stem cell transplantation", *Current opin hematol*, **4**, 395-400 (1997).
2. Zittoun RA, Mandelli F, Willemze, R. et al. "Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia", *New England Journal of Medicine*, **332**, 217-223 (1995).
3. Passweg JR, Socie G, Hinterberger W, et al. "Bone marrow transplantation for severe aplastic anemia: has outcome improved?", *Blood*, **90**, 858-864 (1997).
4. Socie, G. Stone, JMV, Wingard, JR et al. "Long-term survival and late deaths after allogeneic bone marrow transplantation: Implications for cure". Under Review.
5. Cox, D. R. "Regression models and life-tables (With discussion)", *Journal Of The Royal Statistical Society B*, **34**: 187-220 (1972).
6. Horowitz, MM and Bortin MM. "The role of registries in evaluating the results of bone marrow transplanation", In Treleaven J, Barrett J (eds): *Bone Marrow Transplantation in Practice*. Churchill Livingstone, Edinbuh, UK, pp 367-377, 1992.
7. Andersen, PK, Borch-Johnsen, K, Deckert, T, Green, A, Hougaard, P, Keiding, N and Kreiner, S. "A Cox regression model for the relative mortality and its application to diabetes mellitus survival data", *Biometrics*, **41**, 921-932 (1985).
8. Breslow, N, Lubin, P, Marek, P and Langholz, B. "Multiplicative models and cohort analysis", *Journal of the American Statistical Association*, **78**: 1-12 (1983).
9. Andersen, P. K. and Væth, M. "Simple parametric and nonparametric models For excess and relative mortality", *Biometrics*, **45**, 523-535 (1989).
10. Andersen, P. K., Borgan, Ø., and Gill, R. D. and Keiding, N. *Statistical Models Based On Counting Processes*, Springer-Verlag, New York, 1993.
11. Gasser, T. and Müller, H. G. "Kernel estimation of regression functions". In *Smoothing Techniques For Curve Estimation, Lecture Notes In Mathematics*, **757**, 23-68. Springer-Verlag, Berlin, (1979).

Table 1. Country Of Transplant For Study Patients

COUNTRY	SEX/RACE	AML	SAA
AUSTRALIA	MALE	67	28
	FEMALE	57	20
	TOTAL	124	48
BRAZIL	MALE	15	81
	FEMALE	12	42
	TOTAL	27	123
CANADA	MALE	60	31
	FEMALE	50	12
	TOTAL	110	43
DENMARK	MALE	11	9
	FEMALE	13	4
	TOTAL	24	13
ENGLAND (UK)	MALE	99	37
	FEMALE	88	26
	TOTAL	187	63
GERMANY	MALE	68	33
	FEMALE	62	22
	TOTAL	130	55
ITALY	MALE	53	18
	FEMALE	51	11
	TOTAL	104	29
JAPAN	MALE	18	15
	FEMALE	23	9
	TOTAL	41	24
NETHERLANDS	MALE	41	8
	FEMALE	35	6
	TOTAL	76	14
PORTUGAL	MALE	5	6
	FEMALE	5	1
	TOTAL	10	7
SPAIN	MALE	53	44
	FEMALE	52	25
	TOTAL	105	69
SWEDEN	MALE	27	14
	FEMALE	28	3
	TOTAL	55	17
USA	MALE/BLACK	8	14
	FEMALE/BLACK	13	7
	MALE/NON BLACK	232	119
	FEMALE/NON BLACK	241	84
	TOTAL	494	224
	TOTAL	1487	729



Table 2. Frequencies of Covariates

COVARIATE	AML	SAA
Acute GVHD		
Yes	368 (24.7%)	145 (19.9%)
None	1119 (75.3%)	584 (80.1%)
Chronic Gvhd		
None	875 (58.8%)	465 (63.8%)
Resolved By 2 Years	236 (15.9%)	81 (11.1%)
Active At 2 Years	376 (25.3%)	183 (25.1%)
Age		
<16 Years	332 (22.4%)	284 (39.0%)
16-25 Years	350 (23.5%)	251 (34.4%)
>25 Years	805 (54.1%)	194 (26.6%)
Disease Stage		
Early	1132 (75.1%)	
Intermediate	162 (10.9%)	642 (88.1%)
Advanced	193 (13.0%)	87 (11.9%)

**Table 3. Results Of Standard Cox Regression Analysis**

Risk Factor	AML			SAA		
	$\hat{\beta}$	SE	<i>p</i>	$\hat{\beta}$	SE	<i>p</i>
Acute GVHD						
Yes	0.270	0.176	0.125	1.029	0.349	0.003
Chronic GVHD			0.0868 <sup>1</sup>			0.001 <sup>1</sup>
Resolved	0.295	0.224	0.188	0.592	0.616	0.337
Active	0.398	0.185	0.032	1.468	0.408	>0.001
Age			0.0834 <sup>1</sup>			0.958 <sup>1</sup>
16-25	0.141	0.260	0.588	-0.084	0.395	0.831
>25	0.438	0.224	0.050	0.032	0.424	0.940
Disease Stage			< 0.001 <sup>1</sup>			
Intermediate	0.607	0.224	0.007			
Advanced	0.647	0.200	0.001	1.117	0.380	0.003

1. Two degree of freedom Wald test of effect of factor on survival.

**Table 4. Results Of Relative Mortality Regression Analysis**

Risk Factor	AML			SAA		
	$\hat{\beta}$	SE	<i>p</i>	$\hat{\beta}$	SE	<i>p</i>
Acute GVHD						
Yes	0.241	0.175	0.170	1.351	0.396	<0.001
Chronic GVHD			0.0678 <sup>1</sup>			.003 <sup>1</sup>
Resolved	0.300	0.225	0.182	0.468	0.626	0.454
Active	0.414	0.183	0.023	1.344	0.407	0.001
Age			<0.001 <sup>1</sup>			<0.001 <sup>1</sup>
16-25	-0.716	0.260	0.006	-0.863	0.395	0.029
>25	-1.339	0.224	<0.001	-1.614	0.426	<0.001
Disease Stage			0.003 <sup>1</sup>			
Intermediate	0.666	0.224	0.003			
Advanced	0.463	0.201	0.021	1.168	0.360	0.001

1. Two degree of freedom Wald test of effect of factor on survival.

**Table 5. p-Values Of The Test That The Mortality Rate For A Transplanted Patient Is The Same As In The General Population Over The Interval [s,12.6] For An AML Patient Without Acute GVHD**

Age	Chronic GVHD	Disease stage	p-value when s=8	p-value when s=10
<16	None	Early	0.0118	0.2594
16-25	None	Early	0.0370	0.3917
>25	None	Early	0.1631	0.6360
<16	Active	Early	0.0078	0.2222
16-25	Active	Early	0.0177	0.3016
>25	Active	Early	0.0581	0.4570
<16	None	Intermediate	0.0064	0.2070
16-25	None	Intermediate	0.0125	0.2655
>25	None	Intermediate	0.0338	0.3796
<16	Active	Intermediate	0.0051	0.1899
16-25	Active	Intermediate	0.0081	0.2259
>25	Active	Intermediate	0.0116	0.2943
<16	None	Advanced	0.0075	0.2188
16-25	None	Advanced	0.0165	0.2935
>25	None	Advanced	0.0519	0.4399
<16	Active	Advanced	0.0057	0.1973
16-25	Active	Advanced	0.0098	0.2428
>25	Active	Advanced	0.0229	0.3306

**Table 6. p-Values Of The Test That The Mortality Rate For A Transplanted Patient Is The Same As In The General Population Over The Interval [s,12.4] For An Aplastic Anemia Patient**

Age	Chronic GVHD	Disease State	Acute GVHD	p-value when s=2	p-value when s=4	p-value when s=6	p-value when s=8
<16	None	Early	No	0.0011	0.0843	0.3641	0.4244
16-25	None	Early	No	0.1561	0.7968	0.9534	0.9207
>25	None	Early	No	0.9985	1.0000	1.0000	1.0000
<16	Active	Early	No	<0.0001	0.0051	0.0749	0.1459
16-25	Active	Early	No	0.0001	0.0232	0.1810	0.2623
>25	Active	Early	No	0.0048	0.1910	0.5454	0.5691
<16	None	Late	No	<0.0001	0.0064	0.0859	0.1597
16-25	None	Late	No	0.0003	0.0359	0.2308	0.3093
>25	None	Late	No	0.0133	0.3195	0.6865	0.6800
<16	Active	Late	No	<0.0001	0.0021	0.0440	0.1031
16-25	Active	Late	No	<0.0001	0.0037	0.0615	0.1283
>25	Active	Late	No	<0.0001	0.0099	0.1107	0.1888
<16	None	Early	Yes	0.0039	0.0234	0.0982	0.1610
16-25	None	Early	Yes	0.0102	0.0610	0.2054	0.2736
>25	None	Early	Yes	0.0481	0.2453	0.5350	0.5602
<16	Active	Early	Yes	0.0023	0.0130	0.0611	0.1151
16-25	Active	Early	Yes	0.0030	0.0174	0.0774	0.1360
>25	Active	Early	Yes	0.0049	0.0296	0.1180	0.1836
<16	None	Late	Yes	0.0023	0.0135	0.0632	0.1178
16-25	None	Late	Yes	0.0032	0.0191	0.0835	0.1434
>25	None	Late	Yes	0.0059	0.0354	0.1359	0.2031
<16	Active	Late	Yes	0.0020	0.0112	0.0540	0.1055
16-25	Active	Late	Yes	0.0021	0.0123	0.0583	0.1113
>25	Active	Late	Yes	0.0025	0.0147	0.0675	0.1234

# Relative Mortality For AML Patients

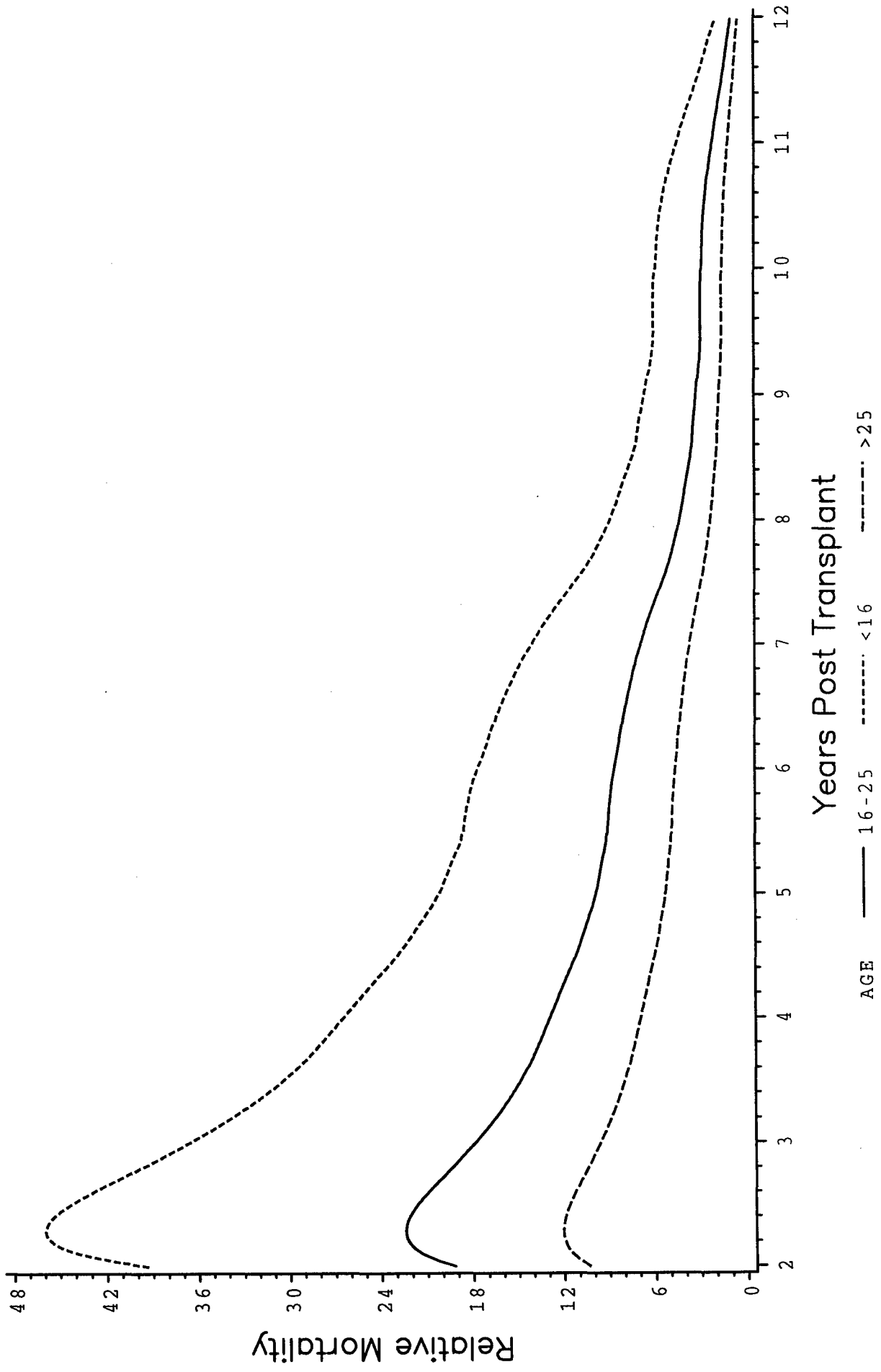


Figure 1

# Relative Mortality For Aplastic Anemia Patients

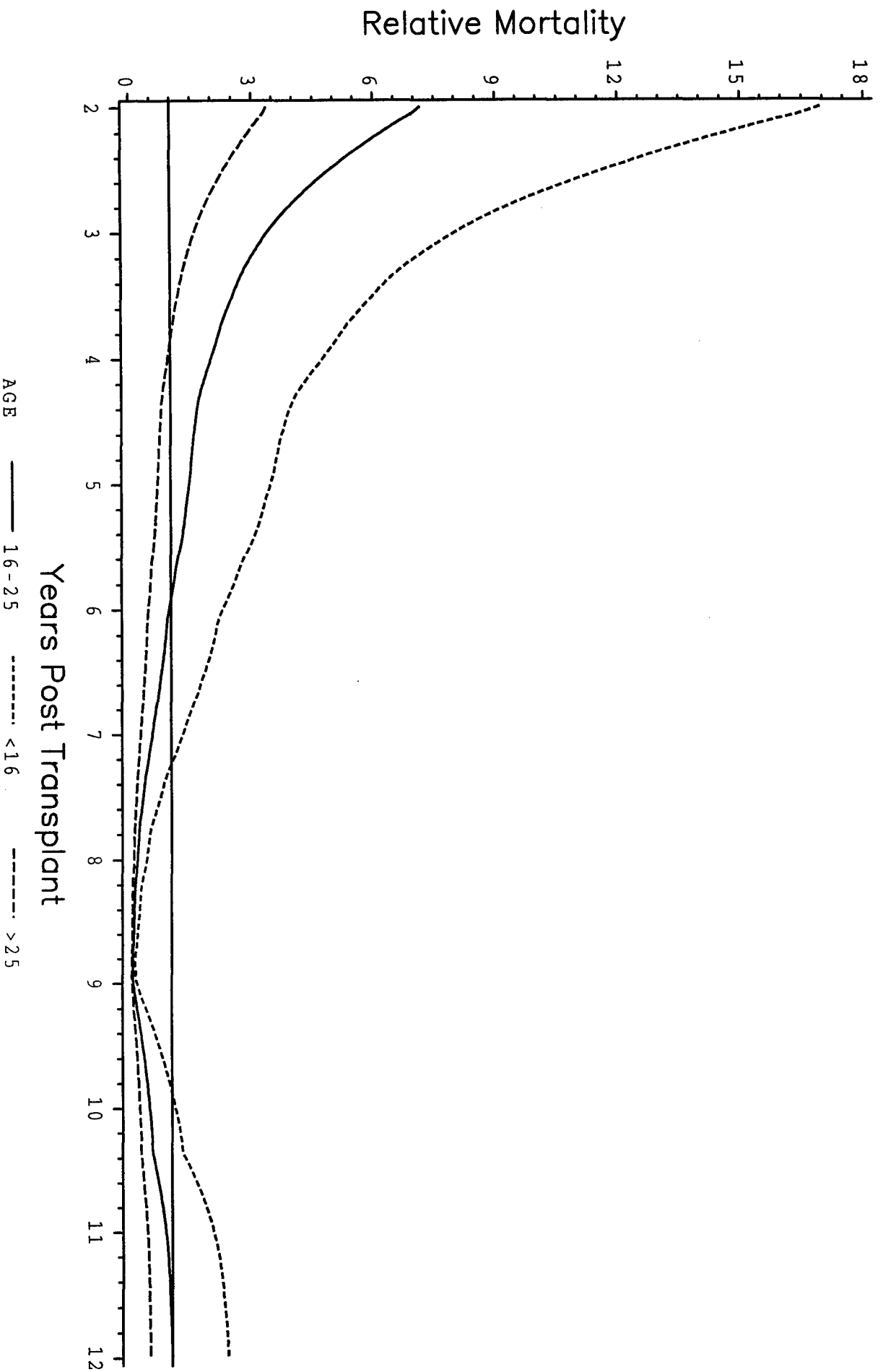


Figure 2

**DETERMINING WHEN THE SURVIVAL RATES  
OF TWO TREATMENTS ARE THE SAME  
BASED ON A CENSORED DATA  
REGRESSION MODEL**

John Klein, Ph.D.  
Mei-Jie Zhang, Ph.D.

**DIVISION OF BIOSTATISTICS**



**MEDICAL  
COLLEGE  
OF WISCONSIN**

**MILWAUKEE, WISCONSIN**



**DETERMINING WHEN THE SURVIVAL RATES  
OF TWO TREATMENTS ARE THE SAME  
BASED ON A CENSORED DATA  
REGRESSION MODEL**

John Klein, Ph.D.  
Mei-Jie Zhang, Ph.D.

Technical Report 21

December 1996

Division of Biostatistics  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee WI 53226  
Phone: (414) 456-8280

# Determining When The Survival Rates Of Two Treatments Are The Same Based On A Censored Data Regression Model

John P. Klein and Mei-Jie Zhang  
Division of Biostatistics  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee, WI 53226

## Abstract

Often when comparing the survival rates of individuals given either of two treatments the analysis stops with a test of the hypothesis of no treatment difference and perhaps a plot of the two survival functions. The hypothesis test is usually a comparison of the two survival curves over the entire observational period. An alternative approach to this problem is to provide an investigator with a confidence set for the set of times at which the survival rates of the two treatments are the same. We discuss how such confidence sets can be constructed when the proportional hazards or additive regression model is used to adjust the comparison of interest for other factors which may influence survival. These approaches are illustrated on retrospective data gathered to compare the survival rates of allogeneic and autologous bone marrow transplants for acute leukemia.

## 1 Introduction

A common problem arising in biomedical applications is the comparison of the survival functions or hazard rates of two treatments. Most standard statistical tests are based on comparing the survival curves or equivalently the hazard functions over a given time period. The time period considered is typically the period from initiation of the treatment to some point in time where observation of the patients ceases. This comparison may be made by the log rank test (cf. Andersen et al. 1993), for example, when there are no other covariates that may influence survival. When there are other covariates that may affect outcome in addition to the treatments under consideration, testing of treatment effects is carried out by some type of regression technique. These tests may be based on any number of parametric or semi-parametric models, but most common are tests based on either the Cox (1972) proportional hazards model or on Aalen's (1989, 1993) additive hazards model.

The results of these analyses tell the investigator whether the two treatments have the same survival rates or not. When the results of the test indicate that the survival curves are different the natural question posed by most clinicians is "At what times are these two treatments different?" The answer to this question is crucial to a patient and physician in deciding which of the two treatments to use. It is of special importance when one treatment has higher early survival but lower long term survival. This question is of particular interest in applications like bone marrow transplantation where, when comparing disease free survival rates, one procedure may have a higher early mortality rate due to treatment toxicity than the other treatment but among survivors of this early period the relapse rate is lower.

In this note we present methods for constructing a confidence set for the times at which the two treatments have the same survival function based on Aalen's additive hazards model. Confidence sets for the times at which one treatment has a survival probability at least as high as the other treatment are also presented. The confidence sets are found by inverting a test that compares the survival rates for the two treatments at fixed points in time. The set of all times for which this test accepts the hypothesis of no treatment difference provides the desired confidence set. Note that the confidence set is based on a comparison of the survival rates or cumulative hazard rates at fixed points in time as opposed to the usual tests which compare survival for the entire curve.

The random sets,  $C_\alpha$  that we construct by this technique are in fact conservative  $(1 - \alpha) \times 100\%$  confidence sets for the set,  $\Theta$ , of all times at which the two survival functions are the same. To see this consider the probability that  $\Theta$  is a subset of  $C_\alpha$ . Let  $t$  be an element of  $\Theta$ . For such a  $t$  the subset of the sample space for which this  $t$  will also be in the set  $A_\alpha$  has probability  $(1 - \alpha)$  by our method of construction. This will be true for any  $t$  in  $\Theta$ , however different  $t$ 's yield different subsets of the sample space. The coverage probability is the probability of the union of these different subsets as indexed by  $t$  in  $\Theta$ . Since each subset has probability exactly  $(1 - \alpha)$  our coverage probability must be at least  $(1 - \alpha)$ .

In the next section we review results from Klein and Zhang (1997) for comparing two treatments, when an adjustment for other covariates is needed, using the Cox (1972) proportional hazards model. We review both the case where there is no interaction between these other covariates and the main treatment comparison and the case where there is an interaction between the main treatment effect and some of the covariates. In this section the confidence sets are based on a stratified Cox regression model.

In section 3 we show how Aalen's additive model can be used to generate these confidence sets. Here the sets are based on fitting the full additive model to the data and inverting a pointwise test that the regression function for treatment is equal to zero.

In Section 4 we present an example of these confidence sets using data from The International Bone Marrow Transplant Registry and The Autologous Blood And Marrow Registry. The primary comparison of interest is between the leukemia free survival rates of autologous and allogeneic bone marrow transplants for acute leukemia patients. Autologous transplants, where a patient's own marrow is used to re grow their immune system, are typically less toxic than allogeneic transplants where the marrow from an HLA matched sibling is used. Patients do not experience graft-versus-host disease which is a leading contributor to death in

the first several months after transplant. It is well known, however, that graft-versus-host disease has some protective effect against the reoccurrence of the leukemia, so allogeneic patients who survive the initial period tend to have lower leukemia relapse rates, offsetting their higher early treatment related mortality. For a patient there is thus a trade off between early high mortality with allogeneic transplants and lower reoccurrence rates. To help in deciding between these two competing treatment modalities a confidence set for the times at which the survival probabilities of the two treatments are the same is of interest. Also, since autologous transplants are easier to perform as no donor is needed, a confidence set for those times where the survival probability for an autologous transplant patient is not smaller than the corresponding survival probability for an allogeneic transplant patient is also of interest.

## 2 Confidence Set Based On Cox's Proportional Hazards Model

### 2.1 Introduction

The Cox (1972) proportional hazards model has found wide acceptance as a tool for making comparisons between treatments adjusting for other covariates. Recently, Klein and Zhang (1997), have shown how this model can be used to construct confidence regions for times at which the survival functions are the same for the two treatments. Their approach, summarized in the next two subsections, is to perform a series of pointwise tests of the hypotheses of no difference in conditional cumulative hazard rates between the two treatments. They model the two cumulative hazards by a proportional hazards model stratified on treatment.

### 2.2 Adjustment For Covariates Not Confounded With Outcome

Let  $\mathbf{Z} = (Z_1, \dots, Z_p)$  be a vector of fixed time covariates that influence survival. We assume that there is no significant interaction between the comparison of interest (treatment) and any of these covariates. Here we fit a proportional hazards model for the explanatory covariates stratifying on the treatment of interest. That is we fit the model

$$\lambda(t|\mathbf{Z}, \text{Treatment}) = \begin{cases} \lambda_{10}(t) \exp\{\beta^T \mathbf{Z}\}, & \text{for treatment 1,} \\ \lambda_{20}(t) \exp\{\beta^T \mathbf{Z}\}, & \text{for treatment 2.} \end{cases} \quad (1)$$

Let  $\hat{\beta}$  and  $I(\hat{\beta})$  be the partial maximum likelihood estimator and the observed information for this model. An estimator of the baseline cumulative hazard rate for treatment  $j$ ,  $j = 1, 2$  is given by Breslow's (1975) estimator

$$\hat{\Lambda}_{j0}(t) = \int_0^t \frac{dN_j(u)}{S_j^{(0)}(\hat{\beta}, u)}, \quad \text{where} \quad (2)$$

$$S_j^{(0)}(\hat{\beta}, u) = \sum_{i=1}^n Y_{ij}(u) \exp\{\beta^T \mathbf{Z}_i\} \quad (3)$$

with  $Y_{ij}(u)$  the indicator of whether the  $i$ th individual is at risk at time  $u$  and is in the  $j$ th group.

For an individual with a covariate vector  $\mathbf{Z}_0$ , the two treatments will have the same survival rate at time  $t_0$  if  $\Lambda(t|\mathbf{Z}_0, \text{Treatment 1}) = \Lambda(t|\mathbf{Z}_0, \text{Treatment 2})$ , which from (1) is equivalent to having  $\Lambda_{10}(t_0) = \Lambda_{20}(t_0)$  or  $\Delta(t_0) = \Lambda_{20}(t_0) - \Lambda_{10}(t_0) = 0$ . Note that this comparison is independent of the value of  $\mathbf{Z}_0$ . The test statistic for this hypothesis is

$$\hat{\Delta}(t_0) = \hat{\Lambda}_{20}(t_0) - \hat{\Lambda}_{10}(t_0). \quad (4)$$

The large sample variance of this statistic is (see Klein and Zhang (1997))

$$Var[\hat{\Delta}(t_0)] = \sum_{j=1}^2 \int_0^{t_0} \frac{dN_j(u)}{[S_j^{(0)}(\hat{\beta}, u)]^2} + \mathbf{W}^T(\hat{\beta}, t_0)[I(\hat{\beta})]^{-1}\mathbf{W}(\hat{\beta}, t_0), \quad \text{where} \quad (5)$$

$$\mathbf{W}^T(\hat{\beta}, t_0) = \int_0^{t_0} \tilde{\mathbf{Z}}_2(\hat{\beta}, u)d\hat{\Lambda}_{20}(u) - \tilde{\mathbf{Z}}_1(\hat{\beta}, u)d\hat{\Lambda}_{10}(u),$$

$$\tilde{\mathbf{Z}}_j(\hat{\beta}, u) = \frac{S_j^{(1)}(\hat{\beta}, u)}{S_j^{(0)}(\hat{\beta}, u)}, \quad \text{and} \quad (6)$$

$$S_j^{(1)}(\hat{\beta}, u) = \sum_{i=1}^n Y_{ij}(u)\mathbf{Z}_i \exp\{\hat{\beta}^T \mathbf{Z}_i\}.$$

An  $\alpha$ -level test of  $H_0 : \Delta(t_0) = 0$  versus  $H_a : \Delta(t_0) \neq 0$  is accepted when

$|\hat{\Delta}(t_0)/\sqrt{Var[\hat{\Delta}(t_0)]}| \leq z_{\alpha/2}$ , where  $z_{\alpha}$  is the  $\alpha$ th upper quantile of a standard normal random variable. Inverting this test yields a  $100 \times (1 - \alpha)$  confidence set for the times at which  $S_1(t) = S_2(t)$  as

$$\begin{aligned} & \{t_0 : -z_{\alpha/2} \leq \hat{\Delta}(t_0)/[Var(\hat{\Delta}(t_0))]^{1/2} \leq z_{\alpha/2}\} \\ & = \{t_0 : \hat{\Delta}(t_0) - z_{\alpha/2}\sqrt{Var(\hat{\Delta}(t_0))} \leq 0 \leq \hat{\Delta}(t_0) + z_{\alpha/2}\sqrt{Var(\hat{\Delta}(t_0))}\} \end{aligned} \quad (7)$$

To find sets of time where we are  $(1 - \alpha) \times 100\%$  confident that  $S_1(t) \leq S_2(t)$  consider testing the hypothesis  $H_0 : \Lambda_1(t_0) \geq \Lambda_2(t_0)$  versus  $H_A : \Lambda_1(t_0) < \Lambda_2(t_0)$ . This is equivalent to testing  $H_0 : \Delta(t_0) \leq 0$  versus  $H_A : \Delta(t_0) > 0$ . The desired confidence set for those points in time where treatment 2 is at least as good as treatment 1 ( $\Delta(t_0) \leq 0$ ) is given by

$$\{t_0 : \hat{\Delta}(t_0)/\sqrt{Var[\hat{\Delta}(t_0)]} < z_{\alpha}\} = \{t_0 : 0 \geq \hat{\Delta}(t_0) - z_{\alpha}\sqrt{Var[\hat{\Delta}(t_0)]}\}.$$

### 2.3 Adjustment For Covariates Confounded With Outcome

In some instances the comparison of the treatments of interest is complicated by some of the explanatory covariates have differential effects on the survival rates for the two treatments. Suppose that the covariate vector can be partitioned as  $\mathbf{Z}^T = (\mathbf{Z}_1^T, \mathbf{Z}_2^T)^T$ , where  $\mathbf{Z}_1$  is a

vector of length  $q_1$  of the covariates confounded with treatment and  $Z_2$  is a vector of length  $q_2$  of the covariates not confounded with treatment.

To construct the confidence set where the survival rates are the same for the two treatments a stratified proportional hazards model is used. We fit the model

$$\lambda(t|\mathbf{Z}, \text{Treatment}) = \begin{cases} \lambda_{10}(t) \exp\{\gamma_1^T \mathbf{Z}_1 + \theta^T \mathbf{Z}_2\}, & \text{for treatment 1,} \\ \lambda_{20}(t) \exp\{\gamma_2^T \mathbf{Z}_1 + \theta^T \mathbf{Z}_2\}, & \text{for treatment 2.} \end{cases} \quad (8)$$

Estimates for  $\beta = (\theta^T, \gamma_1^T, \gamma_2^T)$  are found by fitting a Cox model, stratified on treatment group to the data with an augmented covariate vector  $\mathbf{Z}^T = (\mathbf{Z}_2^T, \mathbf{Z}_1^T I[\text{Treatment} = 1], \mathbf{Z}_1^T I[\text{Treatment} = 2])$ . For a given set of confounding factors,  $\mathbf{Z}_{10}$ , the two treatments will have the same survival rate at time  $t_0$  if

$$\Delta(t_0|\mathbf{Z}_{10}) = \Lambda_{20}(t_0) \exp\{\gamma_2^T \mathbf{Z}_{10}\} - \Lambda_{10}(t_0) \exp\{\gamma_1^T \mathbf{Z}_{10}\} \quad (9)$$

is equal to zero. The estimator of  $\Delta(t_0|\mathbf{Z}_{10})$  given by

$$\hat{\Delta}(t_0|\mathbf{Z}_{10}) = \hat{\Lambda}_{20}(t_0) \exp\{\hat{\gamma}_2^T \mathbf{Z}_{10}\} - \hat{\Lambda}_{10}(t_0) \exp\{\hat{\gamma}_1^T \mathbf{Z}_{10}\}$$

follows from the fitted Cox model with  $\Lambda_{j0}()$  estimated using Breslow's estimator (2).

An estimator of the asymptotic variance of  $\hat{\Delta}(t_0|\mathbf{Z}_{10})$  is (see Klein and Zhang (1997))

$$\begin{aligned} \text{Var}(\hat{\Delta}(t_0|\mathbf{Z}_{10})) &= \sum_{j=1}^2 \int_0^{t_0} \exp\{2\hat{\gamma}_j^T \mathbf{Z}_{10}\} \frac{dN_j(u)}{[S_j^{(0)}(\hat{\beta}, u)]^2} + \\ &+ \left\{ \mathbf{W}_2(\hat{\beta}, t_0) - \mathbf{W}_1(\hat{\beta}, t_0) \right\}^T [\mathbf{I}(\hat{\beta})]^{-1} \left\{ \mathbf{W}_2(\hat{\beta}, t_0) - \mathbf{W}_1(\hat{\beta}, t_0) \right\} \end{aligned}$$

Here

$$\mathbf{W}_j(\hat{\beta}, t_0) = \exp\{\hat{\gamma}_j^T \mathbf{Z}_{10}\} \int_0^{t_0} [\tilde{\mathbf{Z}}_j(\hat{\beta}, u) - \mathbf{Z}_{(j)}] d\hat{\Lambda}_{j0}(u), \quad j = 1, 2$$

with  $\tilde{\mathbf{Z}}_j(\hat{\beta}, u)$ , defined by (6) and  $\mathbf{Z}_{(1)} = (\mathbf{0}^T, \mathbf{Z}_{10}^T, \mathbf{0}^T)$  and  $\mathbf{Z}_{(2)} = (\mathbf{0}^T, \mathbf{0}^T, \mathbf{Z}_{10}^T)$ .

Since at  $t_0$  an  $\alpha$  level test of the equality of the two survival functions for a fixed value  $\mathbf{Z}_{10}$  of  $\mathbf{Z}$  is accepted when  $\hat{\Delta}(t_0|\mathbf{Z}_{10})/[\text{Var}(\hat{\Delta}(t_0|\mathbf{Z}_{10}))]^{1/2}$  is in the interval  $[-z_{\alpha/2}, z_{\alpha/2}]$ , a  $(1 - \alpha) \times 100\%$  confidence set for those times at which the two treatments are not different is given by

$$\{t : -z_{\alpha/2} \leq \hat{\Delta}(t_0|\mathbf{Z}_{10})/[\text{Var}(\hat{\Delta}(t_0|\mathbf{Z}_{10}))]^{1/2} \leq z_{\alpha/2}\}$$

Similarly a confidence set for those points in time where treatment 2 is at least as good as treatment 1 is given by

$$\{t : \hat{\Delta}(t_0|\mathbf{Z}_{10})/[\text{Var}(\hat{\Delta}(t_0|\mathbf{Z}_{10}))]^{1/2} \leq z_{\alpha}\}$$

### 3 Confidence Sets Based On The Additive Hazards Model

#### 3.1 Estimation In The Additive Model

An alternative to the proportional hazards model is the additive hazards model first suggested by Aalen (1980). This model allows for covariate effects which vary over time since the regression coefficients are functions of time as opposed to the Cox model where they are constants. This approach uses a linear model for the conditional hazard rate and estimates regression coefficient functions by a least squares technique.

To define the model suppose we have an individual with covariates  $Z_1(t), \dots, Z_p(t)$ . For such an individual the model for the conditional hazard rate is given by

$$\lambda(t|Z_1(t), \dots, Z_p(t)) = \begin{cases} \alpha_0(t) + \sum_{k=1}^p \alpha_k(t)Z_k(t) & \text{if this individual is at risk at time } t, \\ 0 & \text{otherwise.} \end{cases}$$

Here the  $\alpha_j(t)$ 's,  $j = 0, \dots, p$ , are functions of time to be estimated from the data.

Suppose we observe  $n$  individuals. Associated with each individual is a  $p$ -vector of possibly time dependent covariates,  $\mathbf{Z}_i(t) = (1, Z_i(t), \dots, Z_p(t))$ . (Here the first element of the covariate vector is 1 to allow for a baseline intensity.) Let  $\lambda_i(t)$  denote the intensity at which the event occurs for the  $i$ th subject. To write the model in matrix notation let  $\mathbf{Y}(t)$  be the  $n \times (p+1)$  matrix whose  $i$ th row is  $\mathbf{Z}_i(t)$  if individual  $i$  is at risk at time  $t$  and is a row of zeros if this subject is not at risk at time  $t$ . Then the additive regression model is

$$\lambda(t) = \mathbf{Y}(t)\alpha(t). \tag{10}$$

Here the first element of  $\alpha(t)$  is a baseline intensity and the remaining elements are the regression functions which describe the effect of the covariate over time on survival.

The only restriction on covariates which can be used in this model is that they are predictable in the sense that their value is known just prior to time  $t$  (cf. Aalen 1978). In the data set to be used here to illustrate these techniques all covariates are known at the time of transplant so this condition is satisfied.

Estimation for the additive model is based on a least squares approach. Direct estimation of  $\alpha(t)$  is difficult so we estimate instead the cumulative regression function,  $\mathbf{A}(t) = (A_1(t), \dots, A_p(t))^T$ , where

$$A_j(t) = \int_0^t \alpha_j(t)dt, \quad j = 0, 1, \dots, p.$$

Let  $T_1 < T_2 < \dots$  be the ordered observed times at which events occur. Then Aalen (1980, 1989) shows that the least squares estimator of  $\mathbf{A}(t)$  is given by

$$\hat{\mathbf{A}}(t) = \sum_{T_k \leq t} \mathbf{X}(T_k)\mathbf{I}_k, \quad \text{where} \tag{11}$$

$\mathbf{X}(t)$  is a generalized inverse of  $\mathbf{Y}(t)$ , and  $\mathbf{I}_k$  is the  $n$ -vector of whose  $i$ th element is 1 if subject  $i$  experiences the event at time  $T_k$  and is 0 if they don't. The estimator (11) is only defined over the range where the matrix  $\mathbf{Y}(t)$  is of full rank. Let  $\tau$  be the random point in time where  $\mathbf{Y}()$  loses its full rank.

Any generalized inverse can be used in computing the estimator (10). By analogy to the usual linear models analysis we shall use the generalized inverse suggested by Aalen (1980), Huffer and McKeague (1991), McKeague (1988), namely

$$\mathbf{X}(t) = (\mathbf{Y}(t)^T \mathbf{Y}(t))^{-1} \mathbf{Y}(t)^T \quad (12)$$

An alternative choice of the generalized inverse is a weighted inverse which leads to the analog of a weighted least squares estimate (See Huffer and McKeague (1991), McKeague (1988)).

The variance matrix of  $\hat{\mathbf{A}}(t)$  can be estimated consistently by

$$\Sigma(t) = \sum_{T_k} \mathbf{X}(T_k) \mathbf{D}_k \mathbf{X}(T_k)^T, \quad (13)$$

where  $\mathbf{D}$  is the diagonal matrix with  $\mathbf{I}_k$  as the diagonal. One can show (cf. Aalen 1980, Andersen et al (1993)) that  $\hat{\mathbf{A}}(t)$  converges weakly to a Gaussian process with independent increments under a wide set of regularity conditions. A SAS Macro to perform the calculations need to obtain  $\hat{\mathbf{A}}(t)$  and  $\Sigma(t)$  is described in Howell and Klein (1996).

### 3.2 Confidence Sets Adjusted For Other Covariates Not Confounded With Treatment

As for the proportional hazards model, to find a confidence set for those times where the two treatments are the same adjusting for a  $p$ -variate set of covariates  $Z_1, \dots, Z_p$ , we base the set on a series of pointwise tests of equality of the adjusted cumulative hazard rates for the two treatments. For each individual define the  $p+2$  dimensional vector  $\mathbf{Z}_i(t) = (1, Z_1(t), \dots, Z_p(t), W)$ , where  $W = 1$  if this individual received treatment 2 and 0 otherwise. Using this coding of the covariates we compute  $\hat{\mathbf{A}}(t)$  and  $\Sigma(t)$ . Now the difference in cumulative hazard rates between an individual given treatment 2 and an individual given treatment 1 is

$$\begin{aligned} \Delta(t|\mathbf{Z}) &= \Lambda(t|\mathbf{Z}, \text{Treatment 2}) - \Lambda(t|\mathbf{Z}, \text{Treatment 1}) \\ &= \{A_0(t) + \sum_{k=1}^p A_k(t)Z_k(t) + A_{p+1}(t)\} - \{A_0(t) + \sum_{k=1}^p A_k(t)Z_k(t)\} \\ &= A_{p+1}(t) \end{aligned}$$

The variance of this estimator is found directly from  $\Sigma(t)$ .

An  $\alpha$ -level test of  $H_o : \Delta(t_0) = 0$  versus  $H_a : \Delta(t_0) \neq 0$  is accepted when  $|\hat{\Delta}(t_0)/\sqrt{\text{Var}[\hat{\Delta}(t_0)]}| \leq z_{\alpha/2}$ , where  $z_{\alpha}$  is the  $\alpha$ th upper quantile of a standard normal random



variable. Inverting this test yields a  $100 \times (1 - \alpha)$  confidence set for the times at which  $S_1(t) = S_2(t)$  as

$$\begin{aligned} & \{t_0 : -z_{\alpha/2} \leq \hat{\Delta}(t_0)/[\text{Var}(\hat{\Delta}(t_0))]^{1/2} \leq z_{\alpha/2}\} \\ &= \{t_0 : \hat{\Delta}(t_0) - z_{\alpha/2}\sqrt{\text{Var}(\hat{\Delta}(t_0))} \leq 0 \leq \hat{\Delta}(t_0) + z_{\alpha/2}\sqrt{\text{Var}(\hat{\Delta}(t_0))}\} \end{aligned} \quad (14)$$

To find sets of time where we are  $(1 - \alpha) \times 100\%$  confident that  $S_1(t) \leq S_2(t)$  consider testing the hypothesis  $H_0 : \Lambda_1(t_0) \geq \Lambda_2(t_0)$  versus  $H_A : \Lambda_1(t_0) < \Lambda_2(t_0)$ . This is equivalent to testing  $H_0 : \Delta(t_0) \leq 0$  versus  $H_A : \Delta(t_0) > 0$ . The desired confidence set for those points in time where treatment 2 is at least as good as treatment 1 ( $\Delta(t_0) \leq 0$ ) is given by

$$\{t_0 : \hat{\Delta}(t_0)/\sqrt{\text{Var}[\hat{\Delta}(t_0)]} < z_{\alpha}\} = \{t_0 : 0 \geq \hat{\Delta}(t_0) - z_{\alpha}\sqrt{\text{Var}[\hat{\Delta}(t_0)]}\}.$$

### 3.3 Confidence Sets When The Covariates Are Confounded With Treatment

Suppose that the covariates vector can be partitioned into as a set  $\mathbf{Z}_1$  of dimension  $q_1$  of covariates confounded with treatment and a set  $\mathbf{Z}_2$  of dimension  $q_2$  of covariates not confounded with treatment. For this case we define for each individual the  $q_2 + 2q_1 + 2$  dimensional vector  $\mathbf{Z}_i(t) = (1, \mathbf{Z}_2, W\mathbf{Z}_1, [1 - W]\mathbf{Z}_1, W)$ . Here  $W$  is again the indicator of an individual being in treatment group 2. Note that for this covariate vector we have the following cumulative hazard rates for the two treatment groups:

$$\text{Treatment 2: } A_0(t) + \sum_{k=1}^{q_2} A_k(t)Z_{2k}(t) + \sum_{k=1}^{q_1} A_{1+q_2+k}(t)Z_{1k}(t) + A_{2+2q_1+q_2}(t)$$

$$\text{Treatment 1: } A_0(t) + \sum_{k=1}^{q_2} A_k(t)Z_{2k}(t) + \sum_{k=1}^{q_1} A_{1+q_1+q_2+k}(t)Z_{1k}(t)$$

For an individual with a set  $\mathbf{Z}_{10}$  of covariates for  $\mathbf{Z}_1$ , the survival functions will be the same at time  $t$  if these two cumulative hazard rates are the same. That is if

$$\Delta(t|\mathbf{Z}_{10}) = A_{2+2q_1+q_2}(t) + \sum_{k=1}^{q_1} [A_{1+q_2+k}(t) - A_{1+q_1+q_2+k}(t)]Z_{1k}(t) = 0.$$

Note that if we let  $\mathbf{C} = (\mathbf{0}, \mathbf{Z}_{10}, -\mathbf{Z}_{10}, 1)$ , where  $\mathbf{0}$  is the  $q_2 + 1$  vector of zero's then  $\Delta(t|\mathbf{Z}_{10}) = \mathbf{C}\mathbf{A}(t)$  and the variance of  $\hat{\Delta}(t|\mathbf{Z}_{10}) = \mathbf{C}\hat{\mathbf{A}}(t)$  is estimated by  $\mathbf{C}\Sigma(t)\mathbf{C}^T$ .

Since at  $t_0$  an  $\alpha$  level test of the equality of the two survival functions for a fixed value of  $\mathbf{Z}_1$  is accepted when  $\hat{\Delta}(t_0|\mathbf{Z}_{10})/[\text{Var}(\hat{\Delta}(t_0|\mathbf{Z}_{10}))]^{1/2}$  is in the interval  $[-z_{\alpha/2}, z_{\alpha/2}]$ , a  $(1 - \alpha) \times 100\%$  confidence set for those times at which the two treatments are not different is given by

$$\{t : -z_{\alpha/2} \leq \hat{\Delta}(t_0|\mathbf{Z}_{10})/[\text{Var}(\hat{\Delta}(t_0|\mathbf{Z}_{10}))]^{1/2} \leq z_{\alpha/2}\}$$

Similarly a confidence set for those points in time where treatment 2 is at least as good as treatment 1 is given by

$$\{t : \hat{\Delta}(t_0|\mathbf{Z}_{10})/[\text{Var}(\hat{\Delta}(t_0|\mathbf{Z}_{10}))]^{1/2} \leq z_{\alpha}\}$$

## 4 Example

To illustrate these calculations we consider data from a retrospective study of the effectiveness of bone marrow transplantation for patients with acute myelocytic leukemia (AML). Of interest is the comparison of survival rates between patients given either an autologous (auto) or allogeneic (allo) transplant. The data set consists of data on 1,325 patients reported over a four year period to either the International Bone Marrow Transplant Registry (allo transplants) or the Autologous Blood and Marrow Registry (auto transplants). 381 patients received an autologous transplant and 944 a HLA identical sibling allogeneic transplant.

The comparison of interest is between the leukemia free survival times (LFS) of the two groups. A patient is considered as an event if they die or their leukemia returns. The event time is the smaller of the time of relapse or death. Figure 1 shows the unadjusted Kaplan-Meier estimators for the two treatment groups. The log rank test of equality of the survival functions in the two treatment groups is rejected with a  $p$ -value of 0.007.

In addition to type of transplant, data on each patient includes remission status (1st or second complete remission), age (dichotomized as  $\leq 30$  or  $> 30$ ) and Karnofsky score (dichotomized as  $< 90$  or  $\geq 90$ ) at transplant. For patients in second complete remission the duration of the first complete remission is also recorded (dichotomized as  $\leq 1$  yr or  $> 1$  yr). We wish to determine when the two types of transplants have the same survival rate after adjustment for these fixed explanatory covariates.

We first assume that there is no interaction between these covariates and the type of transplant. For the proportional hazards approach a Cox model is fit, stratified on transplant type, with binary covariates for remission status, age, Karnofsky score and duration of first complete remission. Applying the results in Section 2.2 we find that a 95% confidence set for the times where the survival probabilities for the two transplant types are not different, adjusted for this set of covariates, is the set of time points given by

$$C2 = \{t_0 \mid t_0 \in [0, 0.132) \cup [0.151, 1.242) \cup [2.281, 2.418)\} \text{ years.}$$

A 95% confidence set for those times where patients given an auto transplant have a survival probability at least as high as patients given an allo transplant is given by

$$C1 = \{t_0 \mid t_0 \in [0, 0.861) \cup [0.872, 1.179)\} \text{ years.}$$

For the additive model discussed in Section 3.2 we fit the model with covariates for type of transplant and for the four fixed covariates. The 95% confidence set for the times where the survival probabilities for the two transplant types are not different based on this model is given by

$$C2 = \{t_0 \mid t_0 \in [0, 0.137) \cup [0.143, 0.855) \cup [0.880, 1.102) \cup [1.124, 1.1662)\} \text{ years.}$$

The 95% confidence set for those times where patients given an auto transplant have a survival probability at least as high as patients given an allo transplant based on the additive

model is given by

$$C1 = \{t_0 | t_0 \in [0, 0.526) \cup [0.534, 0.537) \cup [0.611, 0.641) \\ \cup [0.688, 0.726) \cup [0.732, 0.768) \cup [0.959, 0.984)\} \text{ years.}$$

The sets  $C1$  suggest that for a period of time after transplant auto patients do not do any worse than allo patients, but after this period they have smaller survival probabilities. This time interval is estimated to be a little over a year based on the proportional hazards model and a little under a year based on the additive model.

The above intervals assumed that the fixed covariates were not confounded with treatment. However, in this study, based on either the proportional hazards or additive hazards model, it appears that age has a differential effect on the two types of transplants.

To adjust for this confounding factor using the proportional hazards approach, a model stratified on type of transplant is fit to the covariates remission status, Karnofsky score, duration of first complete remission and two interaction covariates. The interaction covariates are  $Z_{11} = 1$  if age > 30 and allo transplant and  $Z_{12} = 1$  if age > 30 and auto transplant.

Using the results in Section 2.2, 95% confidence sets for the times (in years) where the two treatments have the same survival probability are

$$C2_{\leq 30} = \{t_0 | t_0 \in [0, 1.242) \cup [2.349, 2.418)\} \text{ years.}$$

for patients age 30 or less and

$$C2_{>30} = \{t_0 | t_0 \in [0, 0.115) \cup [0.118, 0.129) \cup [0.1590, 5.891)\} \text{ years}$$

for patients over age 30.

A 95% confidence set for those times where patients given an auto transplant have a survival probability at least as high as patients given an allo transplant based on the proportional hazards model is given by

$$C1_{\leq 30} = \{t_0 | t_0 \in [0, 0.858) \cup [0.885, 1.162)\} \text{ years}$$

for patients age 30 or less and

$$C1_{>30} = \{t_0 | t_0 \in [0, 5.891)\} \text{ years,}$$

for patients over age 30.

For the additive model approach we fit a using a covariate vector with components remission status, Karnofsky score, duration of first complete remission,  $Z_{11}$ ,  $Z_{12} = 1$ , and the indicator of type of transplant. Applying the results in Section 3.3 we find that 95% confidence sets for the times (in years) where the two treatments have the same survival probability based on the additive model are

$$C2_{\leq 30} = \{t_0 | t_0 \in [0, 0.398) \cup [0.622, 0.632) \cup [0.696, 0.721) \cup [0.732, 0.855) \\ \cup [0.872, 1.242) \cup [1.672, 2.837) \cup [3.100, 5.052)\} \text{ years}$$

for patients age 30 or less and

$$C2_{>30} = \{t_0 | t_0 \in [0, 0.066) \cup [0.159, 0.162) \cup [0.165, 0.167) \cup [0.189, 0.195) \cup [0.197, 5.05)\} \text{ years}$$

for patients over age 30.

A 95% confidence set for those times where patients given an auto transplant have a survival probability at least as high as patients given an allo transplant based on the additive hazard model is given by

$$C1_{\leq 30} = \{t_0 | t_0 \in [0, 0.356) \cup [2.059, 2.448) \cup [4.260, 5.052)\} \text{ years}$$

for patients age 30 or less and

$$C1_{>30} = \{t_0 | t_0 \in [0, 1.8558) \cup [1.8722, 2.083) \cup [2.215, 2.418) \cup [3.753, 5.052)\} \text{ years}$$

for patients over age 30.

These intervals suggest that for older patients there is little if any advantage in survival for either type of transplant. For younger patients the proportional hazards model suggests that the survival rates are different after about two and a half years. Based on the one sided sets constructed by the additive hazard model, the inference for younger patients is that they have survival given an auto transplant at least as good as if they were given an allo transplant in the first 3 months after transplant, for a brief period in year two and then again after about 3 and three-fourth years.

## 5 Acknowledgments

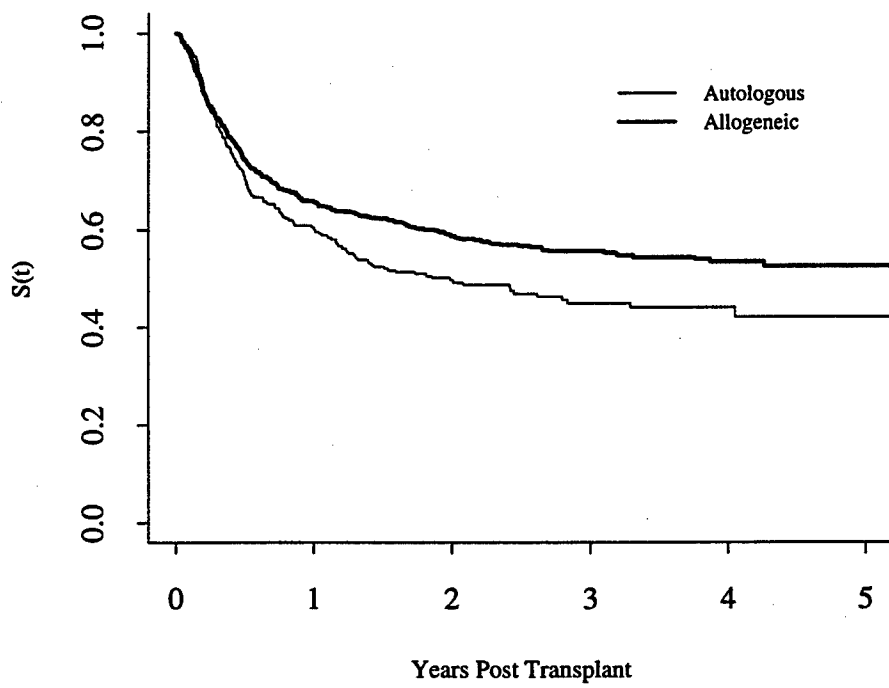
This research was supported by Grant 5 R01 CA54706-05 from the National Cancer Institute for J. P. Klein and M. J. Zhang, and by Grant PO1-CA-40053 from the National Cancer Institute and by Institutional Research Grant 170H from American Cancer Society for M. J. Zhang.

## References

- Aalen, O. O. (1978). Nonparametric Inference For A Family Of Counting Processes. *Annals Of Statistics*, 6, 701-726.
- Aalen, O. O. (1980). A Model For Non-Parametric Regression Analysis of Counting Processes. *Springer Lecture Notes in Statistics*, 2, 1-25, Mathematical Statistics and Probability Theory. W. Klonecki A. Kozek and J. Rosinski, editors.
- Aalen, O. O. (1989). A Linear Regression Model For The Analysis Of Life Times. *Statistics In Medicine*, 8, 907-925.

- Aalen, O. O. (1993). Further Results On The Non-Parametric Linear Regression Model In Survival Analysis. *Statistics In Medicine*, **12**, 1569–1588.
- Andersen, P. K., Bentzon, M. W. and Klein, J. P. (1996). Estimating The Survival Function In The Proportional Hazards Regression Model: A Study Of The Small Sample Size Properties. *Scandinavian Journal Of Statistics*, **23**, 1–12.
- Andersen, P. K., Borgan, Ø., Gill, R. D. and Keiding, N. (1993). *Statistical Models Based On Counting Processes*. Springer-Verlag, New York.
- Breslow, N. E. (1975). Analysis Of Survival Data Under The Proportional Hazards Model. *International Statistics Review*, **43**, 45–58.
- Cox, D. R. (1972). Regression Models And Life-Tables (With Discussion). *Journal Of The Royal Statistical Society B*, **34**, 187–220.
- Howell, A. M and Klein, J. P. (1996). A SAS Marco for the Additive Hazards Regression Model *Technical Report Number 18*, Division of Biostatistics, The Medical College of Wisconsin
- Huffer, F. W. and McKeague, I.W. (1991). Weighted Least Squares Estimation for Aalen's Additive Risk Model. *JASA*, **86**, 114–129.
- Klein, J. P. and Zhang, M.-J. (1997). Confidence Sets For The Equality Of Two Survival Curves *Lifetime Data Analysis*, To Appear.
- McKeague, I.W. (1988). Asymptotic Theory For Weighted Least Squares Estimators In Aalen's Additive Risk Model. *Contemp. Math*, **80**, 139–152.

Figure 1. Kaplan-Meier Estimates Of Leukemia Free Survival



Confidence bands for the difference  
of two survival curves under  
proportional hazards model

Mei-Jie Zhang, Ph.D.

John P. Klein, Ph.D.

**DIVISION OF BIostatISTICS**



**MEDICAL  
COLLEGE  
OF WISCONSIN**

**MILWAUKEE, WISCONSIN**

**Confidence bands for the difference  
of two survival curves under  
proportional hazards model**

Mei-Jie Zhang, Ph.D.  
John P. Klein, Ph.D.

Technical Report 29

February 1998

Division of Biostatistics  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee WI 53226  
Phone: (414)456-8280



# CONFIDENCE BANDS FOR THE DIFFERENCE OF TWO SURVIVAL CURVES UNDER PROPORTIONAL HAZARDS MODEL

MEI-JIE ZHANG AND JOHN P. KLEIN

*Medical College of Wisconsin*

## Abstract.

A common approach to testing for differences between the survival rates of two therapies is to use a proportional hazards regression model which allows for an adjustment of the two survival functions for any imbalance in prognostic factors in the comparison. An alternative approach to this problem is to plot the difference between the two predicted survival functions with a confidence band that provides information about when these two treatments differ. Such a band will depend on the covariate values of a given patient. In this paper we show how to construct a confidence band for the difference of two survival functions based on the proportional hazards model. A simulation approach is used to generate the bands. This approach is used to compare the survival probabilities of chemotherapy and allogeneic bone marrow transplants for chronic leukemia.

## 1. Introduction

A common problem encountered in biomedical applications is the comparison of the survival rates of two treatments. In this comparison one tests whether the two treatments have the same survival function or equivalently the same hazard function over a given time period. When there are additional covariates associated with survival then this testing is typically performed in the framework of a Cox (1972) proportional hazards model.

When the testing results indicate that two survival functions are different, patients and physicians often want to know "at what times are these two treatments different?". This is particularly important when one treatment has a higher early survival but lower long term survival. This question is of particular interest in comparing the survival rates of bone marrow transplantation (BMT) and conventional chemotherapy patients. Here, bone marrow transplantation patients may have a higher early mortality rate, due to treatment toxicity, and a lower late death rate, due to a reduced relapse risk.

To answer this question, it is useful to plot the estimate of the difference between the two survival functions along with a confidence band for the difference. Visually examining these

plots and comparing the confidence bands with the zero line summarizes how the difference between the two survival functions change with time. Recently, Parzen *et al* (1997) used the Kaplan-Meier (1958) estimators of the two survival functions,  $\hat{F}_1(\cdot)$  and  $\hat{F}_2(\cdot)$ , to estimate the difference between the survival functions and they proposed a simulation method to construct a confidence band for this difference.

In many applications there is a need, when comparing two treatments, to make adjustments for other covariates that may affect outcome. When the two treatments are found to have different survival rates then patients and physicians want to know "for a given patient with a certain set of covariates, when are the two treatments different?". In the sequel, we attempt to answer this question by comparing the estimated survival functions for the two treatments using a stratified Cox(1972) proportional hazards model. That is, we estimate the difference between the two conditional survival functions for a particular set of covariate values,  $D(\cdot; z_0) = F_2(\cdot; z_0) - F_1(\cdot; z_0)$ , by  $\hat{D}(\cdot; z_0) = e^{-\hat{\Lambda}_2(\cdot; z_0)} - e^{-\hat{\Lambda}_1(\cdot; z_0)}$  where  $\hat{\Lambda}_i(\cdot; z_0), i = 1, 2$  are the Breslow (1975) type estimate for the cumulative hazard functions.

To find a confidence band for  $D(\cdot; z_0)$ , using the martingale central limit theory one can show that  $\hat{D}(\cdot; z_0)$  converges weakly to a zero mean Gaussian process. It is well known that this limiting Gaussian process does not have independent increments, hence, it is difficult to evaluate this limiting distribution analytically. In the one sample cases, Lin *et al* (1994) proposed a simulation method to construct the confidence bands for  $F(\cdot; z_0)$ . In this paper we propose to use a similar simulation method to construct a confidence band for  $D(\cdot; z_0)$ .

In Section 2, we present the estimates and simulation method used to construct a confidence band for the difference of two survival functions based on a stratified Cox proportional hazards model. In Section 3, we present an example of this technique using chronic leukemia data from The International Bone Marrow Transplant Registry and German CML Study Group.

## 2. Confidence bands for the difference of two survival functions

Let the observations on subject  $j$  of treatment group  $i$  be  $\{X_{ij}, T_{ij}, D_{ij}, Z_{ij}\}$  where  $X_{ij}$  is the left-truncation time,  $D_{ij} = 0$  if subject  $(i, j)$  is censored,  $D_{ij} = 1$  otherwise,  $T_{ij}$  is the observation time of subject  $(i, j)$  which is observed only if  $T_{ij} \geq X_{ij}$ , and  $Z_{ij}$  are the covariates, for  $i = 1, 2$  and  $j = 1, \dots, n_i$ . So the data considered here are left-truncated and right censored. Note that if  $X_{ij} = 0$  for all  $i, j$  then the data is right censored only. We fit a Cox (1972) model stratified on treatment. That is for a patient given treatment  $i, i = 1, 2$ , the hazard function is

$$\lambda_i(t; z) = \lambda_{i0}(t)e^{\beta'z},$$

where  $\lambda_{i0}(t)$  is the baseline hazard functions for treatment  $i, z$  is a  $p$ -vector of covariates that influence survival, and  $\beta$  is a  $p$ -vector of unknown regression coefficients.

Here,  $\beta$  can be estimated by maximizing the stratified Cox partial log likelihood function

$$C(\beta, t) = \sum_{i=1}^2 \sum_{j=1}^{n_i} \int_0^t \beta' Z_{ij} dN_{ij}(u) - \sum_{i=1}^2 \int_0^t \log \left( \sum_{j=1}^{n_i} Y_{ij}(u) e^{\beta' Z_{ij}} \right) d\bar{N}_i(u),$$

where  $N_{ij}(u) = I\{X_{ij} \leq T_{ij} \leq u, D_{ij} = 1\}$ ,  $\bar{N}_i = \sum_i N_{ij}$ , and  $Y_{ij}(u) = I\{X_{ij} \leq u \leq T_{ij}\}$  is the indicator of whether the  $j$ th individual is at risk at time  $u$  and is in the  $i$ th treatment group. Note that an individual is at risk only since his or her truncation time, so that the size of the risk set is initially increasing and then decreases.

To compare two predicted survival curves, we estimate the conditional survival functions for the two treatments for a patient with a particular set of covariates  $z_0$ ,

$$F_i(t; z_0) = P(T > t | z_0, \text{Treatment } i) = e^{-\Lambda_i(t; z_0)},$$

where  $\Lambda_i(t | z_0) = e^{\beta' z_0} \int_0^t \lambda_{i0}(u) du$ . An estimator of the cumulative baseline hazard rate for treatment  $i$ ,  $i = 1, 2$  is given by Breslow's (1975) estimator

$$\hat{\Lambda}_{i0}(t) = \int_0^t \frac{d\bar{N}_i(u)}{\sum_{j=1}^{n_i} Y_{ij}(u) \exp(\hat{\beta}' Z_{ij})}.$$

For convenience we introduce the notations

$$\begin{aligned} S_i^{(k)}(\beta, t) &= \frac{1}{n_i} \sum_{j=1}^{n_i} Y_{ij}(t) Z_{ij}^{\otimes k} e^{\beta' Z_{ij}}, \\ E_i(\beta, t) &= S_i^{(1)}(\beta, t) / S_i^{(0)}(\beta, t), \\ V_i(\beta, t) &= S_i^{(2)}(\beta, t) / S_i^{(0)}(\beta, t) - E_i(\beta, t), \\ s_i^{(k)}(\beta, t) &= E\{S_i^{(k)}(\beta, t)\}, \\ e_i(\beta, t) &= s_i^{(1)}(\beta, t) / s_i^{(0)}(\beta, t), \\ v_i(\beta, t) &= s_i^{(2)}(\beta, t) / s_i^{(0)}(\beta, t) - e_i(\beta, t), \end{aligned}$$

for  $i = 1, 2$ , and  $k = 0, 1, 2$ , where for a column vector  $a$ ,  $a^{\otimes 0} = 1$ ,  $a^{\otimes 1} = a$ , and  $a^{\otimes 2} = aa'$ .

For simplicity of presentation, we assume  $\{X_{ij}, T_{ij}, D_{ij}, Z_{ij}\}$ , ( $j = 1, \dots, n_i$ ) are independent and identically distributed,  $P(T_{ij} \geq X_{ij}) > 0$ , and  $\{Z_{ij}\}$  is bounded. Left-truncated and right-censored survival data has been studied extensively. The more general conditions required to obtain large sample results for this type of data can be found in Woodroffe (1985), Lai and Ying (1991) and Andersen *et al* (1993). Andersen *et al* (1993) argued that the martingale central limit theory can be applied to the left-truncated data, so that the asymptotic results based on right censored data can be extended to the left-truncated and right censored data. Also we assume that two samples are independent. Let  $n = n_1 + n_2$ . Then, if  $n_i/n \rightarrow p_i > 0$ , for  $i = 1, 2$ ,  $\hat{\beta}$  is a consistent estimate of  $\beta$ , and

$$\sqrt{n}(\hat{\beta} - \beta) \xrightarrow{D} N(0, \Sigma^{-1}),$$

where

$$\Sigma = \sum_{i=1}^2 p_i \int_0^{\infty} v_i(\beta, t) s^{(0)}(\beta, t) \lambda_{i0}(t) dt,$$

which is assumed to be positive definite and can be consistently estimated by the observed information matrix

$$\hat{\Sigma} = \frac{1}{n} \sum_{i=1}^2 \int_0^{\infty} V_i(\hat{\beta}, t) d\bar{N}_i(t).$$

To find the limiting distribution of

$$W(t; z_0) = \sqrt{n} \{ [\hat{F}_2(t; z_0) - \hat{F}_1(t; z_0)] - [F_2(t; z_0) - F_1(t; z_0)] \},$$

the delta-method can be used to show that this process behaves asymptotically like

$$W_1(t; z_0) = \sqrt{n} \{ F_1(t; z_0) [\hat{\Lambda}_1(t; z_0) - \Lambda_1(t; z_0)] - F_2(t; z_0) [\hat{\Lambda}_2(t; z_0) - \Lambda_2(t; z_0)] \}.$$

Let  $N_{ij}$  be the observed counting process and define the martingales

$$M_{ij}(t) = N_{ij}(t) - \int_0^t Y_{ij}(u) e^{\beta' Z_{ij}} \lambda_{i0}(u) du, \quad (1)$$

for  $i = 1, 2$  and  $j = 1, \dots, n_i$ . Let  $\bar{M}_i = \sum_{j=1}^{n_i} M_{ij}$ , Andersen and Gill (1982) showed that  $W_1(t; z_0)$  is asymptotically equivalent to

$$\begin{aligned} \bar{W}(t; z_0) &= \sqrt{n} F_1(t; z_0) \int_0^t \frac{e^{\beta' z_0} d\bar{M}_1(u)}{n_1 S_1^{(0)}(\beta, u)} - \sqrt{n} F_2(t; z_0) \int_0^t \frac{e^{\beta' z_0} d\bar{M}_2(u)}{n_2 S_2^{(0)}(\beta, u)} \\ &+ (F_1(t; z_0) h_1(t; z_0) - F_2(t; z_0) h_2(t; z_0))' \Sigma^{-1} \left\{ \frac{1}{\sqrt{n}} \sum_{i=1}^2 \sum_{j=1}^{n_i} \int_0^{\infty} [Z_{ij} - E_i(\beta, u)] dM_{ij}(u) \right\}, \quad (2) \end{aligned}$$

where  $h_i(t; z_0) = \int_0^t e^{\beta' z_0} [z_0 - e_i(\beta, u)] \lambda_{i0}(u) du$ , which can be estimated by

$$\hat{h}_i(t; z_0) = \int_0^t e^{\hat{\beta}' z_0(u)} [z_0 - E_i(\beta, u)] \frac{d\bar{N}_i(u)}{n_i S_i^{(0)}(\hat{\beta}, u)}.$$

By Rebolledo's martingale central limit theorem we can show that  $\bar{W}(t; z_0)$  converges weakly to a zero mean Gaussian martingale on  $[0, \tau]$ , where  $\tau < \inf\{t : EY_{ij}(t) = 0\}$ , with covariate function

$$\begin{aligned} \xi(t, v; z_0) &= \sum_{i=1}^2 \frac{1}{p_i} F_i(t; z_0) F_i(v, z_0) \int_0^{t \wedge v} \frac{e^{2\beta' z_0} \lambda_{i0}(u) du}{s_i^{(0)}(\beta, u)} \\ &+ (F_1(t; z_0) h_1(t; z_0) - F_2(t; z_0) h_2(t; z_0))' \Sigma^{-1} (F_1(v; z_0) h_1(v; z_0) - F_2(v; z_0) h_2(v; z_0)). \end{aligned}$$

It follows that the variance of  $W(t; z_0)$  can be consistently estimated by

$$\begin{aligned} \hat{\sigma}^2(t; z_0) &= \sum_{i=1}^2 \frac{n}{n_i} \hat{F}_i^2(t; z_0) \int_0^t \frac{e^{2\hat{\beta}'z_0} d\bar{N}_i(u)}{[S_i^{(0)}(\hat{\beta}, u)]^2} \\ &+ \left( \hat{F}_1(t; z_0) \hat{h}_1(t; z_0) - \hat{F}_2(t; z_0) \hat{h}_2(t; z_0) \right)' \hat{\Sigma}^{-1} \left( \hat{F}_1(t; z_0) \hat{h}_1(t; z_0) - \hat{F}_2(t; z_0) \hat{h}_2(t; z_0) \right). \end{aligned}$$

The limiting Gaussian process for  $W(t; z_0)$  does not have independent increments, which makes the computation of the distribution of limiting functionals of  $W(t; z_0)$  difficult. To approximate these limiting distributions we shall use a modification of a Monte Carlo technique proposed recently by Parzen *et al* (1997) and Lin *et al* (1994). First, note that the martingales  $\{M_{ij}(u)\}$  in (1) have mean zero and variance  $\{N_{ij}(u)\}$ . By the results in Lin *et al* (1994), if one replaces  $\{M_{ij}(u)\}$  with  $\{G_{ij}N_{ij}(u)\}$ , in (2), where  $G_{ij}$  are independent standard normal random variables, then the limiting distribution of  $\tilde{W}$ , evaluated using the estimated regression coefficients and covariance matrix is the same as that of  $W$ . In particular, to construct the confidence band for  $D(t; z_0) = F_2(t; z_0) - F_1(t; z_0)$ ,  $t \in [t_1, t_2]$ , we simulate  $N$  realizations of

$$\hat{B}(t; z_0) = \hat{W}(t; z_0) / \hat{\sigma}(t; z_0),$$

with

$$\begin{aligned} \hat{W}(t; z_0) &= \sqrt{n} \hat{F}_1(t; z_0) \sum_{j=1}^{n_1} \int_0^t \frac{e^{\hat{\beta}'z_0} G_{1j} dN_{1j}(u)}{n_1 S_1^{(0)}(\hat{\beta}, u)} - \sqrt{n} \hat{F}_2(t; z_0) \sum_{j=1}^{n_2} \int_0^t \frac{e^{\hat{\beta}'z_0} G_{2j} dN_{2j}(u)}{n_2 S_2^{(0)}(\hat{\beta}, u)} \\ &+ \left( \hat{F}_1(t; z_0) \hat{h}_1(t; z_0) - \hat{F}_2(t; z_0) \hat{h}_2(t; z_0) \right)' \hat{\Sigma}^{-1} \left\{ \frac{1}{\sqrt{n}} \sum_{i=1}^2 \sum_{j=1}^{n_i} \int_0^\infty [Z_{ij} - E_i(\hat{\beta}_0, u)] G_{ij} dN_{ij}(u) \right\}. \quad (3) \end{aligned}$$

A  $(1 - \alpha) \times 100\%$  confidence band for  $D(t; z_0)$  over the interval  $[t_1, t_2]$  is given by

$$[\hat{F}_2(t; z_0) - \hat{F}_1(t; z_0)] \pm n^{-1/2} C_\alpha \hat{\sigma}(t; z_0),$$

where  $C_\alpha$  is the  $(1 - \alpha) \times 100$ th percentile of the sample  $\bar{B}^{(k)} = \text{Sup}_{t \in [t_1, t_2]} |\hat{W}^{(k)}(t; z_0) / \hat{\sigma}(t; z_0)|$ , for  $k = 1, \dots, N$ , simulated from (3).

### 3. Example

To illustrate this approach we compare the survival probabilities of chronic phase chronic myelogenous leukemia (CML) patients treated with conventional chemotherapy against patients treated by an allogeneic bone marrow transplants. Patients treated with conventional chemotherapy were from a multicenter trial conducted by the German CML study group. Of the 196 patients in that study, 75 recieved primary treatment with interferon and 121 with hydroxyurea. Patients in this study arm were followed from the time of diagnosis to death or until the end of the study.

The transplant cohort included 548 patients receiving hydroxyurea or interferon pre-treatment and a HLA-identical sibling bone marrow transplant (BMT). All patients were reported to the International Bone Marrow Transplant Registry (IBMTR). IBMTR is a voluntary working group of over 300 transplant centers worldwide that contribute data on their allogeneic bone marrow transplants to a Statistical Center at the Medical College of Wisconsin. Patients in this arm were diagnosed between 1983 and 1991, and were between 15 and 55 years of age. For detailed patient characteristics see Gale *et al* (1998).

The IBMTR only records data on consecutive transplants from member institutions and does not provide data on patients who died while waiting for a transplant. Thus the transplant data is left truncated at the time of transplant. This left truncation can lead to a time-to-treatment bias (See Klein and Zhang (1996)) unless a proper adjustment is made to the risk set. Hence, at each time point, the risk set in the non-transplant cohort consists of all patients still under study while the risk set in the transplant cohort includes only those with a waiting time to transplant less than the current time point who are still under study.

For the CML data, the following covariates were associated with survival: sex (1=female, 0=male), spleen size (1- $\geq 10$  cm, 0=otherwise), year of diagnosis (1- $\geq 1998$ , 0=otherwise), and age at diagnosis (1- $\geq 35$  years, 0=otherwise). A test of interaction indicated that year of diagnosis had a different effect for the two treatments. We fit it separately for the two treatments. Also, the proportionality assumption did not hold for treatment effect, indicating that the relationship between treatment and outcome differed over time. We fit a Cox model stratified on treatment to the time from diagnosis to death. The regression coefficient estimates are given in Table 1.

**Table 1.** Regression coefficient estimates.

Variable	Coefficient Estimate	Standard Error
Sex	-0.434	0.139
Spleen size	0.461	0.146
Age	0.198	0.139
Year of diagnosis:		
Chemotherapy	0.120	0.216
Transplant	-0.553	0.182

When comparing two survival curves based on left-truncated data additional care is required in choosing the comparison interval,  $[t_1, t_2]$ . It is important to choose  $t_1$  such that the risk sets at  $t_1$  consists of a sufficient number of patients for both cohorts in order to make a stable comparison. We choose the comparison interval as  $[6.4, 100.4]$  months since diagnosis. At 6.4 month, the sizes of the risk sets were 189 and 117 for non-transplant and transplant cohort respectively, and at 100.4 month both cohort had at least 10 patients still at risk.

We plot the predicted survival curves and the estimated differences for a particular set of covariates values. The critical value  $C_\alpha$  was approximated based on 5,000 realizations of (3).

Figure 1a shows the estimated survival curves for a recently diagnosed ( $\geq 1988$ ) older ( $\geq 35$  years) male patient with large spleen size  $\geq 10$  cm. Figure 1b shows the estimated difference (BMT-Chemotherapy) between the two survival curves with a 95% pointwise confidence interval and 95% confidence band for such a patient. A similar plot for a patient diagnosed prior to 1988 with the same characteristics is given in Figure 2.

These confidence band plots indicated that the chemotherapy treatment has an early survival advantage due, perhaps, to the toxicity of the bone marrow transplant. There is a significant late survival advantage for transplant patient due to a lower relapse rate. Also for the recently treated cases (Figure 1) BMT had a survival advantage (95% confidence band is  $> 0$ ) starting at 5.50 years after diagnosis. This is in contrast to patients treated prior to 1988 (Figure 2) where BMT started to show an advantage only after 8.29 years since diagnosis. This may be due to the improvement of bone marrow transplant techniques over the years.

In this example, there are 16 sets of possible covariates values. The time points since diagnosis where BMT starts to have a survival advantage are presented in Table 2. These time points ranged from 5.50 years to 8.29 years since diagnosis depending on the given patient characteristics. By contrast to the comparison of two Kaplan-Meier survival curves, this comparison of two predicted survival curves based on the Cox model provides more information to both the physicians and patients.

**Table 2.** Time points  $t_0$  since diagnosis (DX) in years where BMT starts to have survival advantage.

Covariate Values				$C_\alpha$	$t_0$
Sex	Spleen Size	Age	Year of DX		
M	< 10 cm	< 35	< 88	2.96	7.84
M	< 10 cm	< 35	$\geq 88$	2.97	5.97
M	$\geq 10$ cm	< 35	< 88	2.96	7.84
M	$\geq 10$ cm	< 35	$\geq 88$	2.99	5.88
M	< 10 cm	$\geq 35$	< 88	2.99	7.84
M	< 10 cm	$\geq 35$	$\geq 88$	2.95	5.88
M	$\geq 10$ cm	$\geq 35$	< 88	2.96	8.29
M	$\geq 10$ cm	$\geq 35$	$\geq 88$	2.94	5.50
F	< 10 cm	< 35	< 88	2.96	8.29
F	< 10 cm	< 35	$\geq 88$	2.93	5.97
F	$\geq 10$ cm	< 35	< 88	2.99	7.84
F	$\geq 10$ cm	< 35	$\geq 88$	2.98	6.24
F	< 10 cm	$\geq 35$	< 88	2.92	7.84
F	< 10 cm	$\geq 35$	$\geq 88$	2.89	5.97
F	$\geq 10$ cm	$\geq 35$	< 88	2.90	7.84
F	$\geq 10$ cm	$\geq 35$	$\geq 88$	2.92	5.88

#### 4. Remarks

Plotting the confidence band for the difference of two predicted survival functions provides a valuable decision making tool for physicians and patients. The proposed simulation method is easy to program, and offers a flexible way to construct such confidence bands, particularly when the limiting distributions cannot be evaluated analytically. The proposed simulation method can be extended to compare the difference of two survival curves based on other models, such as Aalen's (1989) additive model or other more general models.

The estimated critical value,  $C_\alpha$ , depends on the number of realizations  $N$ . It is important to know what is the appropriate  $N$ . In our example for an early diagnosed young ( $< 35$  yr) male patient with small spleen size ( $< 10$  cm), the estimated  $C'_\alpha$ 's were 3.01, 2.98, 2.97, 3.01, 2.97, and 3.01 for  $N = 500, 1500, 3000, 5000, 8000$  and  $10000$ , respectively. It appears that the estimate of  $C_\alpha$  is reasonably stable after only 500 replications.

#### ACKNOWLEDGMENTS

This research was supported by Grant 2 RO1 CA54706-06 from the National Cancer Institute, and PO1-CA-40053 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases and The National Heart, Lung and Blood Institute. We thank the IBMTR and the German CML Study Group for providing us the CML data

#### REFERENCES

- Aalen, O.O. (1989). "A linear regression model for the analysis of life times", *Statistics In Medicine*, **8**, 907-925.
- Andersen, P.K. and Gill, R.D. (1982), "Cox's regression model for counting processes: a large sample study," *Ann. Statist.*, **10**, 1100-1120.
- Andersen, P., Borgan, O., Gill, R. and Keiding, N. (1993), *Statistical Models Based on Counting Processes*, New York: Springer-Verlag.
- Breslow, N. (1975), "Analysis of survival data under the proportional hazards model", *Internat. Statist. Rev.*, **43**, 45-58.
- Cox, D.R. (1972), "Regression models and life tables (with discussion)", *JRSS*, **B 34**, 187-220.
- Fleming, T.R. and Harrington, D.P., (1991), *Counting Processes and Survival Analysis*, New York: Wiley.



- Gale, R.B., Helmann, R., Zhang, M.J., Hasford, J., Goldman, J.M., Heimpel, H., Klein, J.P., Kolb, H.J., McGlave, P.B., Passweg, J.R., Rowlings, P.A., Sobocinski, K.A., Horowitz, M.M. and the German CML Study Group, (1998), "Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia (CML)", *Blood*, (In Press).
- Kalbfleisch, J.D. and Prentice, R.L. (1980), *The Statistical Analysis of Failure Time Data*, New York: Wiley.
- Kaplan, E.L. and Meier, P. (1958), "Nonparametric estimation from incomplete observations", *Journal of the American Statistical Association*, **53**, 457-481.
- Klein, J.P. and Zhang, M.J. (1996), "Statistical challenges in comparing chemotherapy and bone marrow transplantation as a treatment for leukemia", *Life Data: Models in Reliability and Survival Analysis*, (ed. N.P. Jewell et al), 175-185.
- Lin, D.Y., Fleming, T.R. and Wei, L.J. (1994), "Confidence bands for survival curves under the proportional hazards model," *Biometrika*, **81**, 73-81.
- Lai, T.L. and Ying, Z. (1991), "Estimating a distribution function with truncated and censored data," *Ann. Statist.*, **19**, 417-442.
- Parzen, M.I., Wei, L.J. and Ying, Z. (1997), "Simultaneous confidence intervals for the difference of two survival functions," *Scand J Statist*, **24**, 309-314.
- Woodroffe, M. (1985), "Estimating a distribution function with truncated data," *Ann. Statist.*, **13**, 163-177.

DIVISION OF BIOSTATISTICS  
MEDICAL COLLEGE OF WISCONSIN  
MILWAUKEE, WISCONSIN 53226

Figure 1(a). Predicted Probability of Survival for Recently Diagnosed, Older, Male Patient with Large Spleen Size

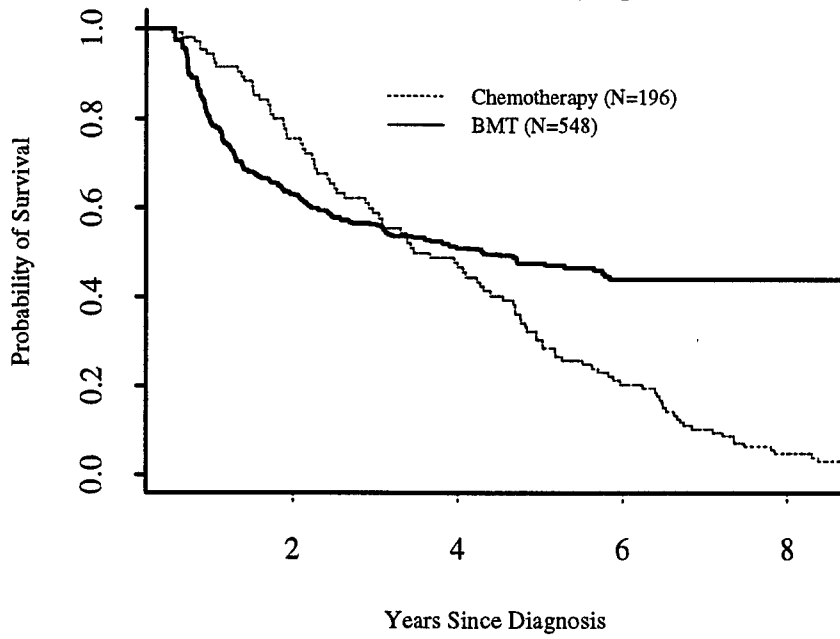


Figure 1(b). Difference of Survival Probabilities (BMT - Chemotherapy) for Recently Diagnosed, Older, Male Patient with Large Spleen Size

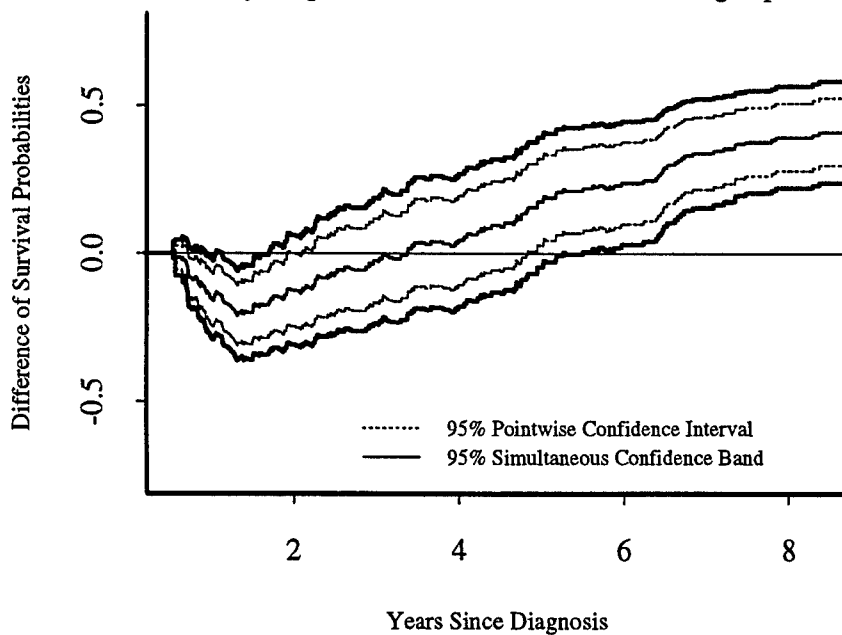


Figure 2(a). Predicted Probability of Survival for Early Diagnosed, Older, Male Patient with Large Spleen Size

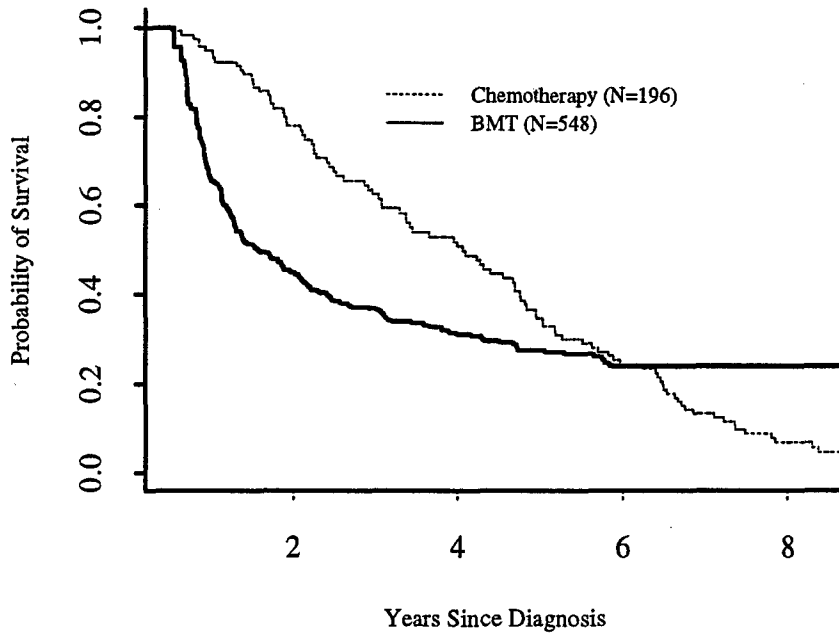
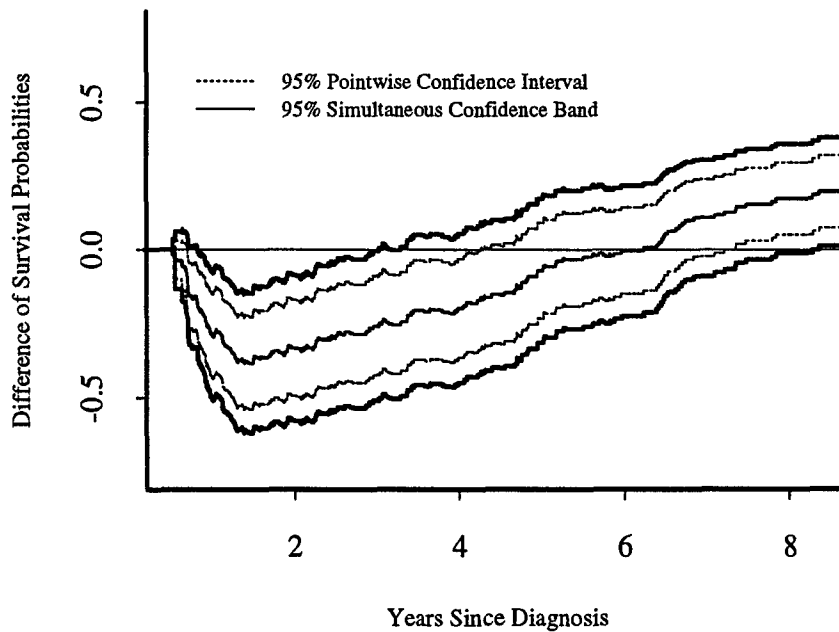


Figure 2(b). Difference of Survival Probabilities (BMT - Chemotherapy) for Early Diagnosed, Older, Male Patient with Large Spleen Size



**Modeling Multistate Survival  
Illustrated In  
Bone Marrow Transplantation**

John P. Klein, Ph.D.

**DIVISION OF BIostatISTICS**



**MEDICAL  
COLLEGE  
OF WISCONSIN**

**MILWAUKEE, WISCONSIN**

**Modeling Multistate Survival  
Illustrated In  
Bone Marrow Transplantation**

John P. Klein, Ph.D.

and

Chunlin Qian, Ph.D.

Technical Report 15

August 1996

Division of Biostatistics  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee WI 53226  
Phone: (414)456-8280

# MODELING MULTISTATE SURVIVAL ILLUSTRATED IN BONE MARROW TRANSPLANTATION

John P. Klein, Chunlin Qian  
John P. Klein, Medical College of Wisconsin, 8701 Watertown Plank Road,  
Milwaukee, WI 53226

KEY WORDS: Proportional hazards models, Time Dependent Covariates, Left Truncation

## 1. INTRODUCTION

In many applications of survival analysis techniques the ultimate outcome of a patient's treatment depends on the occurrence and timing of some intermediate events. This is particularly true when studying the recovery process of a patient from a bone marrow transplant for leukemia. Here a patient can experience one of several terminal events, such as death in remission, reoccurrence of their leukemia or simply death. As the patient recovers from their transplant a number of intermediate events may occur that have an influence on their eventual prognosis. Examples of such intermediate events are the return of the patient's platelets to a "normal" level, the development of various types of infections, the occurrence of acute or chronic graft-versus-host disease, etc.

A natural way to model complex experiments such as this is by using a multistate model. Andersen et al (1991) (See also Andersen et al 1993) has studied such models using a finite state Markov process model where the hazard rates for each possible transition in the multistate model are modeled by a separate Cox (1972) proportional hazards model. Here each of the transition probabilities is estimated using a (left truncated) Cox model. In a multistate model with two intermediate events and two terminal events this entails fitting 12 separate Cox models.

Recently, Klein et al (1993) have suggested an alternative approach to multistate modeling. They suggest fitting a Cox model to each of the events with time dependent covariates used to model the timing of the intermediate events that precede the event of interest. In a multistate model with two intermediate events and two terminal events this entails fitting 4 separate Cox models. This model is discussed in Section 3.

The Klein and Andersen approach are two extremes of how one can model multistate survival. In this report we shall examine how one may model multistate survival experiments where some of the transition rates are assumed to be proportional to others. This general model is discussed in Section 4.

Once the transition rates are modeled it is necessary to synthesize these rates to provide predictions of the patient's eventual prognosis. The patient's prognosis is a dynamic entity that depends on their history at a given point in time. The models we fit allow us to estimate a series of

predictive probabilities based on potential patient histories which may be observed at some time  $t$ . These patient histories include the information known on the patient at entry to the study (the fixed-time covariates) and the knowledge of when the intermediate events have occurred.

Recently, Arjas and Eerola (1994) (cf. Eerola (1993)) have described a framework of "predictive causality" for longitudinal studies that can be used to illustrate how the timing of the occurrences of the time dependent covariates in a patient's recovery process changes the prediction of his or her final prognosis. For a given patient, let  $(T, X) = \{(T_m, X_m); m \geq 1\}$  denote the ordered times,  $0 \leq T_1 \leq T_2 \leq \dots$ , at which events occur during a patient's recovery from transplantation, with description,  $X_m$ , of what has happened to the patient at time  $T_m$ . In the bone marrow transplantation recovery process  $X_m$  may denote return of the platelets to normal levels, the development of acute GVHD, or the occurrence of relapse, or death. A patient history,  $H_t$ , at some time  $t$  post-transplantation consists of all the pre-transplantation information available on the patient (the fixed-time covariates) and the set of marked points,  $\{(T_m, X_m); T_m \leq t\}$ , reflecting what has happened to the patient up to this point in time. We consider the prediction that some event,  $W$ , such as relapse, occurs in time interval,  $E (W \in E)$ , for example within two years post-transplantation. The predicted probability that  $W \in E$  should depend on the patient's history at the time  $t$  at which this prediction is made. We define a prediction process by  $\mu_t(E) = P[W \in E | H_t]$

The prediction process allows us to examine the effect of time dependent (and fixed-time) covariates on the predicted prognosis of a given patient in three ways. First, we can fix the time  $t$  and the history,  $H$ , for a patient up to time  $t$  and see how the predicted probability of  $W$  being in  $E$  changes as the prediction interval  $E$  varies. In the bone marrow transplantation example this will allow us to estimate how the probability of relapse within  $\tau$  years post-transplantation, changes as  $\tau$  varies for a patient with a given history at time  $t$ . That is, given a particular history at a given time for a patient we can provide a prognosis for this patient at times in the future. Second, we can fix a potential history,  $H$ , for a patient and the prediction interval,  $E$ , and see how the  $\mu_t(E)$  changes as  $t$  increases. For example, for a patient with a given history of development of acute GVHD or platelet recovery, this will give insight into how more and more of a patient history allows us to refine our prediction of the chance that he or she would relapse within the first two years post-transplantation, say. Arjas and Eerola call this the learning effect. Finally, we can fix the prediction interval,  $E$ , and the time at which we observe the patient history,  $t$ , and look at the prediction process for patients with different histories. This allows us to study directly the effect of the timing of the intermediate endpoints on the prognosis of future patients. In the bone marrow transplantation recovery process this may suggest to the physician that, if certain events have not occurred by a given time, some additional therapy should be given, based on this model.

The example that is used throughout this paper is from a multicenter bone marrow transplantation study of patients given an HLA identical sibling transplants, conducted between

1985 and 1990, for patients with acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia reported to the International Bone Marrow Transplant Registry. The data set consists of 1823 patients with observation times ranging from 10 days to 2236 days. 957 patients were alive and disease free at their last observation time, 442 died in remission and 424 patients were observed to relapse. In Section 2 a multistate model for this data is presented and in Section 5 we shall present some empirical estimates of the predicted probabilities.

## 2 BONE MARROW TRANSPLANTATION

Bone marrow transplantation is a standard treatment for acute leukemia. Recovery following bone marrow transplantation is a complex process. Prognosis for recovery may depend on risk factors known at the time of transplantation, such as patient's or donor's age and sex, the stage of initial disease, the time from diagnosis to transplantation, and so on. The final prognosis may change as the patient's post-transplantation history develops with the occurrence of events during the recovery process, such as the development of acute or chronic graft-versus-host disease (GVHD), the return of the platelet count to normal levels, the return of granulocytes to normal levels, or the development of infections. Transplantation can be considered a failure when a patient's leukemia returns (relapse) or when he or she dies while in remission (treatment-related death). Of interest is how the probabilities of relapse (denoted by  $R$ ) and treatment-related death (denoted by  $D$ ), as well as leukemia-free survival (the probability of being alive and in remission), depend on the pre-transplantation (fixed-time covariates) and post-transplantation (time dependent covariates) patient history.

Figure 1 shows a simplified diagram of a patient's recovery process based on two intermediate events which may occur in the recovery process. These intermediate events are the development of acute GVHD which typically occurs within the first 100 days following transplantation (denoted by an  $A$ ), and the recovery of the platelet count to a self-sustaining level  $\geq 40 \times 10^9/L$  (called platelet recovery in the sequel and denoted by a  $P$ ). Immediately following transplantation, patients have depressed platelet counts and are free of acute GVHD. At some point in time they may develop acute GVHD or have their platelets recover, at which time their prognosis (probabilities of treatment-related death or relapse at some future time) may change. These events may occur in any order or a patient may die or relapse without any of these events occurring. Patients may then experience the other event, which again modifies their prognosis, or they may die or relapse.



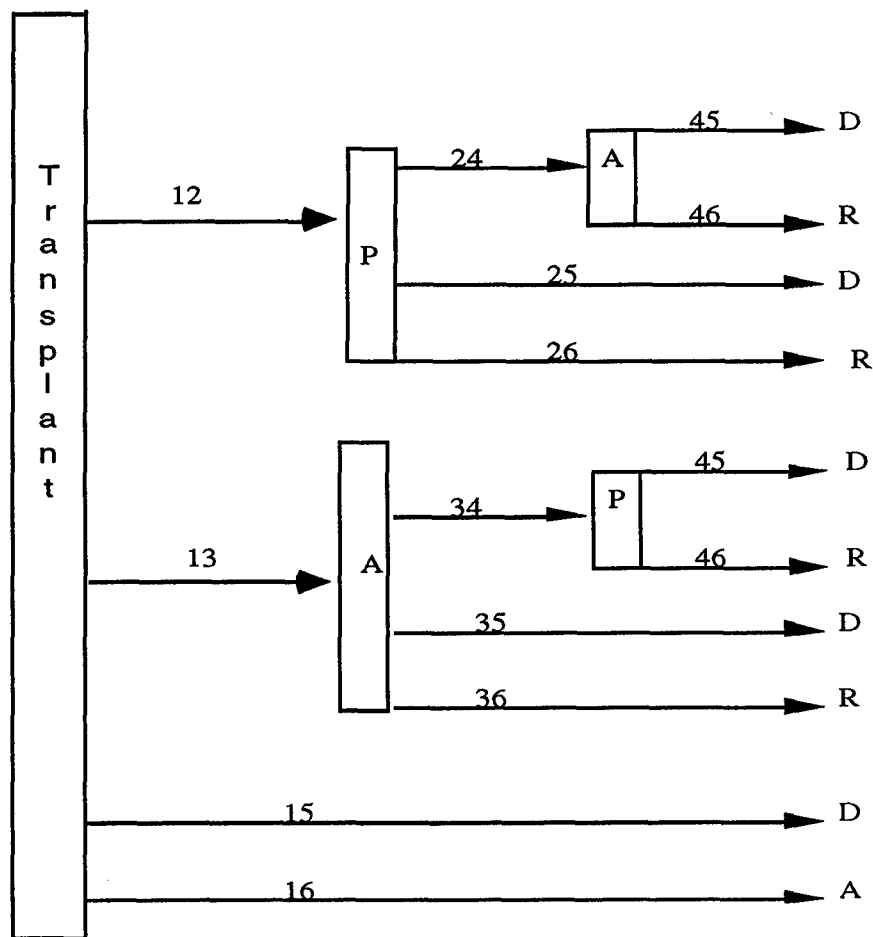


FIGURE 1

Multistate Model For Bone Marrow Transplant Recovery

Figure 1 shows that there are 12 possible transitions that can occur in this multistate model. There are six possible states in which a patient may be in at any given time,  $t$ . These states are:

- 1-  $\{T_P \geq t, T_A \geq t, T_D \geq t, T_R \geq t\}$  (Alive disease free without having GVHD or having had platelets recovered)
- 2-  $\{T_P < t, T_A \geq t, T_D \geq t, T_R \geq t\}$  (Alive disease free without having GVHD with platelets recovered)
- 3-  $\{T_P \geq t, T_A < t, T_D \geq t, T_R \geq t\}$  (Alive disease free without platelets recovered having experienced GVHD)
- 4-  $\{T_P < t, T_A < t, T_D \geq t, T_R \geq t\}$  (Alive disease free with platelets recovered having experienced GVHD)
- 5-  $\{T_D < t, T_R \geq t\}$  (Dead prior to relapse)
- 6-  $\{T_D \leq t, T_R < t\}$  (Relapsed)

### 3. PROPORTIONAL HAZARDS MODEL

In this section we shall present a basic model for multistate survival studies based on a series of Cox regression analysis using time dependent covariates. To model survival we assume that an individual is at risk having any one of the events in some set  $e$ . This set consists of both the intermediate events which may affect a patient's eventual prognosis and the terminal events. In the bone marrow transplant example the set  $e$  is  $\{A, P, R, D\}$ , where  $A$  is the event GVHD has occurred,  $P$  is the event the platelets have recovered,  $R$  is the event relapsed and  $D$  is the event died.

From the events in the set  $e$  we can define a set of states  $s = \{1, 2, \dots, p\}$ . Each element of  $s$  tells us which final event has occurred or what combination of intermediate events has occurred. In the transplant example there are six states listed in the previous section.

For a given model only certain transitions are possible. We let  $t$  be the set of possible transitions. In the transplant example  $t$  has twelve elements as shown in Figure 1. That is  $t = \{12, 13, 15, 16, 24, 25, 26, 34, 35, 36, 45, 46\}$ . For any event  $X \in e$  we define  $t(X)$  as the set of transitions into event  $X$  that are possible. In our example  $t(P) = \{12, 34\}$ ,  $t(A) = \{13, 23\}$ ,  $t(D) = \{15, 25, 35, 45\}$ , and  $t(R) = \{16, 26, 36, 46\}$ .

For any event,  $X$ , in  $e$  we define the ancestor set  $a(X)$  as the set of intermediate events that may happen prior to the occurrence of the event  $X$ . In our example we have  $a(P) = \{A\}$ ,  $a(A) = \{P\}$  and  $a(R) = a(D) = \{A, P\}$ .

To model the transitions rates for this model we shall use a proportional hazards regression model. For each event,  $X$ , in  $e$  we fit a proportional hazards regression model which includes the fixed time covariates specific to the event as well a time dependent covariate for each of the events in the ancestor set of  $X$ . If we let  $Z_F$  be the vector of fixed time covariates that have an influence on any event in  $e$  and let  $\beta_{FX}$  be a vector of risk coefficients for these covariates for the event  $X$ . Note that if a fixed covariate has no effect on the timing of event  $X$  then the risk coefficient for that factor is set to 0. The model for the hazard rate of the time to event  $X$  is given by

$$\lambda(t | Z_F) = \lambda_{0X}(t) \exp \left\{ \beta_{FX} Z_F + \sum_{X' \in a(X)} \beta_{X'X} I[T_{X'} < t] \right\}. \quad (3.1)$$

Here  $I[\ ]$  is the indicator function and  $\beta_{X'X}$  is the risk coefficient for the effect of the occurrence of event  $X'$  on the time to event  $X$ . The baseline hazard rate,  $\lambda_{0X}(t)$ , can be different for distinct levels of some fixed covariates although for simplicity we shall consider the unstratified case in the sequel. The parameters in (4.1) can be estimated from any standard Cox regression package.

Using the model (4.1) the hazard rate for any of the transitions in the set  $t$  can be modeled. Specifying a transition determines  $X$  and the values to be assigned to the indicators  $I[T_X < t]$  for any intermediate event. For example,

$$\lambda_{15}(t | \mathbf{Z}_F) = \lambda_{0D}(t) \exp \{ \beta_{FD} \mathbf{Z}_F \}$$

$$\lambda_{25}(t | \mathbf{Z}_F) = \lambda_{0D}(t) \exp \{ \beta_{FD} \mathbf{Z}_F + \beta_{PD} \}$$

$$\lambda_{35}(t | \mathbf{Z}_F) = \lambda_{0D}(t) \exp \{ \beta_{FD} \mathbf{Z}_F + \beta_{AD} \}$$

and

$$\lambda_{45}(t | \mathbf{Z}_F) = \lambda_{0D}(t) \exp \{ \beta_{FD} \mathbf{Z}_F + \beta_{PD} + \beta_{AD} \}.$$

For any transition,  $ij$ , we define the cumulative transition rate as

$$\Lambda_{ij}(t | \mathbf{Z}_F) = \int_0^t \lambda_{ij}(u | \mathbf{Z}_F) du, \quad i \neq j, \quad i, j \in t$$

$$\Lambda_{ij}(t | \mathbf{Z}_F) = 0 \quad \text{if } i \neq j, \quad i, j \notin t, \quad \text{and}$$

$$\Lambda_{ii}(t | \mathbf{Z}_F) = - \sum_{j \in s} \Lambda_{ij}(u | \mathbf{Z}_F), \quad i \in s.$$

Since  $\Lambda_{ij}(t | \mathbf{Z}_F)$  is absolutely continuous for any  $i, j \in s$  it follows that the matrix  $\Lambda = (\Lambda_{ij})_{p \times p}$  is the transition intensity of a Markov process with state space  $s = \{1, \dots, p\}$  (See Andersen et al pp 92-93). The transition probability matrix of this Markov process is given by

$$\mathbf{P}[s, t | \mathbf{Z}_F] = \prod_{s < u \leq t} [\mathbf{I} + d\Lambda(u | \mathbf{Z}_F)], \quad (3.2)$$

where  $\Pi$  is the product-integral (cf. Gill and Johansen (1990) for details on the matrix product integral) and  $\mathbf{I}$  is the  $p \times p$  identity matrix. This transition probability matrix serves as the basis for making an inference about a patient's eventual prognosis given their current history.

To estimate the transition probability matrix the required Cox models are fit and the estimators of  $\beta$  are obtained. Breslow's estimator of the baseline hazard (Breslow 1972) rates are then computed and substituted into (4.2). For the bone marrow transplant example this yields the following estimators of the predicted probabilities (Here we shall ignore the dependence on  $\mathbf{Z}_F$  for notational convenience)

$$\hat{P}_{ii}(s,t) = \prod_{s < u \leq t} \left\{ 1 - \sum_{j:i < j} \Delta \hat{\Lambda}_{ij}(u) \right\}, \quad i=1, 2, 3, 4;$$

$$\hat{P}_{ij}(s,t) = \sum_{s < u \leq t} \hat{P}_{ii}(s,u-) \hat{P}_{jj}(u,t) \Delta \hat{\Lambda}_{ij}(u), \quad ij=12,13,24, 34,45,46;$$

$$\hat{P}_{ij}(s,t) = \sum_{s < u \leq t} \hat{P}_{ii}(s,u-) [\Delta \hat{\Lambda}_{ij}(u) + \hat{P}_{4j}(u,t) \Delta \hat{\Lambda}_{i4}(u)], \quad ij=25,26, 35, 36;$$

and

$$\hat{P}_{1j}(s,t) = \sum_{s < u \leq t} \hat{P}_{11}(s,u-) [\Delta \hat{\Lambda}_{1j}(u) + \hat{P}_{2j}(u,t) \Delta \hat{\Lambda}_{12}(u) + \hat{P}_{3j}(u,t) \Delta \hat{\Lambda}_{13}(u)], \quad j=4,5,6.$$

The asymptotic distribution of  $\mathbf{P}[s,t | \mathbf{Z}_F]$  can be obtained by basic counting process techniques. Details are found in Qian(1995). The basic result is as follows (Here for ease of exposition we have suppressed the dependence on the fixed covariates,  $\mathbf{Z}_F$ ):

*Theorem 1* Under suitable regularity conditions each of the elements of the random matrix

$\sqrt{n}\{\hat{\mathbf{P}}[s,t | \mathbf{Z}_F] - \mathbf{P}[s,t | \mathbf{Z}_F]\}$  converges weakly to a zero-mean Gaussian martingale with covariance function given by

$$\text{Cov}(\sqrt{n}(\hat{P}_{ij}(s,t), \hat{P}_{km}(s,t))) = \sum_{\mathbf{x} \in \mathbf{e}} \left\{ \int_s^t \frac{F_{ij,\mathbf{X}}(s,u,t) F_{km,\mathbf{X}}(s,u,t)}{s_{\mathbf{X}}^{(0)}(\beta_{\mathbf{X},u})} d\Lambda_{o\mathbf{X}}(u) + \mathbf{G}'_{ij,\mathbf{X}} \Sigma_{\mathbf{X}}^{-1} \mathbf{G}_{km,\mathbf{X}} \right\},$$

where

$$F_{ij,\mathbf{X}} = \sum_{\substack{gh \in t(\mathbf{X}) \\ i \leq g < h \leq j}} D_{ighj,\mathbf{X}}(s,u,t); \quad ij \in s$$

$$\mathbf{G}_{ij,\mathbf{X}}(s,t) = \int_s^t \sum_{\substack{gh \in t(\mathbf{X}) \\ i \leq g < h \leq j}} \{ D_{ighj,\mathbf{X}}(s,u,t) [\mathbf{Z}_{g1} - \mathbf{e}_{\mathbf{X}}(\beta_{\mathbf{X},u})] d\Lambda_{o\mathbf{X}}(u) \}; \quad ij \in s$$

$$D_{ighj,\mathbf{X}}(s,u,t) = \exp\{\beta_{\mathbf{X}} \mathbf{Z}_{gh}\} P_{ig}(s,u-) [P_{hj}(u,t) - P_{gj}(u,t)] \quad ij, gh \in s.$$

$$s_{\mathbf{X}}^{(0)}(\beta_{\mathbf{X},u}) = \sum_{l=1}^n \exp\{\beta_{\mathbf{X}} \mathbf{Z}_{Xl}(u)\} Y_{Xl}(t),$$

$$e_X(\beta_{X,u}) = \frac{\sum_{l=1}^n Z_{Xl}(u) \exp\{\beta_X Z_{Xl}(u)\} Y_{Xl}(t)}{s_X^{(0)}(\beta_X, u)}; \text{ and}$$

$\Sigma_X$  is the covariance matrix of the estimates of  $\beta_X$ .

Here  $Z_{jk}$  is the union of the set of fixed covariates with a set of indicator covariates that tell us that an individual is in state  $j$  at time  $t$ .  $Y_{Xl}(t)$  is the indicator that individual  $l$  is at risk for event  $X$  at time  $t$ , and  $Z_{Xl}(t)$  is the covariate vector for event  $X$  for individual  $l$  at time  $t$ .

Estimators of the variability of the predicted probabilities are obtained by substituting the appropriate estimator into the covariance in Theorem 1. In particular we have that the variance of  $\hat{P}_{ij}(s,t)$  is estimated consistently by

$$\sum_{x \in e} \left[ \int_s^t \left[ \frac{\hat{F}_{ij,X}(s,u,t)}{S_X^{(0)}(\beta_X, u)} \right]^2 dN_X(u) + \hat{G}'_{ij,X} i^{-1}(\hat{\beta}_X) \hat{G}_{ij,X} \right], \quad (3.3)$$

where  $dN_X(t)$  is the number of type  $X$  events occurring at time  $t$  and  $i_X$  is the observed information matrix for the regression estimates for event  $X$ .

#### 4. Child-Event Models

The model constructed in Section 3 assumes that for any event  $X$  in  $e$  the hazard rates of any two  $X$  transitions  $ij, km \in t(X)$  are proportional. This is a testable hypothesis that may fail to be true in some circumstances. In this section we shall look at models that relax this assumption.

To relax this proportionality assumption we consider models with time dependent stratification. Suppose we can divide the ancestor set  $a(X)$  into two disjoint sets  $a_s(X)$  and  $a_c(X)$ . Here  $a_s(X)$  is the set of ancestors of  $X$  for which a time dependent stratification will be used and  $a_c(X)$  is the set of ancestors for which the proportional hazards modeling will be used. Let  $m(X) = 2$  to the power the number of elements in  $a_s(X)$ . Here  $m(X)$  is the total number of distinct baseline hazard rates to be fit in the model. Number the  $m(X)$  baseline hazard rates from  $(0, \dots, 0)$  to  $(1, \dots, 1)$ . At an event time  $T_X$  we shall call an event a type  $X_h$ th event if  $h = (I[T_X' < t], X' \in a_s(X))$ . Thus we have created  $m(X)$  "child-events",  $X_h$ , from each parent-event  $X$ . The  $X_h$  transition set is naturally  $t(X_h) = \{ij \in t(X): \{h = (I[T_X' < t], X' \in a_s(X))\}$  as determined by state  $i\}$ .

For each child event a distinct baseline hazard rate is assumed so that

$$\lambda_{X_h}(t | Z_F) = \lambda_{0X_h}(t) \exp\{\beta_{FX} Z_F + \sum_{X' \in a_c(X)} \beta_{X'X} I\{T_{X'} < t\}\}$$

and the hazard rate for each  $X_h$  transition is

$$\lambda_{ij}(t) = \lambda_{0X_h}(t) \exp\{\beta_X Z_{ij}\}.$$

Here  $Z_{ij}$  consists of the fixed covariates and a vector of 0 and 1's with a 1 in the correct position for any event in  $a_c(X)$  which must have occurred prior to time  $t$  to be in state  $i$ .

Estimates of  $\Lambda_{0X_h}(t)$  and the  $\beta$ 's can be obtained from standard Cox regression packages. As opposed to the proportional hazards model, in this analysis there may be some time dependent stratification so that left truncated regression models must be employed. Once the parameter estimates are obtained and an estimate for  $\Lambda_{ij}(t)$  is obtained then these can be used in (3.2) to obtain estimates of the predicted probabilities.

To illustrate this approach consider the bone marrow transplantation example. One possible time dependent stratification is to fit different baseline rates for the death event for individuals whose platelets have or have not recovered. Consider the parent event  $D$  whose ancestors are the events  $P$  and  $A$ . The set  $a(D)$  is divided into the sets  $a_c(D) = \{A\}$  and  $a_s(D) = \{P\}$ . Two child events,  $D_1$  and  $D_2$  are defined by  $\{T_p \geq T_D\}$  and  $\{T_p < T_D\}$ . Here  $D_1$  is the event death without platelets being recovered and  $D_2$  the event death with platelets recovered. Two proportional hazards models are fit for to the death event. The first model is  $\lambda_{D_1}(t | \mathbf{Z}_F) = \lambda_{0D_1}(t) \exp\{\beta_{FX} \mathbf{Z}_F + \beta_{ADI}[T_A \leq t]\}$ . Individuals are censored for  $\lambda_{0D_1}$  when their platelets recover. For the second model we have  $\lambda_{0D_2}(t) \exp\{\beta_{FX} \mathbf{Z}_F + \beta_{ADI}[T_A \leq t]\}$ . Here the analysis for  $\lambda_{0D_2}$  is based on a left truncated Cox regression model with individuals entering the risk set at the time at which their platelets recover. The four transition rates to the state  $D$  are

$$\lambda_{15}(t | \mathbf{Z}_F) = \lambda_{0D_1}(t) \exp\{\beta_{FX} \mathbf{Z}_F\},$$

$$\lambda_{25}(t | \mathbf{Z}_F) = \lambda_{0D_2}(t) \exp\{\beta_{FX} \mathbf{Z}_F\},$$

$$\lambda_{35}(t | \mathbf{Z}_F) = \lambda_{0D_1}(t) \exp\{\beta_{FX} \mathbf{Z}_F + \beta_{AD}\}; \text{ and}$$

$$\lambda_{45}(t | \mathbf{Z}_F) = \lambda_{0D_2}(t) \exp\{\beta_{FX} \mathbf{Z}_F + \beta_{AD}\}.$$

If in addition to stratifying on the recovery time for the platelets we also stratify for  $D$  on the occurrence of acute GVHD we have  $a_s(D) = \{P, A\}$  and  $a_c(D)$  is the empty set. Now there are four child events for  $D$  corresponding  $h = (0,0), (1,0), (0,1)$  and  $(1,1)$ . These correspond to the states  $\{T_p > T_D, T_A > T_D\}$ ,  $\{T_p \leq T_D, T_A > T_D\}$ ,  $\{T_p > T_D, T_A \leq T_D\}$  and  $\{T_p \leq T_D, T_A \leq T_D\}$ , respectively. The models for the transitions into state  $D$  contain distinct baseline hazard rates for each of these states, and there are no time dependent covariates in the model.

The asymptotic properties of the estimated prediction probabilities are similar to those in theorem one with the simple change of the summations over  $X \in e$  being changed to double sums over both  $X \in e$  and  $h=1, \dots, m(X)$ . For example, the estimated variance of the predicted probability of a type  $ij$  transition in the time period  $(s, t]$  is

$$\hat{V}(\hat{P}_{ij}(s,t)) = \sum_{x \in e} \sum_{h=1}^{m(X)} \left[ \int_s^t \left[ \frac{\hat{F}_{ij,X}(s,u,t)}{S_{x_h}(0)(\beta_X, u)} \right]^2 dN_{X_h}(u) + \hat{G}'_{ij, X_h} i^{-1}(\hat{\beta}_X) \hat{G}_{ij, X_h} \right].$$

In the model presented above the coefficient vector,  $\beta_X$ , is the same for all child events,  $X_h$ . This assumption can be relaxed as well by allowing each child event to have its own  $\beta$ . This involves fitting separate Cox models for each child event. The estimation process follows as above. Here an estimate of the asymptotic variance of  $\hat{P}_{ij}(s,t)$  is

$$\hat{V}(\hat{P}_{ij}(s,t)) = \sum_{x \in e} \sum_{h=1}^{m(X)} \left[ \int_s^t \left[ \frac{\hat{F}_{ij, X_h}(s,u,t)}{S_{x_h}(0)(\beta_{X_h}, u)} \right]^2 dN_{X_h}(u) + \hat{G}'_{ij, X_h} i^{-1}(\hat{\beta}_{X_h}) \hat{G}_{ij, X_h} \right].$$

The extreme case of this model is where all events are divided to their fullest (i.e. each child event corresponds to one and only one transition) and each transition has its own  $\beta$ . This is the usual model for multi-state processes introduced by Andersen et al (1991) (Cf. Andersen et al (1993) Section VII.2).

## 5. BONE MARROW TRANSPLANT EXAMPLE

To illustrate these calculations we shall fit the multistate proportional hazards model to the data from the International Bone Marrow Transplant Registry. As shown in figure 1 we have a model with two intermediate events, platelet recovery (P) and acute GVHD (A) and two terminal events, death in remission (D) and relapse (R). There were 1823 patients in the data set.

After a careful examination of the effects of various fixed time covariates on the four events we found that the most important covariates were the patients Karnofsky score at transplant, their waiting time from diagnosis to transplant and their age. In testing for proportional hazards for each of these covariates using a time dependent covariate approach (See Klein and Moeschberger (1996)) we found that the relapse hazards were not proportional at different ages. In the analysis reported below we have decided to stratify all the analysis on age (two strata age  $\leq 20$  or age  $> 20$ ). The other two risk factors were discretized as Karnofsky Score  $\leq 80$  versus Karnofsky score  $\geq 90$ , and time from diagnosis to transplant  $\leq 10$  weeks versus  $> 10$  weeks.

To apply the proportional hazards model we fit four Cox models to the data, one for each of the four endpoints. For each event,  $X$ , we include a time dependent covariate for each event in  $a(X)$ . The results are found in Table 1.

Table 1

**Estimated Risk Coefficients And Standard Errors For The Proportional Hazards Model**

Covariate	Platelet Recovery	Acute GVHD	Death in Remission	Relapse
Karnofsky Score $\leq 80$	-.333 (.075)	.208 (.109) *	.359 (.108)	.414 (.119)
Waiting Time >10 Weeks	-.062 (.060) *	.014 (.099) *	.411 (.099)	.351 (.102)
Platelet Recovered		-.347 (.166)	-1.405 (.116)	-.322 (.126)
Acute GVHD	-0.433 (.074)		1.172 (.097)	-.283 (.130)

\* Not significant at 5% level

Here we see that patients with a low Karnofsky score tend to take longer to have their platelets recover and are more likely to die or relapse. Patients with a long waiting time to transplant also have an increased risk of relapse and death.

Examining the two time dependent covariates we see that when a patient's platelets recover their risks of GVHD, death and relapse are decreased. When a patient develops GVHD their risk of relapse is decreased but their risk of death is increased. This decrease in relapse risk is the well-known graft-versus-leukemia effect of GVHD.

To examine the fit of the proportional hazards model we also fit the Andersen model with distinct baseline hazard rate (stratified on age) and different covariate values for each transition. Here a standard Cox model is used for transitions 12, 13, 15, 16 and left truncated Cox models are used for all other transitions. The results are in Table 2.



**Table 2**  
**Estimated Risk Coefficients And Standard Errors From Fitting The Andersen Model**

Transition	Karnofsky Score $\leq 80$	Waiting Time $> 10$ Weeks
1->2	-.319 (.083)	-.065 (.065)*
1->3	.251 (.115)	-.013 (.106)
1->5	.422 (.185)	.760 (.170)
1->6	.609 (.251)	.518 (.239)
2->4	-.098 (.364)*	.189 (.288)*
2->5	.959 (.254)	.031 (.267)*
2->6	.332 (.157)	.246 (.127)
3->4	-.334 (.173)	-.040 (.146)
3->5	.142 (.190)*	.330 (.180)*
3->6	1.063 (.454)	.445 (.434)*
4->5	.235 (.273)*	.297 (.233)*
4->6	.133 (.372)*	.474 (.297)*

\* Not significant at 5% level

To examine the fit of the simpler proportional hazards we plot in Figure 1 the logs of the baseline hazards estimated from the Andersen model for each of the transitions. If the proportional hazards model holds true then we should have parallel curves for each transition into one of the four events. A cursory look at these figures does not suggest any marked departure from proportionality.

We shall use the proportional hazards multistate model to examine how a patient's prognosis at one year after transplant depends on their history in the first few weeks of their recovery process. We first estimate the probability of dying in remission in the first year given the patient's history at  $s$  weeks following transplant for each of the four possible states a patient may be in at  $s$  weeks. This estimated probability is given by  $\hat{P}_{15}[7s, 365]$ . Figure 2 shows the estimates under the proportional model for an individual who is under 20 years of age with a Karnofsky score of 90 or more and a waiting time to transplant of less than 10 weeks. Other values of the fixed covariates would give slightly different pictures. Here a patient is initially in the state 1 and we see that when their platelets recover their risk of death drops. The development of GVHD at any point in time elevates the chance of death. This probability is particularly high if the platelets have yet to recover. Figure 3 gives the one year probability of relapsing for each of the four states. Here again a patient is initially in state 1 and has a relatively high likelihood of relapsing. When graft-versus-host disease occurs this probability drops.

Figure 4 gives the leukemia free survival probabilities for the first year given a patient's history at  $s$  weeks. This is the probability of being alive and disease free at the end of the first year after transplant. This probability is given by  $1 - \{P_{i5}[7s,365] + P_{i6}[7s,365]\}$ . The curves naturally increase as a patient survives disease free for a longer time. We see that once a patient has their platelets recover their prognosis is much better. The occurrence of GVHD without the platelets being recovered leads to the least favorable prognosis.

Figure 5 shows 95% confidence intervals and point estimates for the leukemia free survival at one year for each possible history a patient may have at  $s$  weeks. For comparison the proportional hazards and Andersen models are presented. Here we note that the confidence intervals based on the proportional hazards model are shorter. This is to be expected since this model has fewer parameters to estimate.

## 6 DISCUSSION

In our example we have presented estimates of predicted probabilities for some basic outcomes in bone marrow transplantation for a patient with a given history at some point in their recovery process. Similar plots can be used to examine how different values of the fixed time covariates affect the predicted patient prognosis.

We have chosen here to fix the time,  $t$ , to which the prediction is made at one year and to see how changes in the history affect the estimated probabilities. We could have fixed the time at which the history was measured and draw a curve for a range of times. These curves would be predicted survival curves given a patient's history at some time. An example of this approach can be found in Klein et al (1993).

The models presented here can also be used to provide some insight into how changing the rate or the timing of intermediate events effect a patient's eventual prognosis. For example, if some therapy was developed to increase the rate at which platelets recover this hypothetical therapy could be compared to existing therapy by modifying the baseline platelet recovery hazard rate and examining the predicted probabilities of death and relapse. This approach can also be used to examine how changing the rate at which one competing risk occurs affects the occurrence of another competing risk. For example, if the treatment mortality rate were cut in half how does this effect the predicted probability of relapse? This approach is more reasonable than existing methods for analyzing competing risks where one postulates a world in which one of the competing risks can not occur.

The basis of all the models presented here is a sound preliminary analysis of the data using proportional hazards regression models. This analysis involves not only finding important prognostic factors, but also involves checking of the proportionality assumptions of the models to determine the number of child events.

## ACKNOWLEDGMENTS

This research was supported by contract 2R01 CA54706-04A1 from the National Cancer Institute.

## REFERENCES

Andersen, P.K., Borgan, Ø., Gill, R.D. and Keiding, N. (1993). *Statistical Models Based on Counting Processes*. Springer-Verlag.

Andersen, P.K., Hansen, L.S. and Keiding N. (1991). Non- and Semi- parametric Estimation of Transition Probabilities from Censored Observation of a Non- homogeneous Markov Process. *Scand. J. Statist.* **18**: 153-167.

Arjas, E. and Eerola, M. (1993). On predictive Causality in Longitudinal Studies. *J. of Statist. Planning and Inference*, **34**, 361-386.

Breslow, N.E. (1972). Contribution to the discussion on the paper by D.R. Cox, Regression and life table. *J. Roy. Statist. Soc. B.*, **34**: 216-7.

Cox, D.R. (1972). Regression models and life tables (with discussion). *J. Roy. Statist. Soc. B* **34**, 187-220.

Eerola, M. (1993). *On Predictive Causality in the Statistical Analysis of a Series of Events*. Statistical Research Report 14, The Finnish Statistical Society.

Gill, R.D. and Johansen, S. (1990). A survey of product-integration with a view towards application in survival analysis. *Ann. Statist.* **18**, 1501-1555.

Klein, J.P., Keiding, N. and Copelan, E.A. (1993). Plotting Summary Predictions in Multistate Survival Models: Probabilities of Relapse and Death in Remission for Bone Marrow Transplantation Patients. *Statist. Med.*, **12**, 2315-2332.

Klein, J.P. and Moeschberger, M.L. (1996). *Survival Analysis*, Springer, New York, (In Press).

Qian, C. (1995). Time-dependent covariates in a general survival model with any finite number of intermediate and final events unpublished Ph.D. Thesis, The Ohio State University.

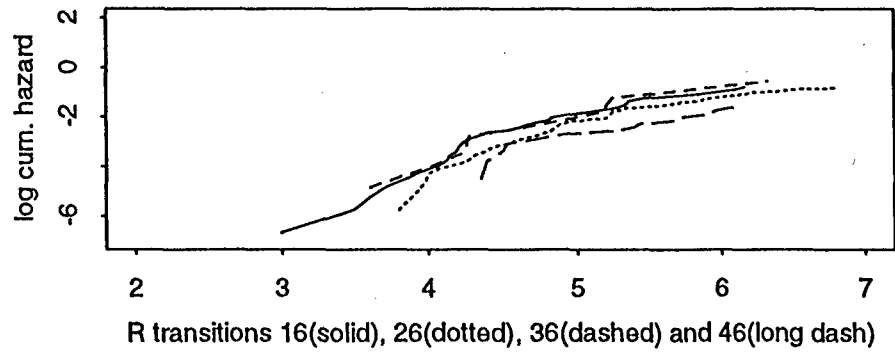
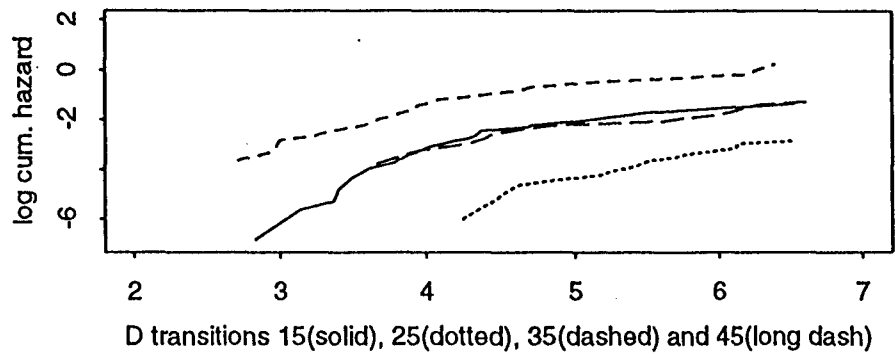
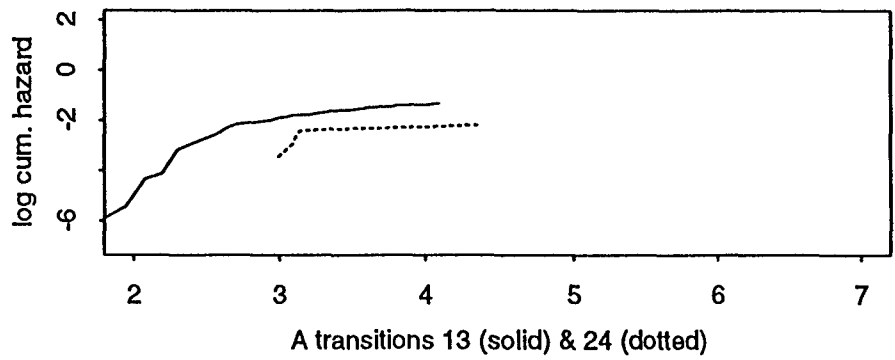
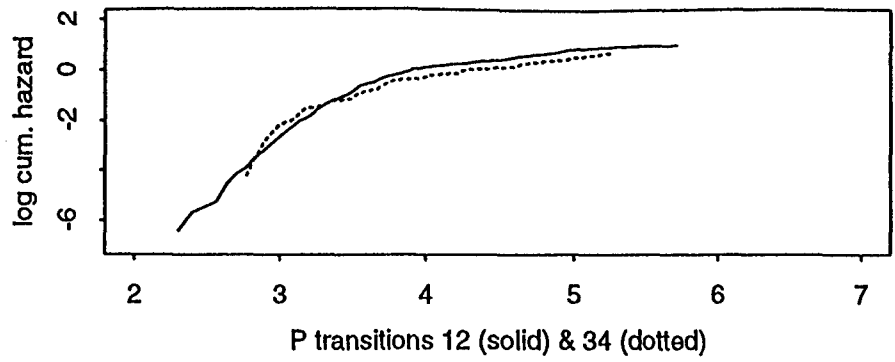


Figure 2: Baseline Log Cumulative Hazards From the Andersen Model

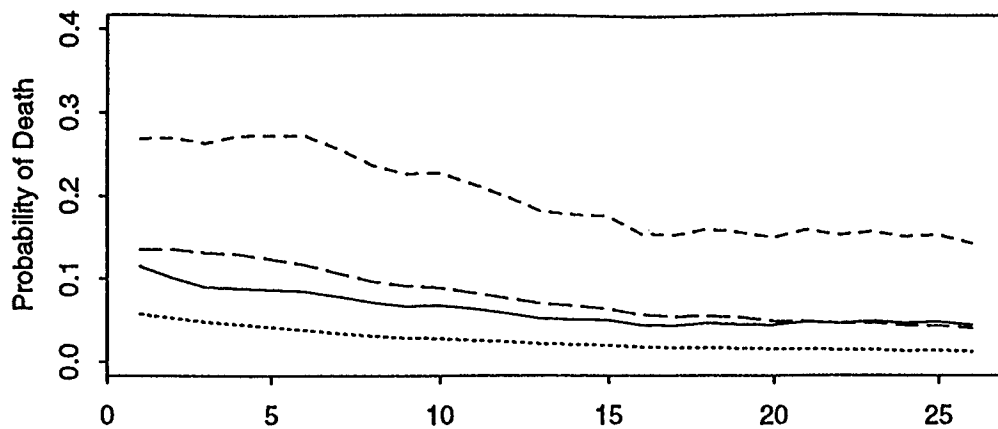


Figure 3: The One Year Death Probabilities Given State =  $i$  (\*)

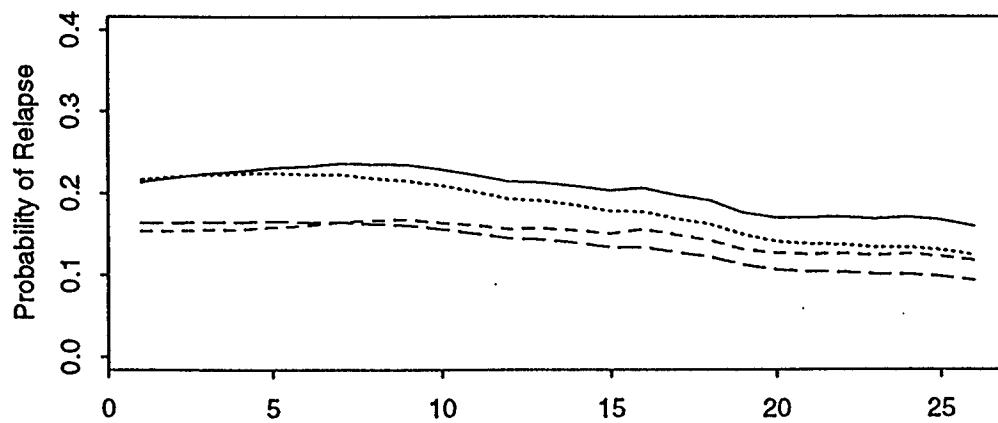


Figure 4: The One Year Relapse Probabilities Given State =  $i$  (\*)

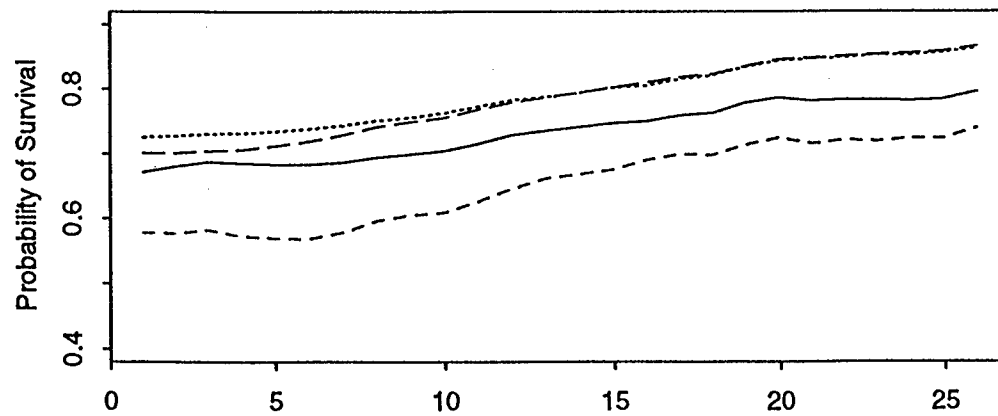
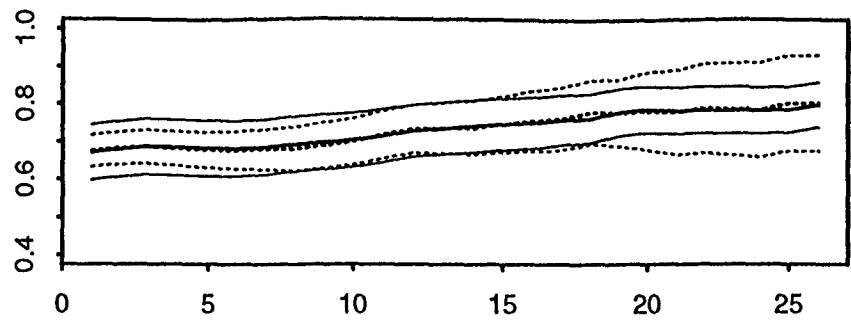


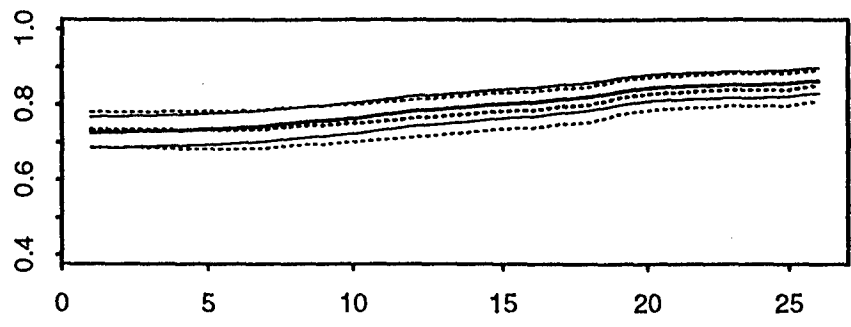
Figure 5: The One Year Leukemia-Free Survival Probabilities Given State =  $i$  (\*)

(\*) The x axes are time in weeks.

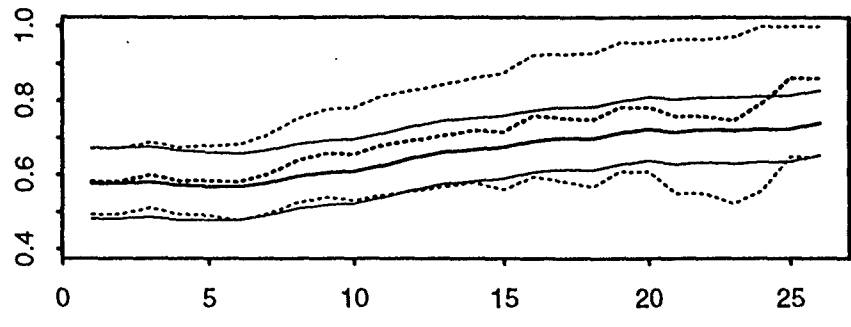
The four curves correspond to the states in the following order:  
 solid :  $i=1$ , dotted :  $i=2$ , dashed :  $i=3$ , and long dash :  $i=4$ .



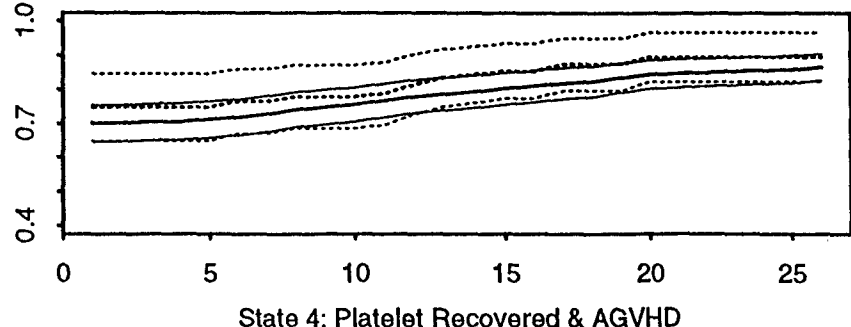
State 1: No Platelet Recovery, No AGVHD



State 2: Platelets Recovered, No AGVHD



State 3: No Platelet Recovery, AGVHD



State 4: Platelet Recovered & AGVHD

Figure 6: One Year Leukemia-Free Survival Probabilities with 95% Confidence Intervals: Proportional Hazards Model (solid line) vs. Andersen Model (dotted line)

**GROUPED FAILURE TIMES  
TIED FAILURE TIMES**

*TWO CONTRIBUTIONS TO THE  
ENCYCLOPEDIA OF BIOSTATISTICS*

Mei-Jie Zhang, Ph.D.

**DIVISION OF BIOSTATISTICS**



**MEDICAL  
COLLEGE  
OF WISCONSIN**

**MILWAUKEE, WISCONSIN**

**GROUPED FAILURE TIMES  
TIED FAILURE TIMES**  
*TWO CONTRIBUTIONS TO THE  
ENCYCLOPEDIA OF BIOSTATISTICS*

Mei-Jie Zhang, Ph.D.

Technical Report 24

February 1997

Division of Biostatistics  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee WI 53226  
Phone: (414)456-8280



## GROUPED FAILURE TIMES

In many investigations for life times, data are grouped prior to their statistical analysis. The grouped survival data consists of occurrence and exposure data over given time intervals and possible covariate strata. For grouped failure times there is an assumed continuous underlying hazard function in contrast to discrete failure time data (Fahrmeir [13]) with an intrinsically discrete time variable, discrete hazards, survival functions etc.

One of the primary reasons for grouping can be found in studies involving large sample sizes such as epidemiologic studies (Breslow [6]). Such studies typically involve the follow-up of large population groups over certain time periods to assess the cause and rate of death and/or to compare death rates among different population groups. Grouping data from such large sample sizes into tabular presentations (life tables) often provides a convenient format for presenting and summarizing life information. Also grouping could be done intentionally, e.g. to economize on data transmission and storage, to reduce computation, to protect the privacy of individual records, or to account for the limitations of a measurement instrument. Moreover, some large data sets are publicly released only in grouped form, as discussed by Haitovsky ([19], [20]). Some examples that illustrate such grouped survival data are: the American Cancer Society study of 1,000,000 men and women (Hammond [18]) to determine the dose-time-response relationships between smoking and lung cancer or heart disease and the life span study of over 100,000 Japanese atom bomb survivors in Hiroshima and Nagasaki (Beebe [4]).

Another important reason for grouping data is that it is often difficult or even impossible to obtain exact life time, because ethical, physical or economic restrictions in research design allow the subjects in the follow-up study to be monitored only periodically. Thus, this type of study only provides the grouped information, i.e., the exact failure time is unknown and the only available information is whether the event of interest occurred between two inspection times. The following study illustrate situations where periodic inspection is used: The National Labor Survey of Youth (NLSY) study of time to weaning of breast-fed newborns in which 927 first-born children of mothers who chose to breast feed their children were interviewed yearly.

Similar to continuous data in survival analysis, grouped survival data can involve censored data (right censoring, left censoring or double censoring) and/or truncated data. Moreover, the exact censoring or truncation times may be unknown for grouped data. For example, in the study of time to weaning of breast fed newborns, some infants are lost follow-up and some infants were withdrawn from the study without being weaned. Also grouped survival data can involve covariates (explanatory variables). Some parametric hazard models and the well-known Cox's proportional hazards model are often fitted to grouped survival data (Prentice and Gloeckler [37]).

The vast literature on grouped survival data involves: deriving the estimators of the hazard function and survival function under nonparametric or parametric models, test statistics for comparing the survival probabilities among different population groups, and large sample properties for these estimators and test statistics. Most estimates are derived based on maximum likelihood methods. Some references to such studies will be given later. The Bayesian approach to analyzing grouped survival data has also been studied in the literature (see Cornfield and Detre [8]; Johnson and Christensen [27]).

### Notation of Grouped Survival Data

Let time be partitioned into a fixed sequence of intervals  $\mathcal{T}_1, \mathcal{T}_2, \dots, \mathcal{T}_m$  with  $\mathcal{T}_j = (t_{j-1}, t_j]$  and  $0 = t_0 < t_1 < \dots < t_m \leq \infty$ . For grouped failure time data the only available information is:

- $n_j$  = number of subjects entering  $\mathcal{T}_j$  not having experienced the event,
- $d_j$  = number of individuals experiencing the event in  $\mathcal{T}_j$ ,
- $w_j$  = number of individuals lost to follow-up or withdrawn during  $\mathcal{T}_j$ ,
- $\mu_j$  = number of individuals left truncated during  $\mathcal{T}_j$ ,
- $Y_j$  = total time of individuals at risk during  $\mathcal{T}_j$ .

Note that all  $\mu_j = 0$  when no left truncation occurs. Also, when the subjects are monitored periodically, the total time at risk  $Y_j$  is unknown. It is often approximated by  $Y_j \approx [n_j - (d_j + w_j)/2](t_j - t_{j-1})$  for right censored data.

### Life Table

The life table is one of the oldest and most commonly used methods of presenting lifetime data. It is a table for presenting and summarizing data, and estimating the survival function, the probability density function and the hazard function along with the variance of these estimators. For more details on the life table, see Gehan [17], Breslow [7] and Hoem [22].

### Interval Censored Grouped Data

For the interval (doubly) censored grouped data, Turnbull ([40], [41]) proposed a "self-consistency" procedure, developed by Efron [11], to estimate the survival function  $S(t)$ . The Turnbull Estimator is a nonparametric maximum likelihood estimator (NPMLE). Frydman [16] discussed derivation and asymptotic properties of the Turnbull Estimator. Sun [39] discussed some alternative approaches to maximizing the NPMLE.

## Log-Rank Test

Comparison of the survival probabilities with treatment groups or covariate strata in the grouped data can be done through rank tests. In the continuous data case Fleming and Harrington [14] studied a class of weighted log-rank tests. These weighted log-rank tests can be extended to the grouped failure time data. The usual log-rank test (or evenly weighted log-rank test) is most commonly and widely used in practice. Here we discuss the grouped data version of the log-rank test. First, let's consider the two sample case. Let  $n_{ij}$  and  $d_{ij}$ ,  $j = 1, \dots, m$ ,  $i = 1, 2$ , be the number at risk at beginning of  $j$ th interval and observed failures in  $j$ th interval, respectively, in sample  $i$ . Take  $n_j$  and  $d_j$  to be the corresponding values in the combined sample. The data can be summarized as

Failure	Sample		Total
	1	2	
Yes	$d_{1j}$	$d_{2j}$	$d_j$
No	$n_{1j} - d_{1j}$	$n_{2j} - d_{2j}$	$n_j - d_j$
Total	$n_{1j}$	$n_{2j}$	$n_j$

corresponding to the  $j$ th time interval. The grouped data based two sample log-rank test can be computed as

$$Q = \left\{ \sum_{j=1}^m (d_{1j} - E_{1j}) \right\}^2 / \left\{ \sum_{j=1}^m V_{1j} \right\},$$

where  $E_{1j}$  and  $V_{1j}$  are the expected value and variance of  $d_{1j}$ , given by

$$E_{1j} = \frac{d_j n_{1j}}{n_j}, \quad \text{and} \quad V_{1j} = \frac{d_j n_{1j} n_{2j} (n_j - d_j)}{n_j^2 (n_j - 1)}.$$

Under the hypothesis of  $S_1(t) = S_2(t)$ , the two-sample log-rank test statistic  $Q$  has approximately the chi-squared distribution with 1 degree of freedom when the sample sizes are moderately large for each sample.

We can extend the two-sample log-rank test to the  $k$ -sample comparison. The  $k$ -sample log-rank test has a quadratic form with  $(d_{1j} - E_{1j})$  replaced by the corresponding values from  $(k - 1)$  samples and with  $V_{1j}$  replaced by the corresponding covariance matrix, where the  $(hl)$ th element is

$$\hat{\sigma}_{hl} = \frac{d_j n_{hj}}{n_j} \left( \delta_{hl} - \frac{n_{hj}}{n_j} \right) \frac{(n_j - d_j)}{(n_j - 1)},$$

and  $\delta_{hl}$  is a Kronecker delta, i.e.,  $\delta_{hl} = 1$  if  $h = l$ , and 0 otherwise.

## Parametric Models and Regression Analysis

In survival analysis some parametric models have been studied extensively. The common parametric distributions considered are Exponential, Gamma, Weibull, Log Normal and Gompertz distributions. These parametric models are often fitted to grouped data as well. The parameters are usually estimated by maximizing the full (unconditional) likelihood or the conditional likelihood. That is the likelihood function for the interval  $(t_{j-1}, t_j]$  conditional on surviving till  $t_{j-1}$ . Many authors have given grouped data version MLE, see Elandt-Johnson and Johnson [12], Lawless [30] and Deddens and Koch [10]. Turnbull [42] studied a likelihood ratio statistic for testing goodness of fit for grouped failure data with possible doubly censoring.

It is important to assess the effects of covariates that may be associated with the lifetimes in many applications of survival analysis. The regression model for the conditional hazard function  $\lambda(t|\mathbf{z})$  of the failure time given covariate  $\mathbf{z}$  could be used to examine the covariate effects. Continuous covariates are often grouped into a fixed number strata and the value for the strata is approximated by the midpoint of the covariate in the stratum. For simplicity we consider a one dimensional covariate case. The methods and results discussed here can be extended to multidimensional cases. Let the cells into which the data are grouped be denoted  $C_{rj} = \mathcal{I}_r \times \mathcal{I}_j$ , where  $\mathcal{I}_1, \dots, \mathcal{I}_{L_n}$  and  $\mathcal{I}_1, \dots, \mathcal{I}_{J_n}$  are the respective calendar periods (time intervals) and covariate strata. Grouped failure time data consist of the total number of failures (occurrence) and the total time at risk (exposure) in each cell  $C_{rj}$ , given by  $d_{rj}$  and  $Y_{rj}$ . In the literature, most early work has been done under the piecewise exponential model, i.e., the hazard function is assumed to be piecewise constant within each grouping cell. The natural estimate of the unknown hazard rate  $\lambda_{rj}$  is  $\hat{\lambda}_{rj} = d_{rj}/Y_{rj}$  (occurrence/exposure rate). Deddens and Koch [10] showed that the maximum likelihood is approximately equivalent to maximizing the piecewise exponential likelihood function

$$L = \prod_{r,j} \lambda_{rj}^{d_{rj}} \{\exp(-\lambda_{rj} Y_{rj})\}.$$

The occurrence/exposure rate estimator can also be obtained by solving the equations of  $\partial \log L / \partial \lambda_{rj} = 0$ .

The counting process approach and martingale techniques are applicable in grouped failure time data analysis. We assume that the counting process  $N_i$ , where  $N_i(t)$  is the number of failures of the  $i$ th individual during time period  $[0, t]$ , has intensity

$$\lambda_i(t) = Y_i(t)\lambda(t, Z_i(t)),$$

where  $Y_i(t)$  is a predictable  $\{0, 1\}$ -valued process indicating that the  $i$ th individual is at risk with  $Y_i(t) = 1$ , and  $Z_i(t)$  is a predictable covariance process. The occurrence and exposure in each cell  $C_{rj}$  can be written as

$$d_{rj} = \sum_i \int_{\mathcal{T}_r} I\{Z_i(t) \in \mathcal{I}_j\} dN_i(t) \quad \text{and} \quad Y_{rj} = \sum_i \int_{\mathcal{T}_r} I\{Z_i(t) \in \mathcal{I}_j\} Y_i(t) dt.$$

When the censoring processes are independent of the survival time, we can show that  $M_i(t) = N_i(t) - \int_0^t \lambda_i(u) du$  are local martingales. Under the piecewise constant model ( $\lambda(t, z) = \lambda_{rj}$ , for  $(t, z) \in C_{rj}$ ),

$$\hat{\lambda}_{rj} = \frac{d_{rj}}{Y_{rj}} = \frac{M_{rj}}{Y_{rj}} + \lambda_{rj} \frac{Y_{rj}}{Y_{rj}},$$

where  $M_{rj} = \sum_i \int_{\mathcal{T}_r} I\{Z_i(t) \in \mathcal{I}_j\} dM_i(t)$  is the martingale part of  $d_{rj}$ . Since each  $t \in \mathcal{T}_r$ ,  $Y_{rj}$  is not predictable, the martingale techniques are not applicable directly. However, under the *iid* cases and some mild conditions, we can show that there exists a piecewise constant function  $f_{rj}$  bounded away from zero such that  $n^{-1}Y_{rj}$  converges to  $f_{rj}$  in probability. Then we can replace  $M_{rj}/Y_{rj}$  by  $M_{rj}/nf_{rj}$  with the difference of  $o_P(1)$ . It follows that

$$\hat{\lambda}_{rj} = \frac{M_{rj}}{nf_{rj}} + \lambda_{rj} + o_P(1),$$

and the predictable variation process of  $M_{rj}/f_{rj}$  is

$$\left\langle \frac{M_{rj}}{f_{rj}} \right\rangle = \frac{\lambda_{rj} Y_{rj}}{f_{rj}^2}.$$

Therefore,  $\hat{\lambda}_{rj}$  is an asymptotic unbiased estimator and the variance can be consistently estimated by

$$\hat{\sigma}_{rj} = \widehat{\text{Var}}(\hat{\lambda}_{rj}) = \frac{d_{rj}}{(Y_{rj})^2}.$$

For the general nonparametric model where the hazard function is unspecified, Holmford [23] noted that this estimator is inconsistent unless the grouping becomes finer as the sample size increases.

The useful models for many applications are the multiplicative and additive risk model. The model equations are given by

$$\lambda_{rj} = \lambda_{r0} \exp(\beta z_j) \quad \text{and} \quad \lambda_{rj} = \lambda_{r0} + \beta z_j,$$

where  $\lambda_{r0}$  is the baseline hazard rate of the  $r$ th time period. The parameters  $\lambda_{r0}$  and  $\beta$  are readily estimated by the MLE. Berry [5] and Frome [15] provide explicit

MLE for this approach. For the multiplicative risk model the hazard function can be written as  $\lambda_{rj} = \exp(\alpha_r + \beta z_j)$  which has a log-linear form. It is often called the log linear piecewise constant model. Holford [24] derived the log likelihood for this model:

$$L = \sum_r \alpha_r d_{r.} + \sum_{r,j} d_{rj} \beta z_j - \sum_{r,j} Y_{rj} \exp(\alpha_r + \beta z_j),$$

where  $d_{r.} = \sum_{j=1}^{J_n} d_{rj}$  is the number of failures in the  $r$ th calendar period. Taking derivatives of  $L$  with respect to  $\alpha_r$  and  $\beta$  and setting them equal to zero, the MLE estimator of  $\beta$  is given by solving the following equation:

$$\sum_{r,j} z_j d_{rj} - \sum_r \frac{\sum_j Y_{rj} z_j \exp(\beta z_j)}{\sum_j Y_{rj} \exp(\beta z_j)} d_{r.} = 0.$$

As we discuss later, this MLE estimator of  $\beta$  also can be obtained by maximizing the grouped data version of Cox's partial likelihood.

The more general models are: Cox's proportional hazards model (Cox [9]) where  $\lambda(t, z) = \lambda_0(t) \exp(\beta z)$ , and Aalen's additive risk model (Aalen [1]) where  $\lambda(t, z) = \lambda_0(t) + \beta(t)z$ .

Cox's proportional hazards model has so far been the most popular model in survival analysis. The parameter estimator  $\hat{\beta}$  is obtained by maximizing Cox's partial likelihood function. Andersen and Gill [3] provide an excellent proof that  $\sqrt{n}(\hat{\beta} - \beta_0) \xrightarrow{P} N(0, V)$ , where  $V^{-1}$  is consistently estimated by  $-n^{-1} \partial U(\hat{\beta}) / \partial \beta$  and  $U$  is the partial likelihood score function  $U(\beta) = \partial \log L(\beta) / \partial \beta$ . The grouped data based estimator  $\hat{\beta}_g$  can be obtained by maximizing the following approximation to the partial likelihood:

$$L_g(\beta) = \prod_{r,j} \left\{ \frac{e^{\beta z_j}}{\sum_k Y_{rk} e^{\beta z_k}} \right\}^{d_{rj}}$$

where the product is over the grouping cells, the sum is over the covariate strata, and  $z_j$  is the midpoint of the  $j$ th covariate stratum. This estimator has been studied by Kalbfleisch and Prentice [28], Holford [23], Prentice and Gloeckler [37], Breslow [6], Hoem [21], Selmer [38], and Huet and Kaddour [25]. It can be interpreted as the maximum likelihood estimator in a Poisson regression model, as shown by Laird and Olivier [29]. Under slightly stronger regularity conditions proposed in Andersen and Gill [3], it can be shown that  $\sqrt{n}(\hat{\beta}_g - \beta_0) \xrightarrow{P} N(0, V)$ , when the time intervals and covariate strata shrink at some suitable rate as the sample size increases. It is important to be able to assess estimation bias caused by grouping and to correct it if necessary. In the general grouped data analysis, A 'Sheppard correction' can be used to reduce the bias to a higher order of the interval width, see Lindley [31]. McKeague and Zhang [36] obtained a Sheppard correction for Cox's proportional

hazards model, provided a consistent estimator for Sheppard correction, and derived the optimal rate of convergence for  $\hat{\beta}_g$ . The grouped data based estimator of the baseline hazard function,  $\lambda_0$ , is

$$\hat{\lambda}_0(t) = \frac{\sum_j d_{rj}}{\sum_j Y_{rj} e^{\hat{\beta}_g z_j}} \quad \text{for } t \in \mathcal{T}_r.$$

Aalen's additive risk model provides a useful and sometimes biologically more plausible alternative to the Cox proportional hazards model. For continuous data, Aalen proposed a least squares estimator for the cumulative hazard functions which has been studied by Aalen ([1], [2]), Mau ([32], [33]), and McKeague [34]. McKeague [35] and Huffer and McKeague [26] fit Aalen's additive risk model to the grouped data (when the covariates are observed for each individual and are non-time dependent), and studied asymptotic results for the grouped data version of the least squares estimator and weighted least squares estimator. The estimators can be generalized to the more general grouped data setting where the only available information is  $d_{rj}$  and  $Y_{rj}$  for each cell  $C_{rj}$ . More work is needed.

Finally, fitting parametric and regression models to grouped failure time data is based on  $d_{rj}$  and  $Y_{rj}$ . As we discussed in the univariate case,  $Y_{rj}$  may not be observable in some applications. It is usually approximated by  $Y_{rj} \approx (n_{rj} - (d_{rj} + w_{rj})/2)l_r$ , where  $n_{rj}$  is the number of individuals at risk at beginning of the time period  $\mathcal{T}_r$  for the  $j$ th covariate stratum,  $w_{rj}$  is the number of individuals who withdrew in cell  $C_{rj}$ , and  $l_r$  is the width of the time interval  $\mathcal{T}_r$ . This approximation is based on the assumption that, on the average, the individuals failed or withdrew at middle of the each time period. However, in most applications, this assumption does not hold true. The bias introduced by this approximation could be severe. Cautions must be taken when grouping the data so that the number of grouping cells are sufficiently large (the width of time periods and covariate strata are relative small), and each grouping cell contains sufficient individuals at risk.

## References

- [1] Aalen, O.O. (1980). A model for non-parametric regression analysis of counting processes. In W. Klonecki, A. Kozek, and J. Rosinski, eds., *Lecture Notes On Mathematical Statistics And Probability*, Vol. 2, Springer-Verlag, New York.
- [2] Aalen, O.O. (1989). A linear regression model for the analysis of life time. *Statistics in Medicine*, **8**, 907-925.
- [3] Andersen, P.K. and Gill, R.D. (1982). Cox's regression model for counting processes: a large sample study. *The Annals of Statistics*, **10**, 1100-1120. New York.

- [4] Beebe, G.W. (1981). The atomic bomb survivors and problem of low dose radiation effects. *American Journal of Epidemiology*, **114**, 761–783.
- [5] Berry, G. (1983). The analysis of mortality by the subject-years method. *Biometrics*, **39**, 173–184.
- [6] Breslow, N.E. (1986). Cohort analysis in epidemiology, In A.C. Atkinson and S.E. Fienberg, eds., *A Celebration of Statistics: the ISI Centenary Volume*. Springer-Verlag, New York, pp. 109–143.
- [7] Breslow, N. and Crowley, J. (1974). A large sample study of the life table and product limit estimates under random censorship. *The Annals of Statistics*, **2**, 437–453.
- [8] Cornfield, J. and Detre, K. (1977). Bayesian life table analysis. *Journal of the Royal Statistical Society Series B*, **39**, 86–94.
- [9] Cox, D.R. (1972). Regression models and life-tables (with discussion). *Journal of the Royal Statistical Society Series B*, **34**, 187–220.
- [10] Deddens, J.A. and Koch, G.G. (1988). Survival analysis, Grouped data, In N.L. Johnson and S. Kotz, eds., *Encyclopedia of Statistical Sciences*, Vol. 9, Wiley, New York, pp. 129–134.
- [11] Efron, B. (1967). The two-sample problem with censored data. *Proceedings of Fifth Berkeley Symposium on Mathematical Statistics and Probability*. University of California Press, **4**, 831–853.
- [12] Elandt-Johnson, R.C. and Johnson, N.L. (1980). *Survival Models and Data Analysis*. Wiley, New York.
- [13] Fahrmeir, Ludwig. (1997). Discrete failure time models. In P.K. Andersen and N. Keiding, eds., *Encyclopedia of Biostatistics, Section: Survival Analysis*, Wiley, New York.
- [14] Fleming, T.R. and Harrington, D.P. (1991). *Counting Processes And Survival Analysis*. Wiley, New York.
- [15] Frome, E.L. (1983). The analysis of rates using Poisson regression models. *Biometrics*, **39**, 665–674.
- [16] Frydman, H. (1997). Turnbull estimator. In P.K. Andersen and N. Keiding, eds., *Encyclopedia of Biostatistics, Section: Survival Analysis*, Wiley, New York.



- [17] Gehan, E.A. (1969). Estimating survival functions from the life table. *Journal of Chronic Disease*, **21**, 629–644.
- [18] Hammond, E.C. (1966). Smoking in relation to the death rates of one million men and women. *National cancer Institute Monograph*, **19**, 127–204.
- [19] Haitovsky, Y. (1973). *Regression estimation from grouped observations*. Charles Griffin, London/Hafner Press, New York.
- [20] Haitovsky, Y. (1983). Grouped data. In N.L. Johnson and S. Kotz, eds., *Encyclopedia of Statistical Sciences*, Vol. 3, Wiley, New York, pp. 527–536.
- [21] Hoem, J. M. (1987). Statistical analysis of a multiplicative model and its application to the standardization of vital rates: a review. *International Statistics Review*, **55**, 119–152.
- [22] Hoem, J. M.. (1997). Life table. In P.K. Andersen and N. Keiding, eds., *Encyclopedia of Biostatistics, Section: Survival Analysis*, Wiley, New York.
- [23] Holford, T.R. (1976). Life tables with concomitant information. *Biometrics*, **32**, 587–597.
- [24] Holford, T.R. (1980). The analysis of rates and of survivalship using log-linear models. *Biometrics*, **36**, 299–305.
- [25] Huet, S. and Kaddour, A. (1994). Maximum likelihood estimation in survival analysis with grouped data on censored individuals and continuous data on failures. *Applied Statistics*, **43**, 325–333.
- [26] Huffer, F.W. and McKeague, I.W. (1991). Weighted least squares estimation for Aalen's additive risk model. *Journal of the American Statistical Association*, **86**, 114–129.
- [27] Johnson, W. and Christensen, R. (1986). Bayesian nonparametric survival analysis for grouped data. *Canadian Journal of Statistics*, **14**, 307–314.
- [28] Kalbfleisch, J.D. and Prentice, R.L. (1973). Marginal likelihoods based on Cox's regression and life model. *Biometrika*, **60**, 267–278.
- [29] Laird, N. and Olivier, D. (1981). Covariance analysis of censored survival data using log-linear analysis techniques. *Journal of the American Statistical Association*, **76**, 231–240.

- [30] Lawless, J.F. (1982). *Statistical Models and Methods for Lifetime Data*. Wiley, New York.
- [31] Lindley, D. V. (1950). Grouping corrections and maximum likelihood equations. *Proceedings. Cambridge Philosophical Society*, **46** 106–110.
- [32] Mau, J. (1986). On a graphical method for the detection of time-dependent effects of covariates in survival data. *Applied Statistics*, **35**, 245–255.
- [33] Mau, J. (1988). A comparison of counting process models for complicated life histories. *Applied Stochastic Models and Data Analysis*, **4**, 283–298.
- [34] McKeague, I.W. (1988a). Asymptotic theory for weighted least squares estimators in Aalen's additive risk model. *Contemporary Mathematics*, **80**, 139–152.
- [35] McKeague, I.W. (1988b). A counting process approach to the regression analysis of grouped survival data. *Stochastic Processes and Their Applications*, **28**, 221–239.
- [36] McKeague, I.W. and Zhang, M.J. (1996). Fitting Cox's proportional hazards model using grouped survival data. In N.P. Jewell, A.C. Kimber, M.L.T. Lee and G.A. Whitmore, eds., *Lifetime Data: Models in Reliability and Survival Analysis*, Kluwer Academic Publishers, pp. 227–232.
- [37] Prentice, R.L. and Gloeckler, L.A. (1978). Regression analysis of grouped Survival data with application to breast cancer data. *Biometrics*, **34**, 57–67.
- [38] Selmer, R. (1990). A comparison of Poisson regression models fitted to multiway summary tables and Cox's survival model using data from a blood pressure screening in the city of Bergen, Norway. *Statistics in Medicine*, **9**, 1157–1165.
- [39] Sun, Jianguo (1997). Interval censoring. In P.K. Andersen and N. Keiding, eds., *Encyclopedia of Biostatistics, Section: Survival Analysis*, Wiley, New York.
- [40] Turnbull, B.W. (1974). Nonparametric estimation of a survival function with double censored data. *Journal of the American Statistical Association*, **69**, 169–173.
- [41] Turnbull, B.W. (1976). The empirical distribution function with arbitrarily grouped, censored and truncated data. *Journal of the Royal Statistical Society Series B*, **38**, 290–295.
- [42] Turnbull, B.W. and Weiss L. (1978). A likelihood ratio statistics for testing goodness of fit with randomly censored data. *Biometrics*, **34**, 367–375.

## TIED FAILURE TIMES

Tied failure times frequently occur in survival studies. Although theoretically a life-time is a continuous variable, in practice it is often measured to a degree of fineness due to measurement limitation, the way failure times are recorded, or the expense of more accurate measurements may outweigh the value of added information. If the number of ties are substantial, discrete failure time models may need to be considered. Therefore, discrete failure time methods or grouped data techniques such as life tables should be used. However, if there are only a few ties, the regular procedures in handling continuous data may be used with some adjustment for tied observations. In the literature adjustment for ties has been proposed and studied for various statistical procedures in survival analysis. See Miller [9], Lawless [8], Kalbfleisch and Prentice [6], Peto and Peto [10], Andersen et al [1], and Klein and Moeschberger [7]. Here we will only discuss adjustment for ties for some common statistical procedures.

Consider the method of handling ties in the Kaplan-Meier or product-limit (PL) estimator of the survival function. If only one individual fails (no ties are present) at time  $t$ , then the factor for the single death in the PL estimator is  $(1 - 1/Y(t))$  where  $Y(t)$  counts the number of individuals at risk at time  $t-$ . For tied uncensored observations, suppose  $d$  failures occur at time  $t$ . Split the times of the  $d$  failures infinitesimally so that the factor for the  $d$  failures in the PL estimator is

$$\left(1 - \frac{1}{Y(t)}\right) \left(1 - \frac{1}{Y(t)-1}\right) \cdots \left(1 - \frac{1}{Y(t)-d+1}\right) = 1 - \frac{d}{Y(t)}.$$

If censored and uncensored observations are tied at time  $t$ , consider the uncensored individuals as having failed just before the censored observations.

In the  $k$ -sample test, the weighted log rank test statistic is

$$Z_h(t) = \int_0^t K(s) dN_h(s) - \int_0^t K(s) \frac{Y_h(s)}{Y(s)} dN(s),$$

for  $h = 1, 2, \dots, (k-1)$ , where  $K$  is the weight function,  $N_h(s)$  and  $Y_h(s)$  are the number of failures during time period  $[0, s]$  and number of individuals at risk prior to time  $s$  for  $h$ th sample, respectively, and  $N = \sum_h N_h, Y = \sum_h Y_h$ . The covariance of  $(Z_h(t), Z_j(t))$  may be estimated consistently by

$$\hat{\sigma}_{hj} = \int_0^t K^2(s) \frac{Y_h(s)}{Y(s)} \left( \delta_{hj} - \frac{Y_j(s)}{Y(s)} \right) dN(s),$$

where  $\delta_{hj}$  is a Kronecker delta, i.e.,  $\delta_{hl} = 1$  if  $h = l$ , and 0 otherwise. In the presence of tied observations, the covariance of  $(Z_h(t), Z_j(t))$  needs to be adjusted to

$$\hat{\sigma}_{hj} = \int_0^t K^2(s) \frac{Y_h(s)}{Y(s)} \left( \delta_{hj} - \frac{Y_j(s)}{Y(s)} \right) \frac{Y(s) - \Delta N(s)}{Y(s) - 1} dN(s).$$

Clearly, when there are no tied observations,  $\hat{\sigma}_{hj}$  and  $\hat{\hat{\sigma}}_{hj}$  coincide.

Cox's partial likelihood has been commonly used to estimate the coefficients,  $\beta$ , in Cox's proportional hazards model. Let  $t_1 < t_2 < \dots < t_k$  be the  $k$  ordered event times. Let the set  $\mathcal{D}_i$  consist of the  $d_i$  individuals who failed at the time  $t_i$  and  $\mathcal{R}_i$  be the risk set prior to  $t_i$ . Denote  $\mathbf{s}_i = \sum_{l \in \mathcal{D}_i} \mathbf{z}_l$ . If there are ties among event times, the following adjusted partial likelihoods have been proposed: Breslow [2] suggests a partial likelihood of

$$L_1(\beta) = \prod_{i=1}^k \frac{\exp(\beta' \mathbf{s}_i)}{\left[ \sum_{l \in \mathcal{R}_i} \exp(\beta' \mathbf{z}_l) \right]^{d_i}}.$$

Efron [5] proposed an alternative partial likelihood of

$$L_2(\beta) = \prod_{i=1}^k \frac{\exp(\beta' \mathbf{s}_i)}{\prod_{j=1}^{d_i} \left[ \sum_{l \in \mathcal{R}_i} \exp(\beta' \mathbf{z}_l) - \frac{j-1}{d_i} \sum_{l \in \mathcal{D}_i} \exp(\beta' \mathbf{z}_l) \right]}.$$

The third partial likelihood due to Cox [3] is based on a discrete time hazard rate model. The discrete logistic likelihood is

$$L_3(\beta) = \prod_{i=1}^k \frac{\exp(\beta' \mathbf{s}_i)}{\sum_{\mathbf{q} \in \mathcal{Q}_i} \exp(\beta' \mathbf{s}_q^*)},$$

where  $\mathcal{Q}_i$  is the set of all subsets of  $d_i$  individuals who could be selected from the risk set  $\mathcal{R}_i$  and  $\mathbf{s}_q^* = \sum_{j=1}^{d_i} \mathbf{z}_{q_j}$ .

The fourth alternative partial likelihood is (see DeLong et al [4])

$$L_4(\beta) = \prod_{i=1}^k \left\{ \int_0^\infty \prod_{j=1}^{d_i} \left[ 1 - \exp \left( - \frac{\exp(\beta' \mathbf{z}_j)}{\sum_{l \in \mathcal{R}_i^*} \exp(\beta' \mathbf{z}_l)} t \right) \right] \exp(-t) dt \right\},$$

where  $\mathcal{R}_i^* = \mathcal{R}_i \setminus \mathcal{D}_i$  is the set of individuals whose event or censored times exceed  $t_i$  or whose censored times are equal to  $t_i$ . It is often called exact likelihood.

Note that when the number of ties is small, Breslow's and Efron's likelihoods are quite close. Of course, if no ties occur at the event times, all four likelihood functions reduce to the regular Cox's partial likelihood.

## References

- [1] Andersen, P.K., Borgan, Ø., Gill, R.D., and Keiding, N. (1993). *Statistical Models Based on Counting Processes*. Springer-Verlag, New York.
- [2] Breslow, N.E. (1974). Covariance analysis of censored survival data. *Biometrics*, **30**, 89-99.
- [3] Cox, D.R. (1972). Regression models and life-tables (with discussion). *Journal of the Royal Statistical Society Series B*, **34**, 187-220.
- [4] DeLong, D.M., Guirguis, G.H. and So, Y.C. (1994). Efficient computation of subset selection probabilities with application to Cox regression. *Biometrika*, **81**, 607-611.
- [5] Efron, B. (1977). The efficiency of Cox's likelihood function for censored data. *Journal of the American Statistical Association*, **72**, 557-565.
- [6] Kalbfleisch, J.D. and Prentice, R.L. (1980). *The Statistical Analysis of Failure Time Data*. Wiley, New York.
- [7] Klein, J.P. and Moeschberger, M.L. (1997). *Survival Analysis: Applied Methods and Examples*. Springer-Verlag, New York.
- [8] Lawless, J.F. (1982). *Statistical Models and Methods for Lifetime Data*. Wiley, New York.
- [9] Miller, R.G. (1981). *Survival Analysis*. Wiley, New York.
- [10] Peto, R. and Peto, J. (1972). Asymptotically efficient rank invariant test procedures (with discussion). *Journal of the Royal Statistical Society Series A*, **135**, 185-206.

**SURVIVAL DISTRIBUTIONS AND  
THEIR CHARACTERISTICS**

*A CONTRIBUTION TO THE  
ENCYCLOPEDIA OF BIOSTATISTICS*

John Klein, Ph.D.

**DIVISION OF BIOSTATISTICS**



**MEDICAL  
COLLEGE  
OF WISCONSIN**

**MILWAUKEE, WISCONSIN**

**SURVIVAL DISTRIBUTIONS AND  
THEIR CHARACTERISTICS**

***A CONTRIBUTION TO THE  
ENCYCLOPEDIA OF BIOSTATISTICS***

**John Klein, Ph.D.**

**Technical Report 22**

**December 1996**

**Division of Biostatistics  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee WI 53226  
Phone: (414) 456-8280**

SURVIVAL DISTRIBUTIONS AND THEIR  
CHARACTERISTICS

*A CONTRIBUTION TO  
THE ENCYCLOPEDIA OF BIOSTATISTICS*

John P. Klein  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee WI 53226



## INTRODUCTION

Many applications in biostatistics involve the modeling of lifetime data. In these applications the outcome of interest is the time  $T$ , until some event occurs. This event may be death, the appearance of a tumor, the development of some disease, recurrence of a disease, conception, cessation of smoking, and so forth. Here  $T$  is a non-negative random variable from a homogenous population.

In this article we shall examine how the distribution of  $T$  can be characterized. Four functions characterize the distribution of  $T$ , namely, the *survival function*, which is the probability of an individual surviving beyond time  $t$ , the *hazard rate* which is approximately the chance an individual of age  $t$  experiences the event in the next instant in time, the *probability density (or mass) function*, which is the approximate unconditional probability of the event occurring at time  $t$ , and the *mean residual life* at time  $t$ , which is the mean time to the event of interest, given the event has not occurred at  $t$ . If we know any one of these four functions, then the other three can be uniquely determined. These functions are introduced for continuous, discrete and mixed random variable in the following sections and the interrelationship among the four functions are discussed.

The distribution of the time to an event can also be characterized by the aging properties of the distribution of  $T$ . Aging classes are based on certain properties of one of the four basic quantities that describe the distribution

of  $T$ . These classes are defined and some basic properties of these classes are discussed in the final section.

## THE SURVIVAL FUNCTION

The basic quantity employed to describe time-to-event phenomena is the survival function. This function, also known as the survivor function or survivorship function, is the probability an individual survives beyond time  $t$ . It is defined as

$$S(t) = Pr [T \geq t].$$

In the context of equipment or manufactured item failures,  $S(t)$  is referred to as the reliability function. Note that the survival function is a non increasing function with a value of 1 at the origin and 0 as  $t$  approaches infinity.

If  $T$  is a continuous random variable then  $S(t)$  is a continuous monotone decreasing function and the survival function is the complement of the cumulative distribution function  $F(t) = Pr [T \leq t]$ . That is  $S(t) = 1 - F(t)$ . The survival function is the integral of the probability density function  $f(t)$ . That is,

$$S(t) = Pr (T \geq t) = \int_t^{\infty} f(u) du$$

Thus, we have the following relationship:

$$f(t) = -\frac{dS(t)}{dt}.$$

Note that  $f(t)\Delta t$  may be thought of as the "approximate" probability of the event occurring at time  $t$  and that  $f(x)$  is a non-negative function with the area under  $f(x)$  being equal to one.

*Example*

A common distribution used in many applications in the Weibull distribution with probability density function  $f(t) = \lambda\alpha t^{\alpha-1} \exp(-\lambda t^\alpha)$ ,  $\lambda > 0$ ,  $\alpha > 0$ . The exponential distribution is a special case of the Weibull distribution when  $\alpha = 1$ . The survival function for the Weibull distribution is  $S(t) = \exp(-\lambda t^\alpha)$ ,  $\lambda > 0$ ,  $\alpha > 0$ . Survival curves with a common median of 6.93 are exhibited in Figure 1 for  $\lambda = .26328$ ,  $\alpha = .5$ ;  $\lambda = .1$ ,  $\alpha = 1$ ; and  $\lambda = .00208$ ,  $\alpha = 3$ .  $\diamond$

When  $T$  is a discrete random variable then the survival function is a non increasing left-continuous step function. If  $T$  can take on values  $t_0 < t_1 < t_2 < \dots$  with probability mass function (p.m.f.)  $p(t_j) = \Pr(T = t_j)$ ,  $j = 1, 2, \dots$  then

$$S(t) = \Pr(X \geq t) = \sum_{j:t_j \geq t} p(t_j).$$

Note that the survival function and probability mass function are related by

$$p(t_j) = S(t_j) - S(t_{j+1})$$

. Here we have defined  $S(t) = Pr[T \geq t]$  as was the case in [3] and [4]. This definition was used to make later formulas for the discrete case simpler. Other authors (c.f. [5] and [6]) have defined  $S(t) = Pr[T > t]$  which makes the relationship  $S(t) = 1 - F(t)$  hold for both the discrete and continuous case.

## THE HAZARD FUNCTION

A basic quantity, foundational in survival analysis, is the hazard function. This function is also known as the conditional failure rate in reliability, the force of mortality in demography, the age-specific failure rate in epidemiology, the inverse of the Mill's ratio in economics or simply as the hazard rate. The hazard rate is defined as

$$h(t) = \lim_{\Delta t \rightarrow 0} \frac{Pr[t \leq T < t + \Delta t | T \geq t]}{\Delta t}. \quad (1)$$

The hazard rate is a non-negative function. It tells us how quickly individuals of a given age are experiencing the event of interest. The quantity  $h(t) \Delta t$  is the approximate probability that an individual who has survived to age  $t$  will experience the event in the interval  $(t, t + \Delta t)$ .

This function is particularly useful in determining the appropriate failure distributions utilizing qualitative information about the mechanism of failure and for describing the way in which the chance of experiencing the event changes with time. There are many general shapes for the hazard rate. Some

generic types of hazard rates are increasing, decreasing, constant, bathtub-shaped or hump-shaped hazard rates. Models with increasing hazard rates arise when there is natural aging or wear-out. Decreasing hazard functions are much less common but find occasional use when there is a very early likelihood of failure such as in certain types of electronic devices or in patients experiencing certain types of transplants. Decreasing hazard rates often arise as models for heterogenous populations where the hazard rates of members of the population are random (See Frailty models). Most often a bathtub-shaped hazard is appropriate in populations followed from birth. Most population mortality data follows this type of hazard function where, during an early period, deaths result primarily from infant diseases after which the death rate stabilizes followed by an increasing hazard rate due to the natural aging process. Finally, if the hazard rate is increasing early and eventually begins declining, then the hazard is termed hump-shaped. This type of hazard rate is often used in modeling survival after successful surgery where there is an initial increase in risk due to infection, hemorrhaging, or other complications just after the procedure, followed by a steady decline in risk as the patient recovers.

If  $T$  is a continuous random variable, then

$$h(t) = f(t) / S(t) = -\frac{d \ln [S(t)]}{dt}$$

A related quantity is the cumulative hazard function  $H(t)$ , defined by

$$H(t) = \int_0^t h(u) du = -\ln [S(t)].$$

Thus for continuous lifetimes we have the following relationship:

$$S(t) = \exp \{-H(t)\} = \exp \left\{ - \int_0^t h(u) du \right\}.$$

One particular distribution, which is flexible enough to accommodate increasing ( $\alpha > 1$ ), decreasing ( $\alpha < 1$ ), or constant hazard rates ( $\alpha = 1$ ), is the Weibull distribution. Hazard rates,  $h(x) = \alpha \lambda x^{\alpha-1}$ , are plotted in Figure 2 for the Weibull distribution with  $\lambda = .26328, \alpha = .5$ ;  $\lambda = .1, \alpha = 1$ ; and  $\lambda = .00208, \alpha = 3$ . One can see that, though the three survival functions have the same basic shape, the three hazard functions are dramatically different.  $\diamond$

When  $T$  is a discrete random variable, the hazard function is

$$h(t_j) = \Pr(T = t_j | T \geq t_j) = \frac{p(t_j)}{S(t_j)}, \quad j = 1, 2, \dots$$

Since  $p(t_j) = S(t_j) - S(t_{j+1})$  we have

$$h(t_j) = 1 - S(t_{j+1})/S(t_j), \quad j = 1, 2, \dots$$

so that the survival function is related to the hazard function by

$$S(t) = \prod_{j:t_j < t} [1 - h(x_j)].$$

For discrete lifetimes the "cumulative hazard" function is defined by

$$H(t) = \sum_{j:t_j < t} h(t_j). \quad (2)$$

Notice that for this definition the relationship  $S(t) = \exp[-H(t)]$  no longer holds true. Some authors (Cox and Oakes [3]) prefer to define the cumulative hazard for discrete lifetimes, as

$$H(t) = \sum_{t_j < t} \ln [1 - h(t_j)], \quad (3)$$

Note that for this definition the relationship for continuous lifetimes,  $S(t) = \exp[-H(t)]$  will then be preserved for discrete lifetimes. If the  $h(t_j)$  are small, (2) will be a first order approximation to (3).

The hazard rate is well-defined quantity for the case where  $T$  has both discrete and continuous components. In this case the hazard function defined by (1) will have a continuous part,  $h_c(t)$  and a discrete part with mass  $h_j$  at time  $t_1 < t_2 < \dots$ . The survival function in this case can be expressed as

$$S(t) = \exp \left\{ - \int_0^t h_c(u) du \right\} \prod_{j: t_j < t} (1 - h_j)$$

For any survival function one can express the relationship between the hazard rate and the survival function by the using the notion of a product integral. For a function,  $G()$ , define the product integral of  $1 - dG(u)$  over the range  $a$  to  $b$  by

$$P_a^b [1 - dG(u)] = \lim_{k \rightarrow \infty} \prod_{k=1}^r \{1 - [G(u_k) - G(u_{k-1})]\},$$

where  $a = u_1 < \dots < u_r = b$  and the limit is taken as  $r \rightarrow \infty$  and  $u_k - u_{k-1} \rightarrow 0$ . Here  $G$  is a function of locally bounded variation which is continuous from

the right and have finite left hand limits. If we define the cumulative hazard rate as

$$H(t) = \int_0^t h_c(u)du + \sum_{j:t_j < t} h_j$$

then the survival function in the continuous, discrete or mixed case is given by

$$S(t) = P_0^t [1 - dH(u)].$$

Because of this property the product integral plays an important role in survival analytic techniques.

### THE MEAN RESIDUAL LIFE FUNCTION

The fourth basic parameter of interest is the mean residual life at time  $t$ . This parameter measures, for individuals of age  $t$ , their expected remaining lifetime. It is defined as

$$mrl(t) = E(T - t | T \geq t).$$

It can be shown, using integration by parts or a partial summation formula, that the mean residual life is the area under the survival curve to the right of  $t$  divided by  $S(t)$ . Note that the mean life,  $\mu = mrl(0)$ , is the total area under the survival curve.

For a continuous random variable we have



$$mrl(t) = \frac{\int_t^{\infty} (u-t)f(u)du}{S(t)} = \frac{\int_t^{\infty} S(u) du}{S(t)}$$

and

$$\mu = E(T) = \int_0^{\infty} uf(u)du = \int_0^{\infty} S(u)du.$$

Also the variance of  $T$  is related to the survival function by

$$Var(T) = 2 \int_0^{\infty} uS(u)du - \left[ \int_0^{\infty} S(u)du \right]^2.$$

In some applications the median residual life, rather than the mean residual life is of interest. To define this quantity recall that the 100th percentile of a random variable  $X$  with cumulative distribution function (survival function)  $F(x)$  ( $S(x)$ ) is the value  $x_p$  such that

$$F(x_p) \geq p \quad \text{and} \quad S(x_p) \geq 1 - p.$$

The median lifetime is the 50th percentile,  $x_{.5}$ , of the distribution of  $X$ . If  $X$  is a continuous random variable then the  $p$ th quantile is found by solving the equation  $S(x_p) = 1 - p$ . It follows that the median lifetime, for a continuous random variable  $X$ , is the value  $x_{.5}$  such that

$$S(x_{.5}) = 0.5.$$

The median residual life time of  $T$  at time  $t$ ,  $mdrl(t)$ , is defined as the median time to the event for an individual who has survived to time  $t$ . That is,  $mdrl(t)$  is solution to the equation

$$\frac{S(\text{mdrl}(t))}{S(t)} = .5.$$

The population median is simply the median residual life at time 0.

To illustrate these quantities consider the three Weibull distributions considered earlier. Figure 3 shows the mean residual life function for the Weibull models with  $\alpha = 0.5, 1.0$  and  $3.0$ . As the figure shows the mean residual life is constant for the exponential distribution ( $\alpha = 1$ ), decreasing for the case where  $\alpha = 3$  and increasing for the case where  $\alpha = 0.5$ . Note that the trend in the mean residual life is reversed from the trend in the hazard rate in that when the hazard rate is increasing, reflecting aging, the mean residual life is decreasing. Figure 4 depicts the median residual life functions for the three Weibull models. The shapes of the functions are quite similar to the shape of the mean residual life functions.

## RELATIONSHIP BETWEEN CHARACTERIZATIONS

Interrelationships between the characterizations discussed earlier, for a continuous lifetime  $T$ , may be summarized as follows:

$$S(t) = \int_t^{\infty} f(u) du$$

$$\begin{aligned}
&= \exp \left\{ - \int_0^t h(u) du \right\} \\
&= \exp \{ -H(t) \} \\
&= \frac{mrl(0)}{mrl(t)} \exp \left\{ - \int_0^t \frac{du}{mrl(u)} \right\};
\end{aligned}$$

$$\begin{aligned}
f(t) &= -\frac{d}{dt} S(t) \\
&= h(t) S(t) \\
&= \left( \frac{d}{dt} mrl(t) + 1 \right) \left( \frac{mrl(0)}{mrl(t)^2} \right) \exp \left\{ - \int_0^t \frac{du}{mrl(u)} \right\}
\end{aligned}$$

$$\begin{aligned}
h(t) &= -\frac{d}{dt} \ln[S(t)] \\
&= \frac{f(t)}{S(t)} \\
&= \left( \frac{d}{dt} mrl(t) + 1 \right) / mrl(t);
\end{aligned}$$

and

$$\begin{aligned}
mrl(t) &= \frac{\int_t^\infty S(u) du}{S(t)} \\
&= \frac{\int_t^\infty (u-t) f(u) du}{S(t)}
\end{aligned}$$

For a discrete random variable we have the following relationships:

$$\begin{aligned}
S(t) &= \sum_{j:t_j \geq t} p(t_j) \\
&= \prod_{j:t_j < t} [1 - h(t_j)].
\end{aligned}$$

If  $T$  is an integer valued random variable with mean residual life at time  $k$  equal to  $m_k$ ,  $k = 0, 1, 2, \dots$  and  $m_0$  is finite then we have

$$S(k) = \frac{1 + m_0}{m_k} \prod_{j=0}^k \frac{m_j}{1 + m_j}.$$

Also, for any discrete survival function, we have

$$\begin{aligned}
p(t_j) &= S(t_j) - S(t_{j+1}) \\
&= h(t_j)S(t_j), j = 1, 2, \dots; \\
h(t_j) &= \frac{p(t_j)}{S(t_j)},
\end{aligned}$$

and

$$mrl(t) = \frac{[t_{k+1} - t]S(t_{k+1}) + \sum_{j:t_j \geq t_{k+1}} [t_{j+1} - t_j]S(t_{j+1})}{S(t)}, \text{ for } t_k \leq t < t_{k+1}$$

## CLASSES OF AGING DISTRIBUTIONS

An important characteristic of survival distribution is its aging properties. There are a number of classes that have been suggested in the literature to categorize distributions based on their aging properties or their dual. The

first aging class is the class of increasing hazard rate (IHR) distributions and the dual class of decreasing hazard rate (DHR) distributions. A survival distribution is said to be in the IHR (DHR) class if and only if

$$\frac{S(t+x)}{S(t)} = S(x|t) \text{ is decreasing (increasing) in } t \text{ for all } x.$$

The definition says that the  $T$  has the IHR aging property if the probability an individual of age  $t$  survives an addition  $x$  period of time is decreasing with time. If  $T$  is a continuous random variable then an equivalent definition of the IHR (DFR) class is that the hazard rate  $h(t)$  is increasing (decreasing) for all  $t$ . Examples of distributions that fall in the IHR class are the Weibull distribution with  $\alpha > 1$  and the gamma distribution with shape parameter greater than one.

A second, more general aging class is the class of increasing (decreasing) hazard rate on the average, IHRA (DHRA), distributions. A distribution is said to fall in the IHRA (DHRA) class if and only if

$$-\left(\frac{1}{t}\right) \ln [S(t)] \text{ is increasing (decreasing) in } t. \quad (4)$$

The definition arises by declaring a distribution to be in the IHRA class when its cumulative hazard rate,  $-\ln [S(t)]$  is increasing faster than the cumulative hazard rate of an exponential random variable,  $t$ . Since the exponential distribution reflects a model with no aging, this class is one of distributions for which individuals are, on the average, aging. There are several equivalent

definitions of a IHRA class. Since (4) implies that  $S^{1/t}(t)$  is increasing in  $t$  we have that  $T$  is in the IHRA class if and only if  $S(\theta t) \geq S^\theta(t)$ . A second characterization of the IHRA class is that if  $T$  is in the IHRA class then for any  $\lambda > 0$  the quantity  $S(t) - e^{-\lambda t}$  has at most one change of sign and if it does have a change in sign then it is from  $+$  to  $-$ . The class of IHRA distributions is larger than the class of IHR distributions in that every IHR distribution is an IHRA distribution but the converse is not true.

A third aging class is the class of decreasing (increasing) mean residual life, DMRL (IMRL) distributions. A distribution is said to be in the DMRL (IMRL) class if

$$mrl(t) = \frac{\int_0^{\infty} S(x)dx}{S(t)} \text{ is decreasing (increasing) in } t.$$

This aging class, which include all IHR models, is one where the mean remaining life of an individual of age  $t$  is becoming shorter as  $t$  increases.

A fourth aging class is the class of new better (worse) than used NBU (NWU) distributions. Here a distribution is in the NBU (NWU) class if and only if

$$S(x+t) \leq (\geq) S(x)S(t) \text{ for any } x \text{ and } t.$$

An equivalent definition for the NBU class is

$$\frac{S(x+t)}{S(t)} = Pr [T \geq x+t | T \geq t] \leq Pr [T \geq x] = S(x).$$

From this second definition we see that  $T$  has an NBU distribution if the probability an individual of age  $t$  lives an additional  $x$  time units is smaller than the probability an individual of age 0 survives to age  $x$ . This aging class includes all the IHRA distributions.

A fifth aging class is the class of new better (worse) than new in expectation, NBUE (NWUE) distributions. A distribution is in the NBUE (NWUE) class if its mean,  $\mu$ , is finite and

$$\int_t^{\infty} S(u)du \leq (\geq) \mu S(t) \text{ for all } t.$$

The NBUE class is one where the mean residual life of an individual of age  $t$  is less than the mean of an individual of age 0.

A final aging class is the class of harmonic new better (worse) than used in expectation, HNBUE (HNWUE) distributions. A distribution is said to be in the HNBUE (HNWUE) class if its mean is finite and

$$\int_t^{\infty} S(u)du \leq \mu \exp(-t/\mu).$$

An equivalent definition for the HNBUE class is

$$\left\{ \frac{1}{t} \int_0^t \frac{dx}{mrl(x)} \right\}^{-1} \leq mrl(0).$$

This means that for a HNBUE distribution the integral harmonic value of the residual life of an individual of age  $t$  is smaller than the same quantity for a newly born individual.

The aging classes are ordered as follows:

$$IHR \Rightarrow IHRA \Rightarrow NBU \Rightarrow NBUE \Rightarrow HNBUE$$

$$IHR \Rightarrow DMRL \Rightarrow NBUE \Rightarrow HNBUE$$

$$DHR \Rightarrow DHRA \Rightarrow NWU \Rightarrow NWUE \Rightarrow HNWUE$$

$$DHR \Rightarrow IMRL \Rightarrow NWUE \Rightarrow HNWUE$$

Further discussion of these failure classes can be found in Barlow and Proschan [1] and Basu and Ebrahimi [2].

#### REFERENCES

1. Barlow, R.E. and Proschan, F. *Statistical Theory of Reliability and Life Testing*. Holt, Rinehart and Winston, New York, 1975.
2. Basu, A.P. and Ebrahimi, N. "HNBUE and HNWUE Distributions - A Survey" in *Reliability and Quality Control* (A.P. Basu Ed.), North-Holland, New York, 1986, pp. 33-47.
3. Cox, D.R. and Oakes, D. *Analysis of Survival Data*. Chapman and Hall, New York, 1984.
4. Lawless, J.F. *Statistical Models and Methods for Lifetime Data*. John Wiley and Sons, New York, 1982.
5. Lee, E.T. *Statistical Methods for Survival Data Analysis*. John Wiley and Sons, New York, 1992.



6. Klein, J.P. and Moeschberger, M.L. *Survival Analysis: Methods for Censored and Truncated Data*. Springer-Verlag, New York, 1997.

Figure 1  
Comparison of Weibull Survival Functions

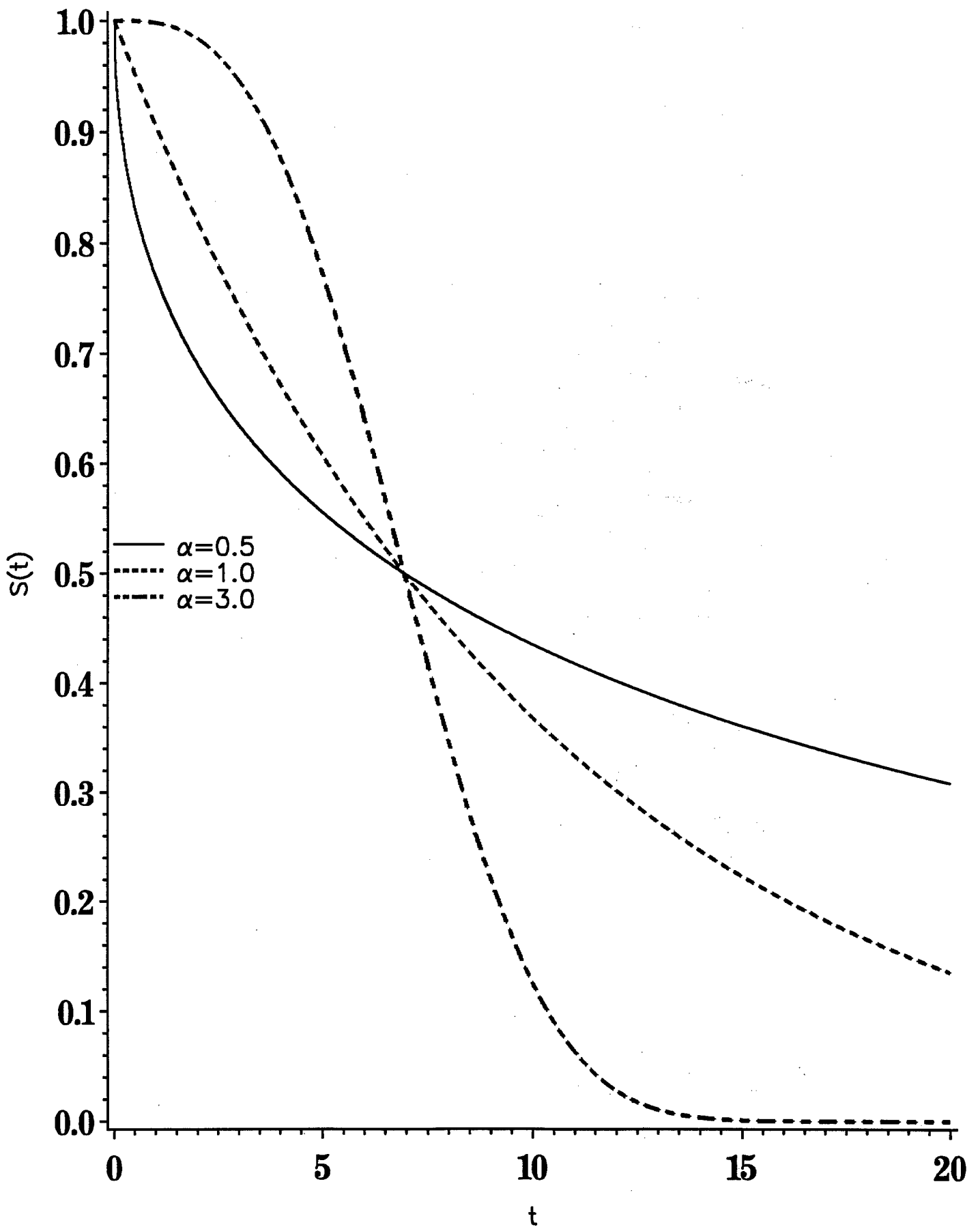


Figure 2  
Comparison of Weibull Hazard Functions

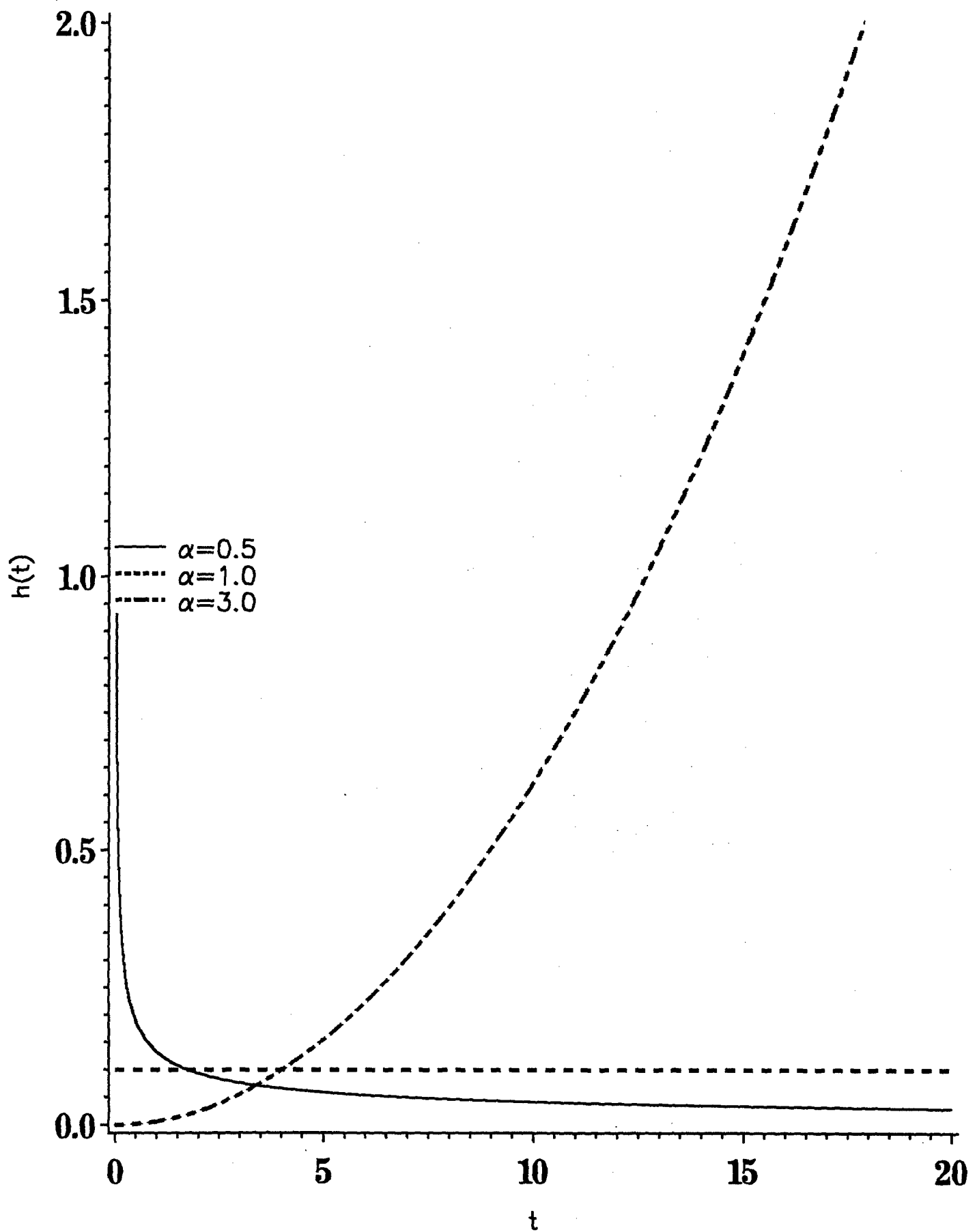


Figure 3  
Comparison of Weibull Mean Residual Life Functions

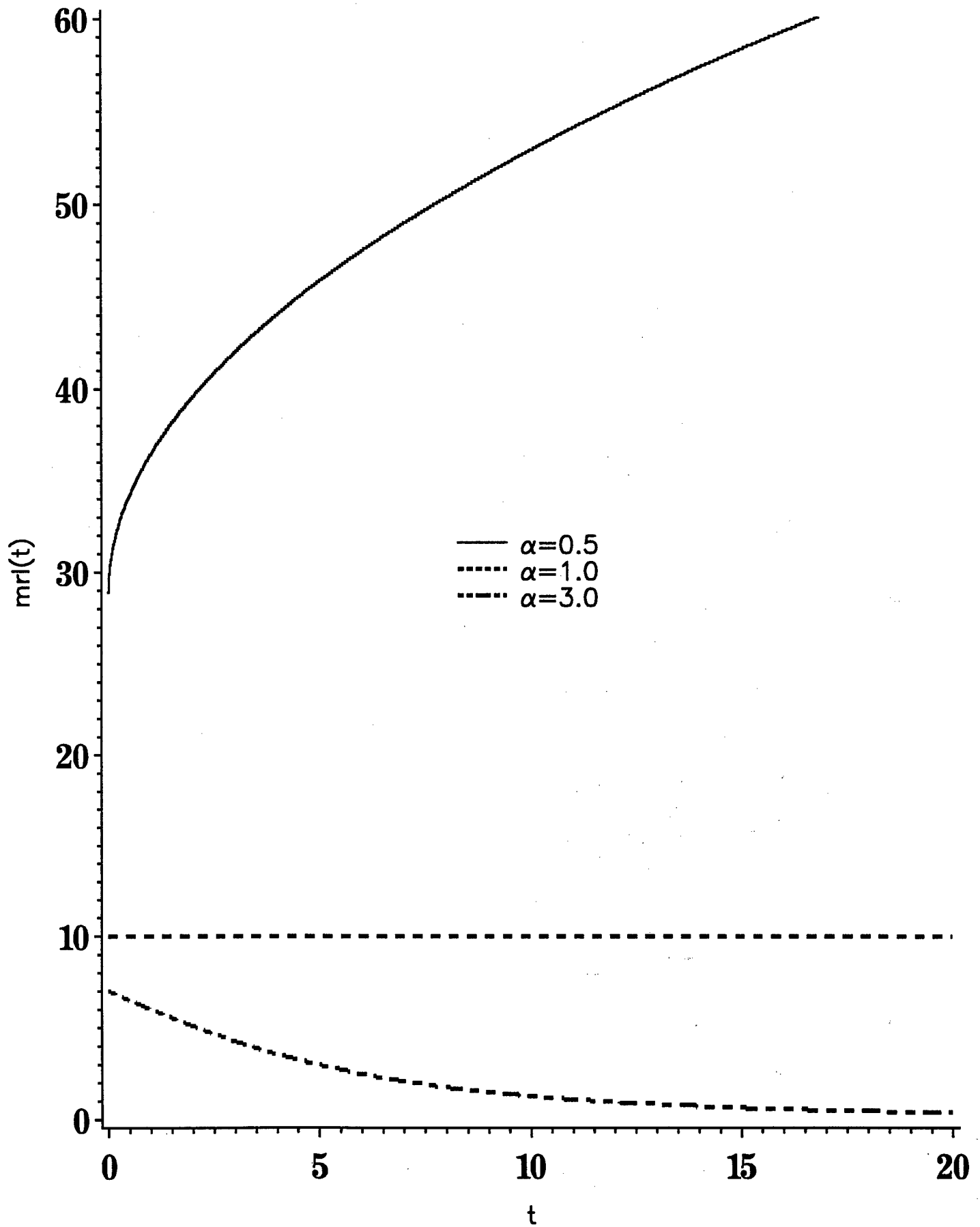
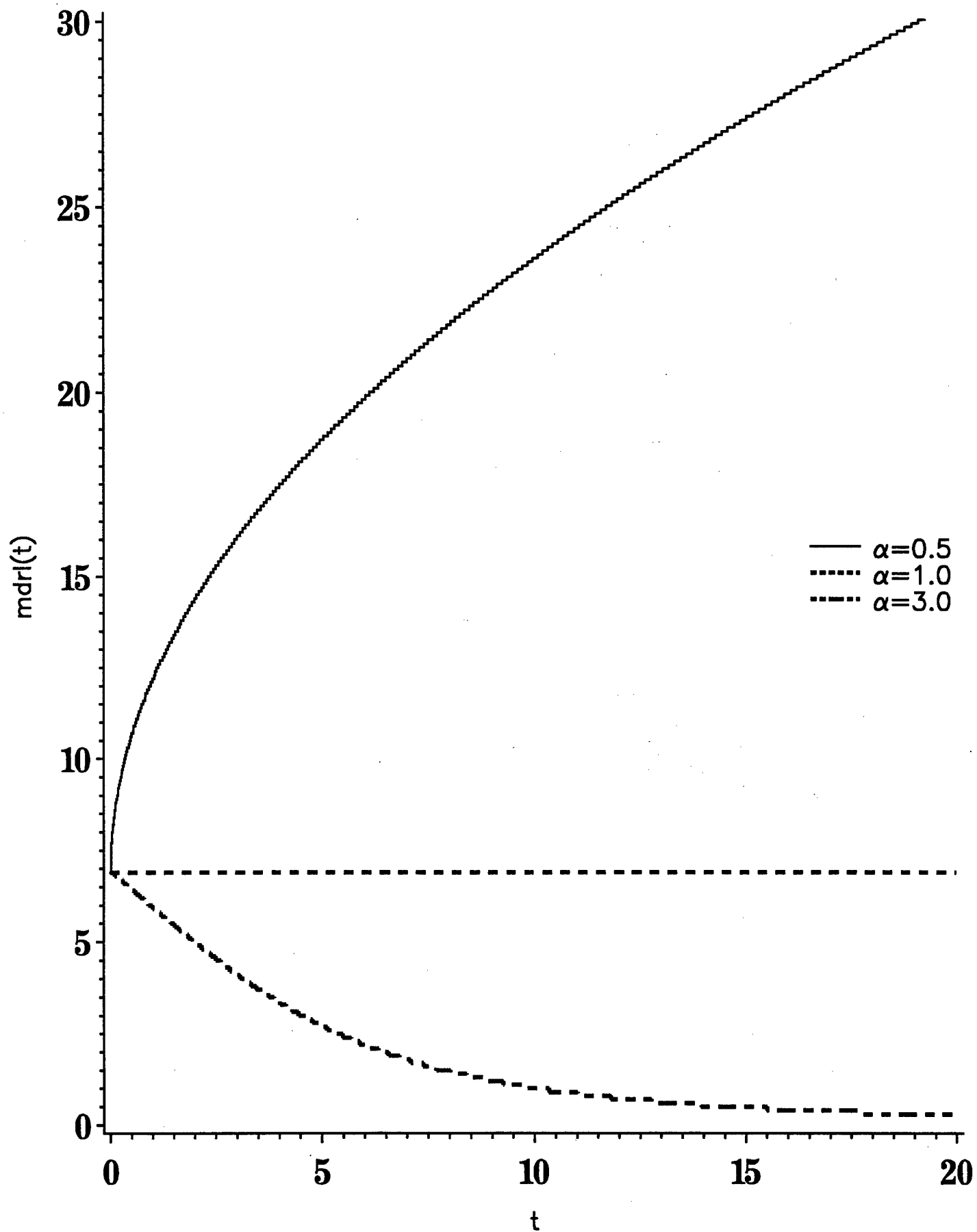


Figure 4  
Comparison of Weibull Median Residual Life Functions



**Regression Models for Survival Data**

Richard A. Johnson  
Department of Statistics  
University of Wisconsin-Madison

and

**DIVISION OF BIOSTATISTICS**



**MEDICAL  
COLLEGE  
OF WISCONSIN**

**MILWAUKEE, WISCONSIN**

# **Regression Models for Survival Data**

Richard A. Johnson  
Department of Statistics  
University of Wisconsin-Madison

and

John P. Klein  
Division of Biostatistics  
The Medical College of Wisconsin

Technical Report 26

August 1997

Division of Biostatistics  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee WI 53226  
Phone: (414)456-8280

## 1. INTRODUCTION

The life length or failure time of equipment or a human subject,  $X$ , can be modeled as a random variable. Frequently, however, the model for survival time can be improved by including relevant explanatory variables  $\mathbf{Z} = (Z_1, \dots, Z_p)^t$  which are also called covariates. In our notation,  $\mathbf{Z}$  consists of  $p$  explanatory variables. In the context of animate subjects,  $\mathbf{Z}$  could include

(i) quantitative variables such as age, blood pressure and weight

(ii) qualitative variables such as gender, race and treatment.

Some of variables may even be time dependent in which case we write  $\mathbf{Z}(x) = (Z_1(x), \dots, Z_p(x))^t$ .

When covariates are included in the model, the primary questions of interest concern the relationship between the failure time  $X$  and the explanatory variables  $(Z_1, \dots, Z_p)^t$ . For instance, this is the case when treatments need to be compared or when risk factors are identified for a particular disease.

Given the explanatory variables  $\mathbf{Z} = \mathbf{z}$  for a subject, the failure time  $X$  will have a conditional cumulative distribution function  $F(\cdot | \mathbf{z})$  which typically depends on the values of the covariates,  $\mathbf{z}$ . We assume throughout that the conditional probability density function,  $f(\cdot | \mathbf{z})$ , exists. The focus of modeling is the conditional survival function or conditional hazard rate function.

$$\text{Survival function: } S(x | \mathbf{z}) = P[X > x | \mathbf{z}] = 1 - F(x | \mathbf{z}) \quad (1.1)$$

$$\text{Hazard function: } h(x | \mathbf{z}) = -\frac{f(x | \mathbf{z})}{S(x | \mathbf{z})} \quad (1.2)$$

These two functions are connected by the well known relations

$$h(x | \mathbf{z}) = -\frac{d \ln[S(x | \mathbf{z})]}{dx} \quad \text{and} \quad S(x | \mathbf{z}) = \exp\left\{-\int_0^x h(t | \mathbf{z}) dt\right\} \quad (1.3)$$

There are two popular approaches to modeling the effects of covariates on survival.

1. Model the log lifetime as a classical linear model.
2. Model the conditional hazard rate.



### 1.1 Models for the Log lifetime

Analogous to the classical linear regression, the first case proceeds by modeling the natural logarithm,  $Y = \ln ( X )$ , as a linear model. That is,

$$Y = \mu + \gamma^t Z + \sigma W, \quad (1.4)$$

where  $W$  is a random variable representing the error. This model is called the accelerated failure-time model because of the following property. When  $z$  is a vector of zero's,  $X = \exp \{ \mu + \sigma W \}$  and we denote its survival function by  $S_0(x)$ . This is the nominal or unstressed case.

Now, under the general linear model, the survival function

$$\begin{aligned} S(x | z) &= P [ X > x | z ] = P [ Y > \ln x | z ] \\ &= P [ \mu + \sigma W > \ln x - \gamma^t z | z ] \\ &= S_0(x \exp[-\gamma^t z]) \end{aligned} \quad (1.5)$$

The effect of the explanatory variables is to change the time scale by the factor  $\exp \{ -\gamma^t Z \}$ . If  $\gamma^t Z$  is negative, the time to failure is accelerated. A life length  $x$  on the original unstressed scale becomes the larger length  $x \exp[-\gamma^t Z]$  when the covariates have value  $z$ . If  $\gamma^t Z$  is positive, time is degraded by the constant factor

In the context of testing very reliable components or systems, the  $z = 0$  case corresponds to the values of variables for ordinary operating conditions. Under nominal operating conditions, it may not be unusual for no failures to occur in any reasonable length of time. Typically, then, harsher temperature, humidity, and mechanical vibrations are employed to accelerate aging and allow for some failures to be observed during a test. The values of  $z$  could then be specified as deviations from the nominal operating conditions.

Note that, for the accelerated failure-time models, the hazard rate

$$h(x | z) = - \frac{S'(x | z)}{S(x | z)} = h_0(x \exp[-\gamma^t Z]) \exp[-\gamma^t Z] \quad (1.6)$$

is related to a baseline hazard rate  $h_0(\cdot) = - S_0'(\cdot)/S_0(\cdot)$  and the constant change of time scale factor  $\exp[-\gamma^t Z]$ .

### 1.2 Models for the Conditional Hazard Function.

To date, the primary approach to modeling the effects of covariates on survival is to model the conditional hazard rate function in terms of covariates. Two classes of models: multiplicative hazards

models and additive hazard rate models have been used to relate the effects of the covariates on survival.

### Multiplicative hazards models

The conditional hazard rate of an individual with covariate vector  $\mathbf{Z} = \mathbf{z}$  is modeled as the product of a baseline hazard rate  $h_0(x)$  and a non-negative function of the covariates  $c(\beta^t \mathbf{z})$

$$h(x | \mathbf{z}) = h_0(x) c(\beta^t \mathbf{z}) \quad (1.7)$$

In practice, the baseline hazard rate function,  $h_0(x)$ , may take a specified parametric form or be left as an arbitrary non negative function. The link function  $c(\cdot)$  can be any non negative function but, for simplicity, the usual choice is the Cox(1972) model  $c(\beta^t \mathbf{z}) = \exp\{\beta^t \mathbf{z}\}$

A key feature of the multiplicative hazards models is the following proportionality property. Consider the case where all of the covariates are determined at time 0 and they are fixed. Then, for two individuals with covariate values  $\mathbf{z}_1$  and  $\mathbf{z}_2$ , respectively

$$\frac{h(x | \mathbf{z}_1)}{h(x | \mathbf{z}_2)} = \frac{h_0(x) c(\beta^t \mathbf{z}_1)}{h_0(x) c(\beta^t \mathbf{z}_2)} = \frac{c(\beta^t \mathbf{z}_1)}{c(\beta^t \mathbf{z}_2)} \quad (1.8)$$

which is a positive constant. That is, the two hazard rate functions are proportional for all times  $x$ . When this is the case, we refer to the model (1.8) as a proportional hazards model.

In terms of the conditional survival function, applying the relation (1.3) to the model (1.7), we see that

$$S(x | \mathbf{z}) = S_0(x | \mathbf{z})^{c(\beta^t \mathbf{z})} \quad (1.9)$$

so the conditional survival function is the baseline survival function raised to the power  $c(\beta^t \mathbf{z})$ . In nonparametric statistics, these are known as Lehmann alternatives.

Further specializing to the Cox model,  $c(\beta^t \mathbf{z}) = \exp\{\beta^t \mathbf{z}\}$  if the  $i$ -th individual has covariate values  $\mathbf{z}$  we have

$$\ln[-\ln(S(x | \mathbf{z}_i))] = \beta^t \mathbf{z}_i + \ln[-\ln(S_0(x))] \quad (1.10)$$

The logarithms of the negative logarithm of the survival functions of  $X$ , given the covariates  $\mathbf{z}_i$ , are parallel. This relation will provide a check on the assumption of a proportional hazards model.

### Additive hazard rate models

Here, the conditional hazard rate is modeled as a baseline hazard rate plus additional hazard components due to the covariates. That is,

$$h(x | z) = \beta_0 + \sum_{j=1}^p z_j(x) \beta_j(x) \quad (1.11)$$

where the regression coefficients  $\beta_j(x)$ , as well as the explanatory variables  $z_j(x)$ , are allowed to vary over time. Here  $\beta_0$  is a baseline hazard rate when all the covariates are zero. The  $p$  regression functions  $z_j(x) \beta_j(x)$  may be positive or negative but they are constrained so that  $h(x | z)$  is positive.

## 2. CENSORING AND TRUNCATION

Before discussing inference procedures in the following sections, we first review the basic types of censoring and truncation. We also introduce the basic notation that enables us to obtain expressions for likelihoods.

We first consider Type I censoring where a lifetime  $X$  is right-censored at a fixed censoring time  $C_r$ . The observation is represented by a pair of random variables  $(T, \delta)$  where  $T = \min(X, C_r)$  and  $\delta = 1$  if failure is observed so  $T = X$ , and  $\delta = 0$  if the observation is censored so  $T = C_r$ .

In the context of testing electronic units, sometimes all items may be placed on test at the same time. If the test is stopped when a specified number of failures occur, the lifetimes of the remaining units are said to be Type II censored.

A lifetime  $X$  is left-censored at a fixed censoring time  $C_L$  if it is only known to be smaller than  $C_L$ . The observation is represented by a pair of random variables  $(T, \varepsilon)$  where  $T = \max(X, C_L)$  and  $\varepsilon = 1$  if failure is observed so  $T = X$ , and  $\varepsilon = 0$  if the observation is censored so  $T = C_L$ .

A more general form, called interval censoring occurs when it is only known that the individual's lifetime lies in an interval  $[L, R)$ .

Truncation differs from censoring. When a lifetime is left-truncated at  $Y_L$ , the lifetime  $X$  will be observed only if  $X \geq Y_L$ . However, if  $X < Y_L$  the investigator will be unaware of the individual.

We summarize the contributions to the likelihood

exact lifetimes	-	$f(x)$	
right censored observations	---	$S(C_r)$	(2.1)
left censored observations	---	$1 - S(C_L)$	
left truncated observations	---	$f(t) / S(Y_L)$	
interval censored observations	---	$[S(L) - S(R)]$	

When the data contain only exact or censored lifetimes, the likelihood consists of the product of four types of contributions.

$$L \propto \prod_{i \in D} f(X_i) \prod_{i \in R} S(C_{ri}) \prod_{i \in L} (1-S(C_{Li})) \prod_{i \in I} [S(L_i) - S(R_i)], \quad (2.2)$$

where D is the set of death times, R the set of right censored observations, L the set of left censored observations, and I the set of interval censored observations.

One other censoring model is frequently invoked. When the time of right censoring,  $C_r$ , is a random variable, the censoring is called random censoring. It is usually assumed that  $C_r$  is distributed as  $G(\cdot)$ , independent of the lifetime  $X$ . Then  $T = \min(X, C_r)$  depends both on the distribution of  $X$  and  $G(\cdot)$ . In terms of  $(T, \delta)$ , the contribution to the likelihood is

$$f(T)^\delta G(T)^\delta g(T)^{1-\delta} S(T)^{1-\delta} \quad (2.3)$$

If the censoring distribution  $G(\cdot)$  is free of the regression parameters and scale parameter, the likelihood for those parameters will not depend on  $G(\cdot)$ .

### 3. ESTIMATION FOR PARAMETRIC REGRESSION MODELS

In this section, we discuss estimation of parametric models that have the accelerated failure-time feature and where the log of failure time has a linear model representation.

According to the accelerated failure-time model (1.5), with  $\theta$  in place of  $\gamma$ ,

$$S(x|z) = S_0(x \exp\{\theta^t z\}) \quad (3.1)$$

where  $\exp\{\theta^t z\}$  is the acceleration factor.

One consequence of this model is that the hazard rate for an individual with covariate values  $z$  is related to the baseline hazard rate by

$$h(x|z) = \exp\{\theta^t z\} h_0(x \exp\{\theta^t z\}) \quad (3.2)$$

where the baseline hazard rate is  $h_0(\cdot) = -S_0'(\cdot) / S_0(\cdot)$ .

Another consequence of the model (3.1) is that the median time to failure with covariate  $z$  is the median time to failure under baseline conditions multiplied by the acceleration factor  $\exp\{\theta^t z\}$ .

A second important representation of the accelerated failure time model is available. The logarithm of survival time is assumed to follow a usual linear model. From (1.4),

$$Y = \mu + \gamma^t Z + \sigma W \quad (3.3)$$

where  $\gamma^t = (\gamma_1, \dots, \gamma_p)$  is a vector of regression coefficients and  $W$  is a random variable representing the error or variation about the regression function.

The two representations (3.1) and (3.3) are closely related. If  $S_0(x)$  is the survival function of the random variable  $\exp(\mu + \sigma W)$ , then the linear log-time model (3.3) is equivalent to the accelerated failure-time model (3.1) with  $\theta = -\gamma$ .

The number of useful parametric models for  $W$  is quite limited. The three most popular are the two parameter Weibull, which includes the negative exponential, the log logistic distribution, and the log normal distribution.

Under the linear model,  $Y_j = \ln X_j$  and when the  $j$ -th individual has covariate vector  $z_j$  we have

$$f_j(y_j | z_j) = \frac{1}{\sigma} f_W\left(\frac{y_j - \mu - \gamma^t z_j}{\sigma}\right) \quad (3.4)$$

where  $f_W(\cdot)$  is the probability density function for the error  $W$ .

The survival function, obtained by integration, is

$$S_j(y_j | z_j) = S_W\left(\frac{y_j - \mu - \gamma^t z_j}{\sigma}\right) \quad (3.5)$$

Similar to (2-1), the censored data likelihood is

$$\begin{aligned} L \propto & \prod_{j \in D} \frac{1}{\sigma} f_W\left(\frac{y_j - \mu - \gamma^t z_j}{\sigma}\right) \prod_{j \in R} S_W\left(\frac{\ln C_{rj} - \mu - \gamma^t z_j}{\sigma}\right) \\ & \times \prod_{j \in L} \left(1 - S_W\left(\frac{\ln C_{Lj} - \mu - \gamma^t z_j}{\sigma}\right)\right) \\ & \times \prod_{j \in I} \left[ S_W\left(\frac{\ln L_j - \mu - \gamma^t z_j}{\sigma}\right) - S_W\left(\frac{\ln R_j - \mu - \gamma^t z_j}{\sigma}\right) \right]. \end{aligned} \quad (3.6)$$

For most error distributions, maximum likelihood estimators of the model parameters based on (3.6) are found numerically. Under appropriate regularity conditions these estimators are

consistent and have an asymptotic normal distribution with a covariance matrix estimated consistently by the observed information matrix (See Borgan 1984 for details for right censored data).

### 3.1 Estimation with Weibull Errors

The two parameter Weibull distribution has survival function

$$S_X(x) = \exp\{-\lambda x^\alpha\}, \quad x \geq 0, \alpha, \lambda > 0,$$

and hazard rate function

$$h_X(x) = \lambda \alpha x^{\alpha-1}.$$

Then, the log transform of time,  $Y = \ln(X)$ , has the extreme value distribution

$$S_Y(y) = \exp\{-\lambda e^{\alpha y}\}.$$

Covariates are incorporated through the linear model for the log lifetime

$$Y = \mu + \gamma^t Z + \sigma W$$

with  $W$  distributed as the standard extreme value distribution having probability density function

$$f_W(w) = \exp\{w - e^w\}, \quad -\infty < w < \infty \quad (3.7)$$

and survival function

$$S_W(w) = \exp\{-e^w\}, \quad -\infty < w < \infty. \quad (3.8)$$

This leads to a proportional hazards model for  $X$  with

$$h(x | z) = \lambda \alpha x^{\alpha-1} \exp\{\beta^t z\} \quad (3.9)$$

where the baseline hazard,  $h_0(x) = \lambda \alpha x^{\alpha-1}$ , is the Weibull hazard rate,  $\alpha = 1/\sigma$ ,  $\lambda = \exp(-\mu/\sigma)$ , and  $\beta_j = -\sigma^{-1}\gamma_j$ ,  $j=1, \dots, p$ .

Alternatively, the accelerated failure-time representation of the Weibull regression model specifies that

$$\exp\{\theta^t z\} h_0(x \exp\{\theta^t z\}) = \lambda \alpha x^{\alpha-1} \exp\{\alpha \theta^t z\} \quad (3.10)$$

is the hazard rate for an individual with covariate vector  $\mathbf{z}$  using the baseline hazard  $\lambda \alpha x^{\alpha-1}$ .

Comparing (3.9) and (3.10), we see the two are the same when  $\theta = \beta / \alpha = -\gamma$ . The Weibull distribution is the only continuous distribution that produces both a proportional hazards model and an accelerated failure-time model.

The estimates of the parameters in the Weibull regression model must be obtained numerically. The estimates and their estimated covariance matrix, based on the log linear model (3.6), are obtained by most statistical packages.

By the invariance of maximum likelihood estimators, these can be converted to the maximum likelihood estimates

$$\hat{\beta} = -\hat{\gamma}\hat{\sigma}^{-1}, \hat{\alpha} = 1/\hat{\sigma}, \text{ and } \hat{\lambda} = \exp\{-\hat{\mu}/\hat{\sigma}\}. \quad (3.11)$$

Using the delta method, the variances and covariances can be expressed in terms of the covariance matrix of the estimators for the log linear model.

$$\begin{aligned} \text{Cov}[\hat{\beta}_j, \hat{\beta}_k] = & \frac{\text{Cov}[\hat{\gamma}_j, \hat{\gamma}_k]}{\hat{\sigma}^2} - \frac{\hat{\gamma}_j \text{Cov}[\hat{\gamma}_j, \hat{\sigma}]}{\hat{\sigma}^3} - \frac{\hat{\gamma}_k \text{Cov}[\hat{\gamma}_k, \hat{\sigma}]}{\hat{\sigma}^3} \\ & + \frac{\hat{\gamma}_j \hat{\gamma}_k \text{Var}[\hat{\sigma}]}{\hat{\sigma}^4}, \quad j, k=1, \dots, p; \end{aligned} \quad (3.12)$$

$$\text{Var}[\hat{\lambda}] = \exp\{-2\frac{\hat{\mu}}{\hat{\sigma}}\} \left\{ \frac{\text{Var}[\hat{\mu}]}{\hat{\sigma}^2} - 2\frac{\hat{\mu} \text{Cov}[\hat{\mu}, \hat{\sigma}]}{\hat{\sigma}^3} + \frac{\hat{\mu}^2 \text{Var}[\hat{\sigma}]}{\hat{\sigma}^4} \right\} \quad (3.13)$$

$$\text{Var}[\hat{\alpha}] = \frac{\text{Var}[\hat{\sigma}]}{\hat{\sigma}^4} \quad (3.14)$$

$$\begin{aligned} \text{Cov}[\hat{\beta}_j, \hat{\lambda}] = & \exp\{-\frac{\hat{\mu}}{\hat{\sigma}}\} \left\{ \frac{\text{Cov}[\hat{\gamma}_j, \hat{\mu}]}{\hat{\sigma}^2} - \frac{\hat{\gamma}_j \text{Cov}[\hat{\gamma}_j, \hat{\sigma}]}{\hat{\sigma}^3} \right. \\ & \left. - \frac{\hat{\mu} \text{Cov}[\hat{\mu}, \hat{\sigma}]}{\hat{\sigma}^3} + \frac{\hat{\gamma}_j \hat{\mu} \text{Var}[\hat{\sigma}]}{\hat{\sigma}^4} \right\}, \quad j=1, \dots, p; \end{aligned} \quad (3.15)$$

$$\text{Cov}[\hat{\beta}_j, \hat{\alpha}] = \frac{\text{Cov}[\hat{\gamma}_j, \hat{\sigma}]}{\hat{\sigma}^3} - \frac{\hat{\gamma}_j \text{Var}[\hat{\sigma}]}{\hat{\sigma}^4} \quad j=1, \dots, p; \quad (3.16)$$

$$\text{Cov}[\hat{\lambda}, \hat{\alpha}] = \exp\left\{-\frac{\hat{\mu}}{\hat{\sigma}}\right\} \left\{ \frac{\text{Cov}[\hat{\mu}, \hat{\sigma}]}{\hat{\sigma}^3} - \frac{\hat{\mu} \text{Var}[\hat{\sigma}]}{\hat{\sigma}^4} \right\}. \quad (13.17)$$

SAS, S-Plus, and BMDP provide maximum likelihood estimates of  $\mu$ ,  $\sigma$  and  $\gamma$  and allow for right-, left-, or interval censored data.

### 3.2 Estimation with Log Logistic Errors

Recall that the log logistic distribution has survival function

$$S_X(x) = \frac{1}{1 + \lambda x^\alpha}. \quad (3.18)$$

Its hazard rate is not monotone but first increases and then decreases.

The log of failure time  $Y = \ln(X)$  has the logistic survival function

$$S_Y(x) = \frac{1}{1 + \lambda \exp^{\alpha y}} \quad (3.19)$$

Three equivalent models can be used to include covariates. Consider first the linear model for log time where

$$Y = \mu + \gamma'Z + \sigma W$$

with  $W$  distributed as the standard logistic distribution having probability density function

$$f_W(w) = \frac{e^w}{(1+e^w)^2} \quad (3.20)$$

The second representation of the log logistic is as the accelerated failure-time model (3.1) with a log logistic baseline survival function.

The third representation is obtained by replacing  $\lambda$  in (3.18) by  $\bar{\lambda} \exp\{\beta^t z\}$ . The conditional survival function of the time to failure is then



$$S_X(x|z) = \frac{1}{1 + \lambda \exp\{\beta^t z\} x^\alpha} \quad (3.21)$$

Again, as with the Weibull model, these latter parameters are related to those of the log linear model by

$$\hat{\beta} = -\hat{\gamma}\hat{\sigma}^{-1}, \hat{\alpha} = 1/\hat{\sigma}, \text{ and } \hat{\lambda} = \exp\{-\hat{\mu}/\hat{\sigma}\}. \quad (3.22)$$

The maximum likelihood estimates of  $\beta$ ,  $\lambda$ , and  $\alpha$  and their estimated covariance matrix can be obtained from the maximum likelihood results for  $\mu$ ,  $\sigma$ , and  $\gamma$  in the log linear model. The same covariance relations (3.12) - (3.17) pertain.

The factor  $\exp\{-\beta^t z\}$  has a nice interpretation in this model. Consider the odds for survival beyond time  $x$

$$\frac{S_X(x|z)}{1 - S_X(x|z)} = \frac{1}{\lambda \exp\{\beta^t z\} x^\alpha} = \exp\{-\beta^t z\} \frac{S_X(x|z=0)}{1 - S_X(x|z=0)} \quad (3.24)$$

We see that  $\exp\{-\beta^t z\}$  is just the relative odds of survival for an individual with covariates  $z$  compared to an individual having the baseline characteristics  $z = 0$ .

The log logistic model is the only parametric model that has both a proportional odds model and an accelerated failure-time representation.

SAS, S-Plus, and BMDP provide maximum likelihood estimates of  $\mu$ ,  $\sigma$  and  $\gamma$  and allow for right-, left-, or interval censored data.

### 3.3 Estimation with Other Error Distributions.

Another choice for the distribution of  $W$  is the log normal distribution. The logarithm of the time to failure then follows the classical linear model

$$Y = \mu + \gamma^t Z + \sigma W$$

with  $W$  distributed as the standard normal distribution having probability density function

The conditional survival function is

$$S_X(x|z) = 1 - \Phi[(\ln x - \mu - \gamma^t z)/\sigma]$$

where  $\Phi(\cdot)$  is the standard normal cumulative distribution function.

The general shape of the hazard rate is similar to that of the log logistic distribution. Typically, the regression models based on the normal errors are quite close to the models based on the log logistic distribution.

One further distribution, the generalized gamma, should also be mentioned. It includes the exponential and Weibull distributions as special cases and the log normal is a limiting case.

$$f(w) = \frac{|\phi| \{ \exp[\phi w] / \phi^2 \}^{(1/\phi^2)} \exp\{-\exp\{\phi w\} / \phi^2\}}{\Gamma[1/\phi^2]}, \quad -\infty < w < \infty. \quad (3.25)$$

When  $\phi$  is equal to one this model reduces to the Weibull regression model and when  $\phi$  is equal to 0 it reduces to the log normal distribution. When  $\phi=1$  and  $\sigma=1$  in (3.25), then this reduces to the exponential regression model. The generalized gamma distribution is rarely used as a final model but rather serves to help choose between the Weibull and log normal models.

SAS provides maximum likelihood estimates for the log normal and the generalized gamma model. It allows for right-, left-, or interval censored data.

### 3.4 Diagnostics.

If a parametric model fits the data, it usually provides more precise estimates of the parameter of interest than can be obtained by nonparametric or semi-parametric methods. However, poorly fitting parametric models can yield misleading estimates. How do we check a parametric regression model? Graphical checks are preferred because tests of fit have low power for small samples and they almost always reject for large samples. The graphical techniques help identify models that are inappropriate. Often, we are left with a few different models that fit reasonably well.

The key to obtaining a graphical diagnostic procedure is the, conditional, cumulative hazard rate

$$H(x|z) = \int_0^x h(u|z) du. \quad (3.26)$$

If  $X$  has a cumulative hazard rate  $H(\cdot)$  then the random variable  $H(X)$  has a unit exponential distribution, since by (1.3),  $P[H(X) > w] = P[X > H^{-1}(w)] = \exp\{-H[H^{-1}(w)]\} = \exp\{-e\}$ .

Diagnostic plots are based on residuals. The Cox-Snell residuals are defined as

$$r_j = \hat{H}(t_j | z_j) \quad (3.27)$$

where the  $j$ -th individual has on study time  $t_j$  and covariate vector  $z_j$ . Here  $\hat{H}(t_j | z_j)$  is the cumulative hazard for the fitted parametric model.

If the underlying parametric model is essentially correct, the residuals  $r_j$  should follow a standard exponential distribution. For the parametric regression models discussed in this Section, the Cox-Snell residuals are

$$\text{Exponential} \quad r_i = t_i \exp\{\hat{\beta}'\mathbf{Z}_i\} \quad (3.28)$$

$$\text{Weibull} \quad \exp\{\hat{\beta}'\mathbf{Z}_i\} t_i^{\hat{\alpha}} \quad (3.29)$$

$$\text{Log logistic} \quad \ln\left[\frac{1}{1 + \exp\{\hat{\beta}'\mathbf{Z}_i\} t_i^{\hat{\alpha}}}\right] \quad (3.30)$$

and

$$\text{Log normal} \quad \ln\left\{1 - \Phi\left[\frac{\ln[t_i] - \hat{\mu} - \hat{\gamma}'\mathbf{Z}_i}{\hat{\sigma}}\right]\right\}. \quad (3.31)$$

The primary diagnostic plot is a plot of the residuals from the parametric fit,  $r_j$ , versus the nonparametric Nelson-Aalen estimator of the cumulative hazard of the  $r_j$ 's. This should result in a straight line pattern having slope 1, if the parametric model is reasonable.

An alternative, but equivalent approach, is based on the log time linear model representation (3.3). Analogous to the classical normal linear model theory, standardized residuals

$$s_j = \frac{\ln[t_i] - \hat{\mu} - \hat{\gamma}'\mathbf{Z}_i}{\hat{\sigma}} \quad (3.32)$$

can be defined. Under the log normal model, these residuals approximate a, possibly censored, random sample from a standard normal distribution. If the Weibull model holds, the standardized residuals should behave like a censored sample from the standard extreme value distribution (3.7).

Under the log logistic model (3.18), the standardized residuals are nearly a censored sample from the standard logistic distribution (3.21). The hazard plots obtained from this approach are exactly the same as those obtained by the exponential hazard plot for the Cox-Snell residuals.

### 3.5 Example

To illustrate these procedures we consider a sample of 877 women diagnosed with an initial infection of either gonorrhea or chlamydia. While both of these disease are treated quite easily it remains a mystery why the re infection rate remains high for these diseases in some sub-populations. To study risk factors for re infection, patients were followed until they had a re infection or until the

closing date of the study. During the study period 347 (40%), of the women experienced a re infection. The follow-up time on the 877 women ranged from 1 to 1,529 days with a median of 247 days. In this example we have selected three of the factors considered by investigators: years of schooling (median 11.4 years with a range of 6-18 years), condom use (6% always, 58% sometimes and 34% never), and the indicator of whether the patient had oral sex within the 12 months prior to diagnosis (33%). Years of schooling is treated as a continuous covariate, while condom use is coded as two binary covariates (sometime and never use condoms). A complete data set can be found at [www.biostat.mcw.edu:80/klein/std.html](http://www.biostat.mcw.edu:80/klein/std.html).

Using the SAS<sup>®</sup> procedure LIFEREG we fit the Weibull, log logistic and log normal regression models to this data. Using the linear models formulation  $Y = \mu + \gamma'Z + \sigma W$ , the estimates and standard errors of  $\gamma$  and  $\sigma$  are in Table 1.

**Table 1**  
**Maximum Likelihood Estimators Based On The Linear Models Formulation**

Effect	Weibull			Log Logistic			Log Normal		
	$\hat{\gamma}$	SE	p	$\hat{\gamma}$	SE	p	$\hat{\gamma}$	SE	p
Intercept	4.786	0.571	<.0001	4.067	0.643	<.0001	3.786	0.694	<.0001
Z <sub>1</sub> : Years of School	0.163	0.044	.0002	0.171	0.048	.0004	0.186	0.053	.0004
Z <sub>2</sub> : Oral sex	0.613	0.172	.0003	0.618	0.183	.0008	0.627	0.196	.0014
Z <sub>3</sub> : Sometime use Condom	0.066	0.300	.8252	0.232	0.355	.5147	0.386	0.364	.2892
Z <sub>4</sub> : Never use Condom	0.393	0.310	.2048	0.587	0.365	.1080	0.760	0.376	.0432
$\sigma$	1.304	0.058		1.112	0.050		2.085	0.083	
Log Likelihood		-976.44			-982.47			-991.33	

While the models presented in Table 1 are not nested, the value of the maximum likelihood provides a means of selecting the best fitting parametric model. Here the Weibull model appears to fit the data the best. Using this model one can compute the estimates of  $\lambda$ ,  $\beta$ , and  $\alpha$  using (3.11)-(3.17). The estimates and their standard errors are given in the following table.

**Table 2**  
**Estimates based on the Weibull model**

Parameter	Estimate	Stand. Err
$\lambda$	0.02549	0.01221
Z <sub>1</sub> : Years of School	-0.12561	0.03375
Z <sub>2</sub> : Oral sex	-0.47008	0.13001
Z <sub>3</sub> : Sometime use Condom	-0.05074	0.22963
Z <sub>4</sub> : Never use Condom	-0.30109	0.23721
$\alpha$	0.76660	0.03421

Note that the model suggests that patients who had fewer years of schooling and who had oral sex in the last year tend to re infected later and that condom use is not related to the re infection rate.

Figure 1 shows the Cox-Snell residual plots for the three parametric models. The curves, which all should be equal to the 45° line, all suggest that the models fitted here are plausible. Again, the Weibull plot seems to be closest to the 45° line.

#### 4. Semi-Parametric Regression Models

In this Section we shall discuss the estimation of regression parameters for the multiplicative hazards regression model. For this model, most commonly called the proportional hazards model or the Cox model, the conditional hazard rate of X given  $z(x)$  is given by

$$h(x|z) = h_0(x) \exp\{\beta^t z(x)\}, \quad (4.1)$$

where  $z(x)$  is a p-vector of possibly time dependent covariates,  $\beta$  is a p-vector of regression coefficients and  $h_0(x)$  is a baseline hazard rate. In most applications of this model the main interest is on the estimation of the regression coefficients and thus the baseline hazard rate  $h_0(\cdot)$  is left unspecified.

Estimation for the Cox model is based on a partial likelihood rather than a full likelihood. For right censored and left truncated data Andersen et al (1993) have shown that in most cases the large sample properties of maximum partial likelihood estimates are similar to the usual properties of a maximum likelihood estimator based on the complete likelihood. That is the maximum partial likelihood estimators of  $\beta$  are consistent and asymptotically normal with a covariance estimated consistently by the inverse of the observed information.

#### 4.1 Partial Likelihoods

To estimate the risk coefficients,  $\beta$ , we need a partial likelihood function. For simplicity we shall assume we have only right censored data,  $(t_j, \delta_j, \{Z_j(t), 0 \leq t \leq t_j\})$ ,  $j=1, \dots, n$ , where  $t_j$  is the time on study for the  $j$ -th patient,  $\delta_j$  is the event indicator for the  $j$ -th patient ( $\delta_j=1$  if event has occurred, 0 if the lifetime is right censored) and  $Z_j(t) = (Z_{j1}(t), \dots, Z_{jp}(t))^T$  is the vector of covariates for the  $j$ -th individual at time  $t$ . For the covariate process we assume that the values of  $Z_j(t)$  are known for any time point at which the subject is under observation. We assume that censoring is non informative in that, given  $Z_j(t)$ , the event and censoring time for the  $j$ -th patient are independent. We first assume that all the event times are distinct. Let  $T_1 < T_2 < \dots < T_D$  denotes the ordered event times,  $Z_{(j)}(T_j)$  is the covariate associated with the individual whose failure time is  $T_j$  and  $R(T_j)$  is the risk set at time  $T_j$  (that is  $R(T_j)$  is the set of all individuals who were still under study at a time just prior to  $t_j$ ). The partial likelihood function is

$$L(\beta) = \prod_{i=1}^D \frac{\exp\{\beta^T z_{(i)}(T_i)\}}{\sum_{j \in R(T_i)} \exp\{\beta^T z_j(T_i)\}} \quad (4.2)$$

This is treated as a usual likelihood and inference is carried out by usual means. It is of interest to note that the numerator of the likelihood depends only upon information from the individual who experiences the event, whereas the denominator utilizes information on all individuals who have not yet experienced the event (including some individuals who will be censored later).

When there is more than one death at a given time several partial likelihoods have been proposed. Again let  $T_1 < T_2 < \dots < T_D$  denote the  $D$  distinct ordered event times. At time  $T_i$  let  $d_i$  be the number of deaths,  $\mathbf{D}_i$  be the set of individuals who die,  $s_i = \sum_{j \in \mathbf{D}_i} z_j(T_i)$ , and  $R(T_i)$  be the risk set at

time  $T_i$

The first partial likelihood is due to Breslow (1974) and is the default partial likelihood in most statistical packages. Here

$$L_1(\beta) = \prod_{i=1}^D \frac{\exp\{\beta^T s_i\}}{[\sum_{j \in R(T_i)} \exp\{\beta^T z_j(T_i)\}]^{d_i}} \quad (4.3)$$

Efron (1977) suggests a partial likelihood of

$$L_2(\beta) = \prod_{i=1}^D \frac{\exp\{\beta^t s_i\}}{\prod_{j=1}^{d_i} \left[ \sum_{k \in R(T_i)} \exp\{\beta^t z_k(T_i)\} - \frac{j-1}{d_i} \sum_{k \in \mathbf{D}_i} \exp\{\beta^t z_k(T_i)\} \right]} \quad (4.4)$$

When the number of ties are small, Efron's and Breslow's likelihoods are quite close.

The third partial likelihood, due to Cox(1972), is based on a discrete time hazard rate model. If we let  $h(t|Z)$  denote the conditional probability of death in the interval  $(t, t+1)$  given survival to the start of the interval and if we assume

$$\frac{h(t|Z)}{1-h(t|Z)} = \frac{h_0(t)}{1-h_0(t)} \exp\{\beta^t z(t)\}$$

then this likelihood is the proper partial likelihood. To construct the likelihood, let  $Q_i$  denote the set of all subsets of  $d_i$  individuals who could be selected from the risk set  $R(T_i)$ . Each element of  $Q_i$  is a  $d_i$ -tuple of individuals who could have been one of the  $d_i$  failures at time  $T_i$ . Let  $q=(q_1, \dots, q_{d_i})$  be one of these elements of  $Q_i$  and define  $s_q^* = \sum_{j=1}^{d_i} z_{q_j}(T_i)$ . Then the discrete partial likelihood is

$$L_3(\beta) = \prod_{i=1}^D \frac{\exp\{\beta^t s_i\}}{\sum_{q \in Q_i} \exp\{\beta^t s_q^*\}} \quad (4.5)$$

When there are no ties between the event times all these likelihoods reduce to the likelihood (4.2).

The partial likelihoods (4.2)-(4.5) can be extended in a natural way to allow for left truncated or delayed entry data. To do this one needs to redefine the risk set to be the set of all individuals under observation at time  $t$  with an entry time into the study less than  $t$  who are still alive or are dead at time  $t$ .

### 4.3 Inference for $\beta$

Inference for the regression coefficients,  $\beta$ , is based on the partial likelihood. For ease of exposition we shall restrict our discussion to the case of right censored data with distinct death times and fixed time covariates. In this case from (4.2) we see that the log likelihood is

$$LL(\beta) = \sum_{i=1}^D \sum_{k=1}^p \beta_k Z_{(i)k} - \sum_{i=1}^D \ln \left[ \sum_{j \in R(T_i)} \exp\{\beta^t z_j\} \right] \quad (4.6)$$

The partial maximum likelihood (pmle) estimates are found by maximizing (4.2), or equivalently, (4.6). The efficient score equations are found by taking partial derivatives of (4.6) with respect to the  $\beta$ 's as follows. Let  $U_h(\beta) = \partial LL(\beta) / \partial \beta_h$ ,  $h=1, \dots, p$ . That is,

$$U_h(\beta) = \sum_{i=1}^D Z_{(i)h} - \sum_{i=1}^D \frac{\sum_{j \in R(T_i)} Z_{jh} \exp\{\beta^t z_j\}}{\sum_{j \in R(T_i)} \exp\{\beta^t z_j\}}. \quad (4.7)$$

The information matrix is the negative of the matrix of second derivatives of the log likelihood and is given by  $I(\beta) = (I_{gh}(\beta))_{p \times p}$  with the  $(g, h)$ th element given by

$$I_{gh}(\beta) = \sum_{i=1}^D \frac{\sum_{j \in R(T_i)} Z_{jg} Z_{jh} \exp\{\beta^t z_j\}}{\sum_{j \in R(T_i)} \exp\{\beta^t z_j\}} - \sum_{i=1}^D \left\{ \frac{\sum_{j \in R(T_i)} Z_{jg} \exp\{\beta^t z_j\}}{\sum_{j \in R(T_i)} \exp\{\beta^t z_j\}} \right\} \left\{ \frac{\sum_{j \in R(T_i)} Z_{jh} \exp\{\beta^t z_j\}}{\sum_{j \in R(T_i)} \exp\{\beta^t z_j\}} \right\}. \quad (4.8)$$

For large samples there are three test statistics that are commonly used to test the global hypothesis that  $\beta = \beta_0$ . The first test is based on the asymptotic normality of the pmle. Let  $\mathbf{b}$  denote the pmle's, then for large samples  $\mathbf{b}$  has a  $p$ -variate normal distribution with mean  $\beta$  and variance-covariance estimated consistently by  $I^{-1}(\mathbf{b})$ . The test statistic is

$$X_W^2 = (\mathbf{b} - \beta_0)^t I(\mathbf{b}) (\mathbf{b} - \beta_0), \quad (4.9)$$

which has a limiting chi-squared distribution with  $p$  degrees of freedom when  $\beta = \beta_0$ .

The second test is the likelihood ratio test with test statistic

$$X_{LR}^2 = 2\{LL(\mathbf{b}) - LL(\beta_0)\}, \quad (4.10)$$



which also has a limiting chi-squared distribution with  $p$  degrees of freedom when  $\beta = \beta_0$ .

The third test is based on the limiting distribution of the efficient score vector  $U$ . For large samples,  $U(\beta)$  is asymptotically  $p$ -variate normal with mean  $0$  and covariance  $I(\beta)$ . The test statistic is

$$X_{SC}^2 = U(\beta_0)^t I^{-1}(\beta_0) U(\beta_0) \quad (4.11)$$

which has a large sample chi-squared distribution with  $p$  degrees of freedom when  $\beta = \beta_0$ .

Wald, likelihood ratio and score tests can also be used to test local hypotheses about subsets of  $\beta$ . Let  $\beta = (\beta_1^t, \beta_2^t)^t$ , where  $\beta_1$  is a  $q \times 1$  vector of the  $\beta$ 's of interest and  $\beta_2$  is the vector of the remaining  $p-q$   $\beta$ 's. We wish to test the hypothesis that  $\beta_1 = \beta_{10}$ . To construct the Wald test we partition the information matrix as

$$I = \begin{pmatrix} I_{11} & I_{12} \\ I_{21} & I_{22} \end{pmatrix},$$

where  $I_{11}$  ( $I_{22}$ ) is the  $q \times q$  ( $(p-q) \times (p-q)$ ) sub matrix of second partial derivatives of the minus the log likelihood with respect to  $\beta_1$  ( $\beta_2$ ) and  $I_{12}$  and  $I_{21}$  the matrices of mixed second partial derivatives. The Wald test statistic is

$$X_W^2 = (b_1 - \beta_{10})^t (I^{11}(b))^{-1} (b_1 - \beta_{10}) \quad (4.12)$$

where  $I^{11}(b)$  is the upper  $q \times q$  sub matrix of  $I^{-1}(b)$ .

For the other two tests, we let  $b_2(\beta_{10})$  be the pmle of  $\beta_2$  based on the log likelihood with the first  $q$   $\beta$ 's fixed at a value  $\beta_{10}$ . The likelihood ratio statistic is

$$X_{LR}^2 = 2\{LL(b) - LL[\beta_{10}, b_2(\beta_{10})]\}. \quad (4.13)$$

For the score tests let  $U_1[\beta_{10}, b_2(\beta_{10})]$  be the  $q \times 1$  vector of scores for  $\beta_1$  evaluated at the hypothesized value of  $\beta_1$  and at the restricted pmle for  $\beta_2$ . Then

$$X_{SC}^2 = U_1[\beta_{10}, b_2(\beta_{10})]^t [I^{11}(\beta_{10}, b_2(\beta_{10}))] U_1[\beta_{10}, b_2(\beta_{10})]. \quad (4.14)$$

For large samples all three statistics have a limiting chi-square distribution with  $q$  degrees of freedom when  $\beta_1 = \beta_{10}$ .

Most major statistics packages provide point estimates and both global and local tests for right censored data. SAS, BMDP and SPlus also allow for left truncated data.

#### 4.4 Estimation of the Survival function

Once the pmle's of  $\beta$ , are obtained the baseline cumulative hazard rate and the baseline survival function can be estimated. These estimates are only appropriate when all the covariates are fixed at time 0. The most common estimator is Breslow's (1974) estimator. Let  $\mathbf{b}$ , be the pmle of  $\beta$  and  $\hat{\mathbf{V}}(\mathbf{b})$ , be the estimated covariance matrix of  $\mathbf{b}$ , obtained from the inverse of the information matrix. Let  $T_1 < T_2 < \dots < T_D$  denote the distinct death times and  $d_i$  be the number of deaths at time  $T_i$ . Define

$$W(T_i; \mathbf{b}) = \sum_{j \in R(T_i)} \exp\{\mathbf{b}^t \mathbf{z}_j\}. \quad (4.15)$$

The estimate of the baseline cumulative hazard rate,  $H_0(t) = \int_0^t h_0(u) du$  is

$$\hat{H}_0(t) = \sum_{T_i \leq t} \frac{d_i}{W(T_i; \mathbf{b})}, \quad (4.16)$$

which is a step function with jumps at the observed death times. The estimator of the baseline survival function,  $S_0(t) = \exp\{-H_0(t)\}$ , is given by

$$\hat{S}_0(t) = \exp\{-\hat{H}_0(t)\}. \quad (4.17)$$

This is an estimator of the survival function of an individual with a baseline set of covariate values,  $\mathbf{z} = \mathbf{0}$ . To estimate the survival function for an individual with a covariate vector  $\mathbf{z} = \mathbf{z}_0$ , we use the estimator

$$\hat{S}(t | \mathbf{Z} = \mathbf{z}_0) = \hat{S}_0(t) \exp(\mathbf{b}^t \mathbf{z}_0) \quad (4.18)$$

Under rather mild regularity conditions (See Andersen et al (1993)) this estimator, for fixed  $t$ , has an asymptotic normal distribution with mean  $S(t | \mathbf{Z} = \mathbf{z}_0)$  and a variance which can be estimated by

$$\hat{\mathbf{V}}[\hat{S}(t | \mathbf{Z} = \mathbf{z}_0)] = [\hat{S}(t | \mathbf{Z} = \mathbf{z}_0)]^2 \{Q_1(t) + Q_2(t; \mathbf{z}_0)\}, \quad (4.19)$$

where

$$Q_1(t) = \sum_{T_i \leq t} \frac{d_i}{W(T_i, \mathbf{b})^2} \quad (4.19)$$

which is an estimator of the variance of  $\hat{H}_0(t)$  if  $\mathbf{b}$  were the true value of  $\beta$ . The term

$$Q_2(t; \mathbf{Z}_0) = \mathbf{Q}_3(t; \mathbf{Z}_0)^t \hat{V}(\mathbf{b}) \mathbf{Q}_3(t; \mathbf{Z}_0) \quad (4.20)$$

with  $\mathbf{Q}_3$  the  $p$ -vector whose  $k$ -th element is defined by

$$Q_3(t, \mathbf{Z}_0)_k = \sum_{T_i \leq t} \left[ \frac{W^{(k)}(T_i; \mathbf{b})}{W(T_i; \mathbf{b})} - Z_{0k} \right] \left[ \frac{d_i}{W(T_i, \mathbf{b})} \right], \quad k=1, \dots, p \quad (4.21)$$

where

$$W^{(k)}(T_i; \mathbf{b}) = \sum_{j \in R(T_i)} Z_{jk} \exp(\mathbf{b}^t \mathbf{Z}_j),$$

reflects the uncertainty in estimation processes added by estimation of  $\beta$ .

SAS, BMDP and SPlus have routines which provide estimates of the survival function following a Cox regression analysis.

#### 4.5 Stratified Proportional Hazards Models

In some instances the proportionality assumption in the Cox model does not hold for some covariate. In this case it is possible to fit a proportional hazards model with a distinct baseline hazard rate for each level of the covariate. Suppose the covariate has  $s$  levels or strata and suppose that for the  $j$ -th level the baseline hazard rate is  $h_{0j}(t)$ . The stratified proportional hazards model is

$$h_j(t | \mathbf{Z}(t)) = h_{0j}(t) \exp\{\beta^t \mathbf{Z}(t)\}, \quad j = 1, \dots, s. \quad (4.22)$$

Here the regression coefficients are assumed to act in a similar manner in each of the stratum.

Estimation and hypothesis testing methods follow as before where the partial log likelihood function is

$$LL(\beta) = \{LL_1(\beta)\} + \{LL_2(\beta)\} + \dots + \{LL_s(\beta)\}, \quad (4.23)$$

where  $LL_j(\beta)$  is the log partial likelihood using only the data for those individuals in the  $j$ -th stratum.

## 4.5 Diagnostics

A number of diagnostic tests and plots have been suggested for the proportional hazards model. In this section we shall review a few of these techniques. Other techniques can be found in Chapter 11 of Klein and Moeschberger (1997).

We shall first look at methods for checking the proportional hazards assumption for a given covariate. A common approach to checking this assumption for a fixed covariate  $z_1$  is to create an artificial time dependent covariate,  $z_2(t)$ , defined as  $z_2(t) = z_1 \times g(t)$  for some known function of  $t$  (typically  $\log[t]$ ). Here the model for the conditional hazard rate is

$$h(t | z_1) = h_0(t) \exp\{\beta_1 z_1 + \beta_2 [z_1 \times g(t)]\}$$

which reduces to the proportional hazards model when  $\beta_2$  is equal to zero.

Several graphical checks are available to check for proportional hazards. Consider checking for proportional hazards for a discrete covariate  $z_1$  after adjustment for other covariates,  $z_2$ . One technique is to fit a proportional hazards model to  $z_2$ , stratified on  $z_1$ . That is, we fit the model

$$h(t | z_1 = j, z_2) = h_{0j}(t) \exp\{\beta_2' z_2\}.$$

If the model has proportional hazards for  $z_1$  then we must have  $h_{0j}(t) = h_0(t)e^{b_1 z_1}$ , so that the cumulative baseline hazard rates for each level of  $z_1$  are constant multiples of each other or equivalently the logs of the cumulative baseline hazard rates are parallel. Let  $\hat{H}_{0j}(t)$  be the estimated baseline hazard rate (4.16). If the proportionality assumption holds then a plot of  $\ln[\hat{H}_{01}(t)]$ , ... ,  $\ln[\hat{H}_{0K}(t)]$  versus  $t$  should yield parallel lines. An alternative is to plot  $\ln[\hat{H}_{0j}(t)] - \ln[\hat{H}_{01}(t)]$ ,  $j=2, \dots, K$  versus  $t$  which should yield a series of constant curves. Andersen (1982) suggests a plot of

$\hat{H}_{0j}$ ,  $j=2, \dots, K$  versus  $\hat{H}_{01}$  for all  $t$ . If proportionality holds these should be straight lines. If  $H_{0j}(t) = \exp(\gamma_j)H_{01}(t)$  then the slope of these lines is a crude estimate of  $\gamma_j$ . Gill and Schumacher (1987) have shown that if the plot of  $\hat{H}_{0j}(t)$  versus  $\hat{H}_{01}(t)$  is a convex (concave) function then the ratio  $h_{0j}(t)/h_{01}(t)$  is an increasing (decreasing) function of  $t$ . If the plot is piecewise linear then this ratio is piecewise constant. All three plots should be interpreted with some care since the variances of the curves are not constant over time.

If the proportional hazards assumption is valid then the martingale residual can be used to check the appropriate form of the regression function. To define this residual we let  $z_j(t)$  denote the covariate vector for the  $j$ -th individual. Let  $N_j(t)$  be a counting process with the value 1 if at time  $t$  the  $j$ -th individual is dead and 0 if they are alive. Define  $Y_j(t)$  as the indicator that person  $j$  is under study at time  $t$ . Finally, let  $\hat{b}$  and  $\hat{H}_0(\cdot)$  be the pmle of  $\beta$  and  $H_0(\cdot)$ , respectively. The martingale residual for the  $j$ -th observation is

$$\hat{M}_j = N_j(\infty) - \int_0^{\infty} Y_j(t) \exp\{\mathbf{b}'\mathbf{Z}_j(t)\} d\hat{H}_0(t), j=1, \dots, n. \quad (4.24)$$

The residuals have the properties that they sum to zero and for large samples behave like an uncorrelated sample from a population with a zero mean. If the true values of  $\beta$  and  $H_0(\cdot)$  were used in (4.24) then the functions  $M_j$  would be martingales. The residuals can be interpreted as the difference over time of the observed number of events minus the expected number of events under the assumed Cox model.

Martingale residuals are most commonly used to determine the best functional form for a given covariate assuming the model is known for the remaining covariates. Suppose  $\mathbf{z} = (\mathbf{z}_1, \mathbf{z}_2)$  with a Cox model assumed for  $\mathbf{z}_2$ . The model is

$$h(t | \mathbf{z}_1, \mathbf{z}_2) = h_0(t) \exp\{\beta_2' \mathbf{z}_2 + f(\mathbf{z}_1)\}$$

with  $f(\cdot)$  to be determined from the data. To find  $f(\cdot)$  we fit a Cox model using  $\mathbf{z}_2$  and compute the martingale residuals. A plot of  $(\mathbf{z}_j, \hat{M}_j)$  is made and a smooth (Cleveland (1979)) is fit to the scatter diagram. The smoothed curve is the suggested form of  $f(\cdot)$ . For example, if the smooth is linear then no transformation of  $\mathbf{z}_1$  is needed while if the curve has a threshold then a discretized version of the covariate is used. A detailed derivation of these results is found in Fleming and Harrington (1991) or Therneau et al (1990).

The martingale residuals can also be used to check for outliers, but since the residuals lie in the interval  $(-\infty, 1)$  they tend to be highly skewed. A residual which tends to have a more normal shape is the deviance residual, defined by

$$D_j = \text{sgn}[\hat{M}_j] \{-2[\hat{M}_j + \delta_j \log(\delta_j - \hat{M}_j)]\}^{1/2} \quad (4.25)$$

This residual has a value of 0 when  $\hat{M}_j$  is zero. The logarithm tends to inflate the value of the residual when  $\hat{M}_j$  is close to 1 and shrink large negative values of  $\hat{M}_j$ . To check for outliers we plot  $D_j$  versus  $\mathbf{b}'\mathbf{z}_j$ . When there is light to moderate censoring the  $D_j$  should look like a sample of normally distributed noise. When there is heavy censoring a large collection of points near zero will distort the normal approximation. In either case potential outliers will have deviance residuals which are too large in absolute value.

While the deviance residual is useful for checking for outliers in a data set, the score residuals, are used for checking the influence an observation has on the estimate of  $\beta$ . The score residual is defined for the  $j$ -th observation and the  $k$ -th covariate as

$$S_{jk} = \delta_i\{Z_{jk} - \bar{Z}_k(t_i)\} - \sum_{h=1}^n \{Z_{jk} - \bar{Z}_k(t_h)\} \exp\{\mathbf{b}'\mathbf{Z}_j\} d\hat{H}_0(t_h), \quad (4.26)$$

for  $j=1, \dots, n$  and  $k=1, \dots, p$ . Here

$$\bar{Z}_k(t) = \frac{\sum_{j=1}^n Y_j(t) Z_{jk}(t) \exp\{\mathbf{b}'\mathbf{Z}_j(t)\}}{\sum_{j=1}^n Y_j(t) \exp\{\mathbf{b}'\mathbf{Z}_j(t)\}}$$

and  $d\hat{H}_0(t_h)$  is the size of the jump in  $\hat{H}_0(\cdot)$  at  $t_h$ . The first term  $\delta_i\{Z_{jk} - \bar{Z}_k(T_j)\}$  is the partial residual of Schoenfeld (1982) and is the difference between the covariate  $Z_{jk}$  at the failure time and the expected value of the covariate at this point in time.

The standardized score residual vector,  $\Delta = \mathbf{I}(\mathbf{b})^{-1}(S_{j1}, \dots, S_{jp})^t$ , is an approximation of the difference in the pmle of  $\beta$  based on the complete data and the pmle of  $\beta$  based on a data set with the  $j$ -th observation removed. Plots of these standardized residuals versus the case number, the covariate or time are used to check the influence of the  $j$ -th observation on the  $k$ -th covariate.

#### 4.6 Example

We shall continue the example discussed in Section 3.5 by analyzing the data using a proportional hazards model. To illustrate the methods we shall restrict ourselves to those methods available in SAS. As a first step in the analysis we fit a Cox model to the five covariates  $z_1$ : Years of Schooling,  $z_2$ : Oral sex in last year (1=yes, 0=no),  $z_3$ : Occasional Condom use (1-Sometime use, 0-always or never) and  $z_4$ : No condom use (1-never use condom, 0- Sometime of always). The ANOVA table for this model is

**Table 3**  
**PMLE For The Simple Cox Model**

	Estimate	SE	Chi-Square	p
$\beta_1$ Schooling	-0.127	0.338	14.13	0.002
$\beta_2$ Oral Sex	-0.465	0.120	12.79	0.003
$\beta_3$ Sometime Use Condom	-0.042	0.230	0.03	.8556
$\beta_4$ Never use Condom	-0.309	0.237	1.69	.1933

This model gives results quite similar to those found using the parametric models.

To check for proportional hazards, we fit four time dependent covariates  $z_{i+4} = z_i \ln(t)$ ,  $i=1, \dots, 4$ . The ANOVA table for this model is

**Table 4**  
**Checking The Proportionality Assumption**

	Estimate	SE	Chi-Square	p
$\beta_1$ Schooling	-0.153	0.106	2.07	0.150
$\beta_2$ Oral Sex	-0.345	0.427	0.65	0.419
$\beta_3$ Sometime Use Condom	-1.108	0.588	3.55	0.059
$\beta_4$ Never use Condom	-1.682	0.646	6.79	0.009
$\beta_5$ : $Z_1 \ln(t)$	0.005	0.021	0.06	0.806
$\beta_6$ : $Z_2 \ln(t)$	-0.024	0.083	0.08	0.773
$\beta_7$ : $Z_3 \ln(t)$	0.229	0.124	3.39	0.065
$\beta_8$ : $Z_4 \ln(t)$	0.289	0.133	4.71	0.029

This model suggests that the proportional hazards assumption is not valid for the factor representing condom use. Figures 2 and 3 confirm this observation. Figure 2 looks at the difference in log baseline hazard rates based on the models with  $z_1$  and  $z_2$ , stratified on the three levels of condom use. Figure 3 is the Andersen plot of the cumulative hazard rate for the baseline group (always use condom) versus the other two groups. Both plots show a marked departure from what one would expect if the proportionality assumption held.

To account for the non proportionality of the condom factor we could either consider models which stratify on condom use or we could model condom use by time dependent covariates. We prefer the later approach here. We shall create four time dependent covariates for the condom use factor:

$$z_9(t) = z_3 I[t \leq \tau] \text{ ("early" effect of occasional condom use)}$$

$$z_{10}(t) = z_4 I[t \leq \tau] \text{ ("early" effect of no condom use)}$$

$$z_{11}(t) = z_3 I[t > \tau] \text{ ("late" effect of occasional condom use)}$$

$$z_{12}(t) = z_4 I[t > \tau] \text{ ("late" effect of no condom use)}$$

and fit the model  $z_1, z_2, z_9(t), \dots, z_{12}(t)$ . To find  $\tau$  we fit a series of models with different values of  $\tau$  and pick the model which gives the largest partial likelihood. While  $\tau$  can be any re infection time found in the data, our grid search was over the grid 10, 20, ..., 1000. We found the "best" value of  $\tau$  to be 70 days. Using  $\tau=70$  days one can check for proportional hazards for each of the time dependent covariates  $z_9(t), \dots, z_{10}(t)$  by creating 4 additional time dependent covariates  $z_{k+12}(t) = z_{8+k} \ln(t), k=1, \dots, 4$ . In this model proportional hazards held.

Before presenting the final we model we need to check on the appropriateness of the functional form for  $z_1$ . While martingale residuals are well defined for time dependent covariates to date they are not available in SAS. In figure 4 we present the martingale residual plot and the smooth

for years of schooling based on a model using  $z_1$  and  $z_2$ , only. The dashed curve, which appears, roughly linear suggest that no transformation of  $z_1$  is needed in the final model. The final model is

**Table 5**  
**Final Proportional Hazards Model**

	Estimate	SE	Chi-Square	p
$\beta_1$ Schooling	-0.128	0.034	14.33	0.0002
$\beta_2$ Oral Sex	-0.463	0.130	12.67	0.0004
$\beta_9$	-0.602	0.341	3.11	0.0777
$\beta_{10}$	-1.058	0.379	7.80	0.0052
$\beta_{11}$	0.287	0.313	0.83	0.3596
$\beta_{12}$	0.074	0.319	0.05	0.8155

The model suggest that frequency of condom use is related to re infection for the first 70 days after diagnosis and that after that point in time there is no effect.

Figure 5 shows a plot of the deviance residuals by year of schooling in the model with  $z_1$  and  $z_2$  only. If the model is correct then these residuals should look like a sample of standard normal noise at each level of schooling. Figures 6 and 7 are the standardized score residuals for years of schooling and oral sex, respectively. Figure 6 show that the following three patients have the greatest effect on the estimate of the risk coefficient:

<u>Time To Re infection</u>	<u>Re infection</u>	<u>Years In School</u>	<u>Residual</u>
4	Yes	6	-0.0052
11	Yes	17	0.0069
131	Yes	16	0.0051

Here, the last two patients are women with a long period of schooling who are re infected earlier then expected by the model. For the oral sex covariate the three most influential patients are:

<u>Time To Re infection</u>	<u>Re infection</u>	<u>Oral Sex</u>	<u>Residual</u>
1005	no	yes	-0.0156
5	yes	yes	0.0143
3	yes	yes	0.0145



Here the first patient is a women who had not had oral sex but had a re infection time longer than expected by the model. The last two are women who had oral sex that had re infection time shorter than predicted by the model.

### 5. Additive Hazards Regression

The additive hazard rate model (1.11) assumes a linear regression formulation for the conditional hazard rate. The model can be formulated as follows. Let  $h_i(t)$  be the hazard rate for the  $i$ -th individual and let  $\mathbf{h}(t) = (h_1(t), \dots, h_n(t))^t$ . Define the  $n \times (p+1)$  matrix  $\mathbf{Y}(t)$  as follows: if the  $i$ -th individual is at risk at time  $t$  (i.e. alive and under observation just prior to  $t$ ) then the  $i$ -th row of  $\mathbf{Y}(t)$  is  $(1, z_{1i}, \dots, z_{pi})^t$ . Otherwise the corresponding row of  $\mathbf{Y}(t)$  is set to zero. Then

$$\mathbf{h}(t) = \mathbf{Y}(t) \boldsymbol{\beta}(t), \tag{5.1}$$

where  $\boldsymbol{\beta}(t) = (\beta_0(t), \dots, \beta_p(t))^t$  is a  $p+1$  vector of regression functions.

Direct estimation of  $\boldsymbol{\beta}(t)$  is difficult. However, Aalen (1989), has derived least squares estimators of the cumulative regression functions,

$$B_j(t) = \int_0^t \beta_j(u) du, \quad j=0, \dots, p. \tag{5.2}$$

Let  $T_1 < T_2 < \dots$  be the ordered event times. Let  $\mathbf{X}(T_k)$  be any generalized inverse of  $\mathbf{Y}(t)$  and  $\mathbf{I}_k$  be a  $n$  vector of zeros except for a one in the position for the subjects who die at  $T_k$ . The least squares estimator of  $\mathbf{B}(t)$  is

$$\hat{\mathbf{B}}(t) = \sum_{T_k \leq t} \mathbf{X}(T_k) \mathbf{I}_k. \tag{5.3}$$

In practice any generalized inverse of  $\mathbf{Y}(\cdot)$  can be used. Aalen (1989) suggest a local least squares approach with

$$\mathbf{X}(t) = [\mathbf{Y}(t)^t \mathbf{Y}(t)]^{-1} \mathbf{Y}(t)^t. \tag{5.4}$$

Note that  $\mathbf{B}(t)$  is estimable only as long as  $\mathbf{Y}(\cdot)$  is of full rank. Estimates of the regression coefficients,  $\boldsymbol{\beta}(\cdot)$  are obtained by kernel smoothing techniques discussed in Ramlau-Hansen (1983).

The estimator (5.2) is a stochastic integral with respect to a martingale (See Aalen (1978)) so the estimator is almost unbiased (i.e. it is unbiased up to the time at which  $Y(t)$  is no longer of full rank) and is asymptotically normal with an estimated covariance matrix given by

$$V(t) = \sum_{T_k \leq t} X(T_k) I_k^d X(T_k)^t \quad (5.5)$$

where  $I_k^d$  is a diagonal matrix with  $I_k$  on the diagonal.

Aalen (1989) discusses tests of the hypothesis  $H_j: \beta_j(t)=0$  which are based on the weighted integral of the estimates of  $\beta_j(t)$ . Here we consider a more general problem of testing if a linear combination of the  $\beta$ 's are equal to 0. Let  $C$  be a  $r \times p+1$  matrix. Consider testing the hypothesis  $H_0: C \beta(t) = 0$ . A test statistic for  $H_0$  is based on the vector

$$U_c = \sum_{T_k \leq \tau} K_C(T_k) C X(T_k) I_k \quad (5.6)$$

where  $K_C(T_k)$  is an  $r \times p+1$  matrix of predictable weights. While any predictable matrix can be used for the weight matrix by analogy to the ordinary least squares regression problem where the variance of  $C \beta$  is proportional to  $C(Y(t)^t Y(t))^{-1} C^t$  we propose using as weights:

$$K_C(t) = \{C(Y(t)^t Y(t))^{-1} C^t\}^{-1} \quad (5.6)$$

This choice of a weight function reduces to Aalen(1989)'s "TST" test of  $H_j: \beta_j(t)=0$ , when  $C$  is a diagonal matrix with 1's along the main diagonal. It allows for a natural test for contrasts between regression functions.

One can show that the variance matrix for  $U_C$  is

$$V_C = \sum_{T_k \leq \tau} K_C(T_k) C X(T_k) I_k^d X(T_k)^t C^t K_C(t)^t \quad (5.7)$$

and that  $U_C$  has a limiting multivariate normal distribution. The test statistic for  $H_0$  is

$$X^2 = U_C^t V_C^{-1} U_C \quad (5.8)$$

which has a limiting chi squared distribution with  $r$  degrees of freedom.

## 5.2 Example

We shall use the additive model to examine the effect of years of schooling, condom use and oral sex on the time to re infection of a sexual disease. While the additive model is not available in standard statistical packages, a SAS IML macro is available on the Medical College Of Wisconsin Division Of Biostatistics web site at [www.biostat.mcw.edu](http://www.biostat.mcw.edu) (See Howell and Klein 1996 for details). This macro was used to produce the results reported here.

We fit the additive model to the factors years of schooling, oral sex in the last 12 months, and condom use (sometimes or never). The one degree of freedom tests of the hypothesis of no effect for a given covariate are:

**Table 6**  
**Anova Table For The Additive Hazards Model**

Effect	Chi-square	d.f..	p-value
$\beta_1$ Schooling	15.1969	1	<0.0001
$\beta_2$ Oral Sex	16.9033	1	<0.0001
$\beta_3$ Sometime Use Condom	5.2974	1	0.0214
$\beta_4$ Never use Condom	2.7936	1	0.0946

The two degree of freedom test of the hypothesis that  $\beta_3(t)=\beta_4(t) =0$  for all  $t$  based on (5.6)-(5.8), has a chi-square of 5.3641 with a p-value of 0.0684.

Figures 8-12 show the estimates of  $B(t)$  and pointwise 95% confidence intervals. The estimates are valid in the range 0 to 1482 days, after which  $Y(\cdot)$  is singular. The slope of these curves gives a crude estimate of  $\beta(t)$ .

### Acknowledgments

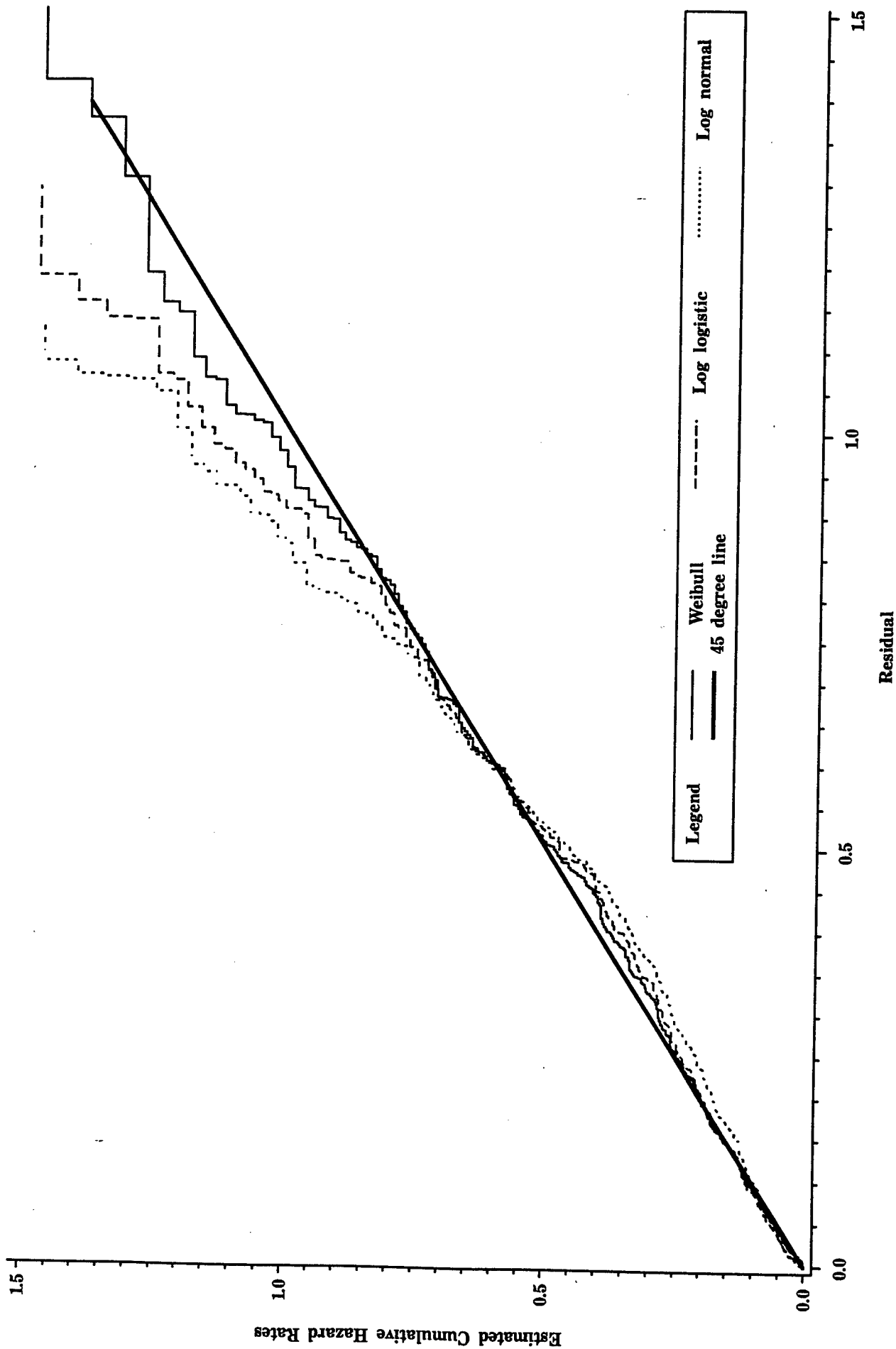
Professor Johnson's research was supported by a grant from the Wisconsin Alumni Research Fellowship. Professor Klein's research was supported by contract R01-CA54706-06 from the National Cancer Institute.

### References

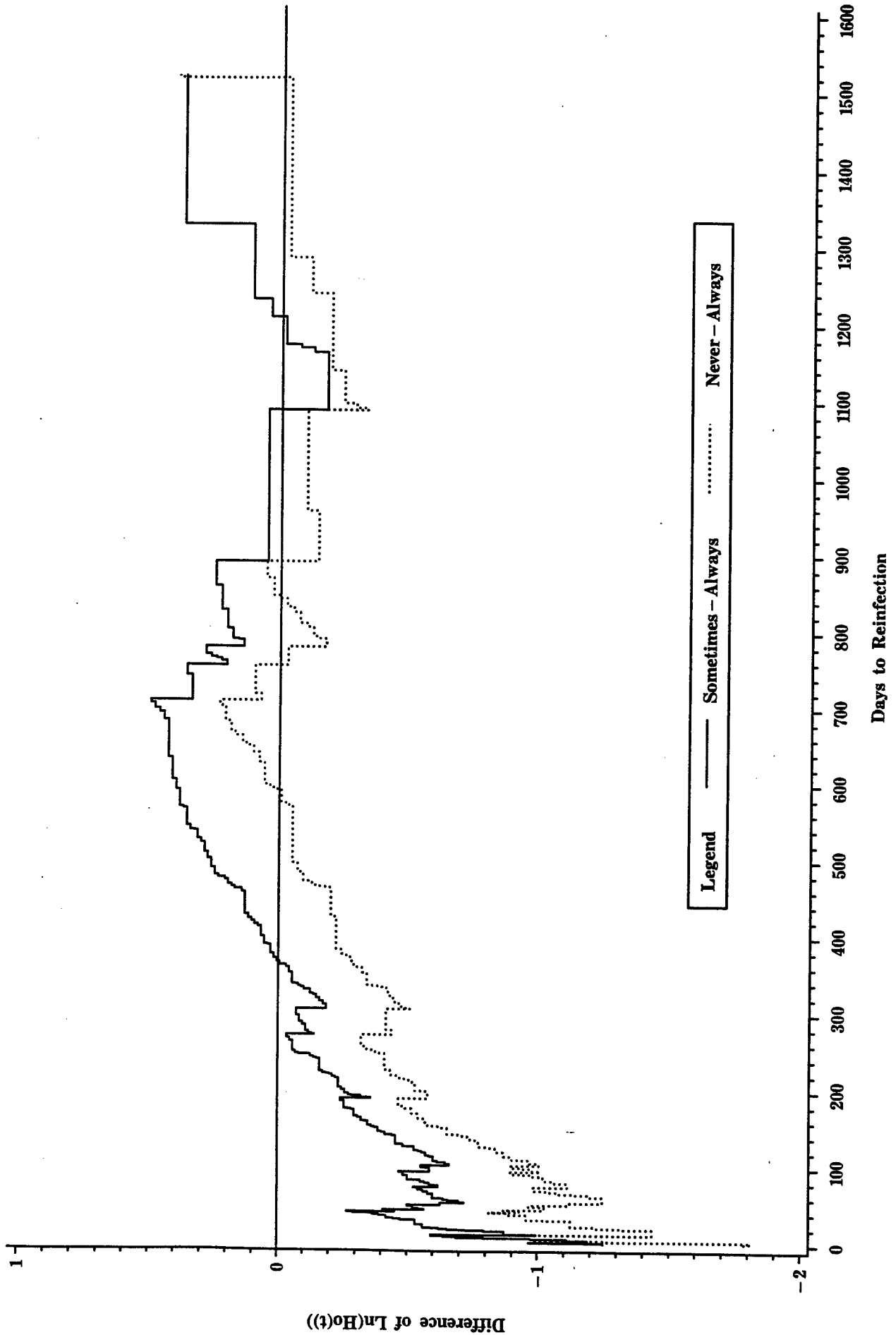
- Aalen, O. O. (1978) Nonparametric Inference For A Family Of Counting Processes. *Annals Of Statistics*, 6, 701-726.
- Aalen, O. O. (1980). A Model For Non-Parametric Regression Analysis Of Counting Processes. In W. Klonecki, A. Kozek, and J. Rosinski, Editors. *Lecture Notes On Mathematical Statistics And Probability*, 2, pp. 1-25. Springer-Verlag, New York.
- Aalen, O. O. (1989). A Linear Regression Model For The Analysis Of Life Times. *Statistics In Medicine*, 8, 907-925.

- Andersen, P. K. (1982). Testing Goodness-Of-Fit Of Cox's Regression And Life Model. *Biometrics*, 38, 67-77. Correction: 1984, 40, 1217.
- Andersen, P. K., Borgan, Ø., and Gill, R. D. and Keiding, N. (1993). *Statistical Models Based On Counting Processes*. Springer-Verlag, New York.
- Borgan, Ø. (1984) Maximum Likelihood Estimation In Parametric Counting Process Models, With Applications To Censored Failure Time Data. *Scand. J Statist.* 11, 1-16 Correction: 11, 275 (1984)
- Breslow, N. E. (1974). Covariance Analysis Of Censored Survival Data. *Biometrics*, 30, 89-99.
- Cleveland, W. S. (1979). Robust Locally Weighted Regression And Smoothing Scatter plots. *Journal Of The American Statistical Association*, 74, 829-836.
- Cox, D. R. (1972). Regression Models And Life-Tables (With Discussion). *Journal Of The Royal Statistical Society B*, 34, 187-220.
- Efron, B. (1977). The Efficiency Of Cox's Likelihood Function For Censored Data. *Journal Of The American Statistical Association*, 72, 557-565.
- Fleming, T. R. and Harrington, D. P. (1991). *Counting Processes And Survival Analysis*. John Wiley and Sons, New York.
- Gill, R. D. and Schumacher, M. (1987). A Simple Test Of The Proportional Hazards Assumption. *Biometrika*, 74, 289-300.
- Howell, A. M. and Klein, J.P. A SAS Macro For The Additive Hazards Regression Model *Proceedings Of The Statistical Computing Section Of The American Statistical Society*, 282-7, 1996.
- Klein, J. P. and Moeschberger, M.L. (1997) *Survival Analysis: Techniques For Censored And Truncated Data* Springer-Verlag, New York.
- Ramlau-Hansen, H. (1983). Smoothing Counting Process Intensities By Means Of Kernel Functions. *Annals Of Statistics*, 11, 453-466.
- Schoenfeld, D. (1982). Partial Residuals For The Proportional Hazards Regression Model. *Biometrika*, 69, 239-241.
- Therneau, T. M., Grambsch, P. M., and Fleming, T. R. (1990). Martingale-Based Residuals For Survival Models. *Biometrika*, 77, 147-160.

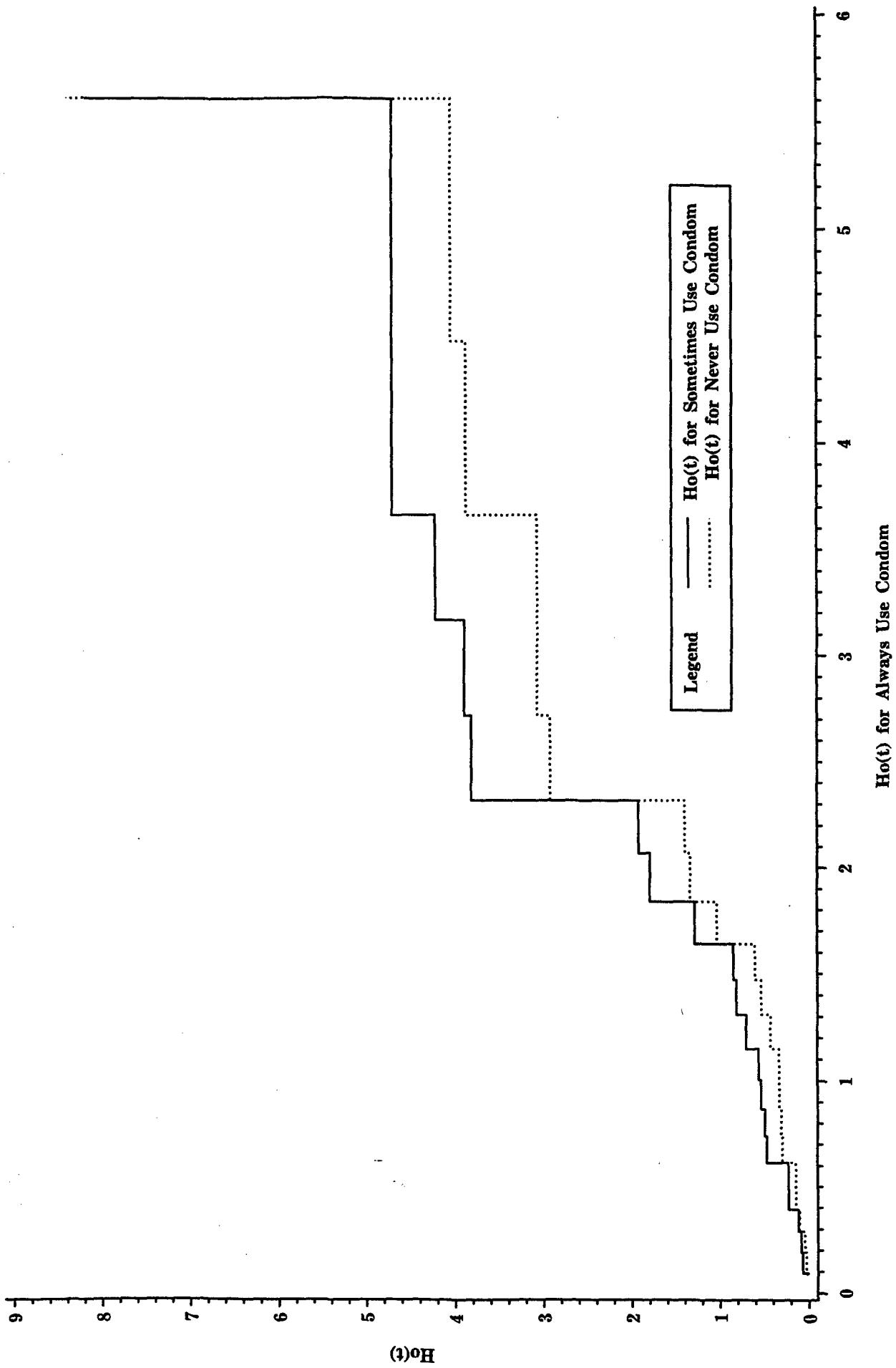
**Figure 1**  
**Cox-Snell Residuals for Parametric Models**



**Figure 2**  
**Plot of Difference of  $\ln(Ho(t))$  for Condom Use**



**Figure 3**  
**Plot of  $H_o(t)$  for Condom Use**

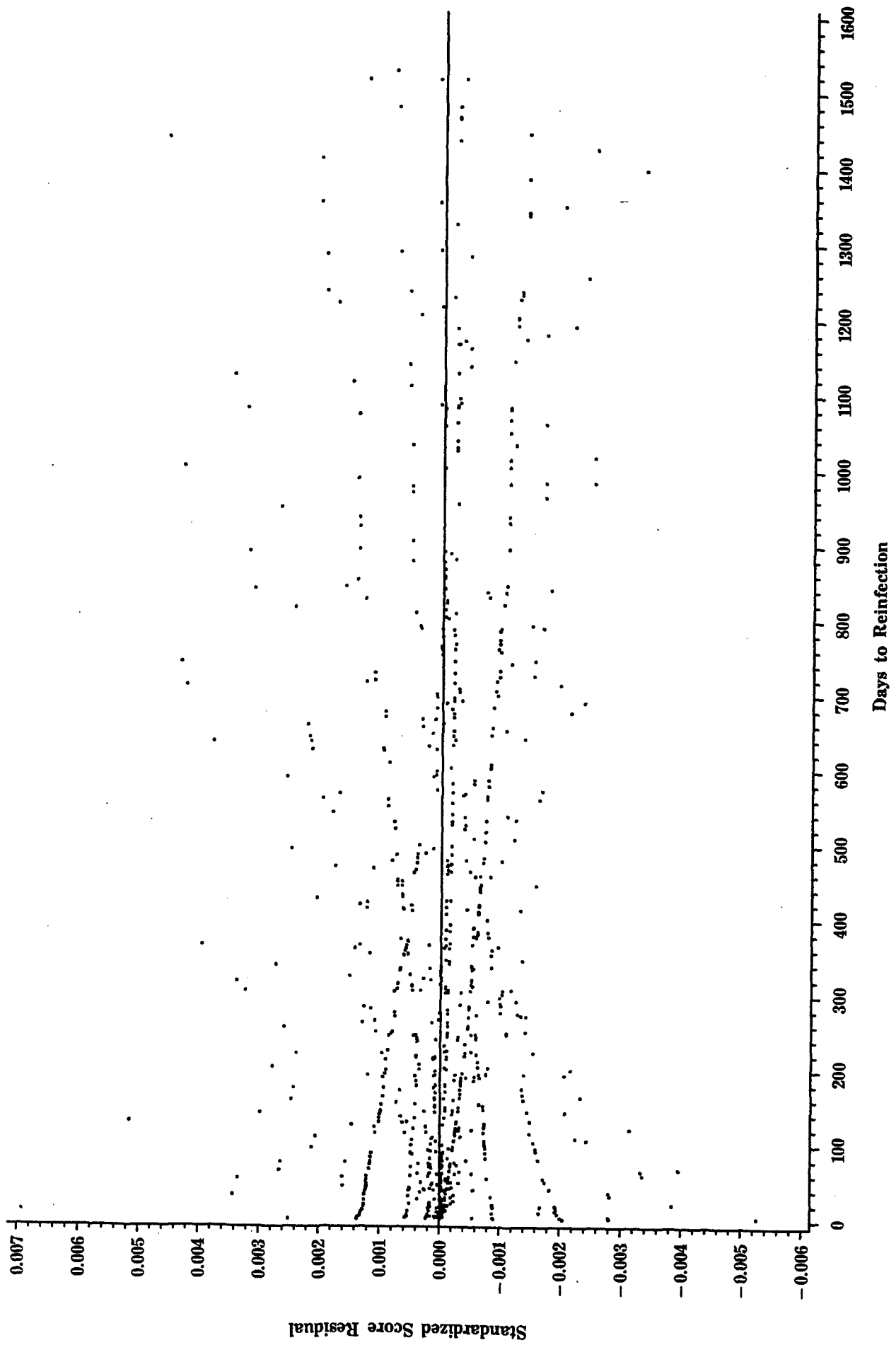




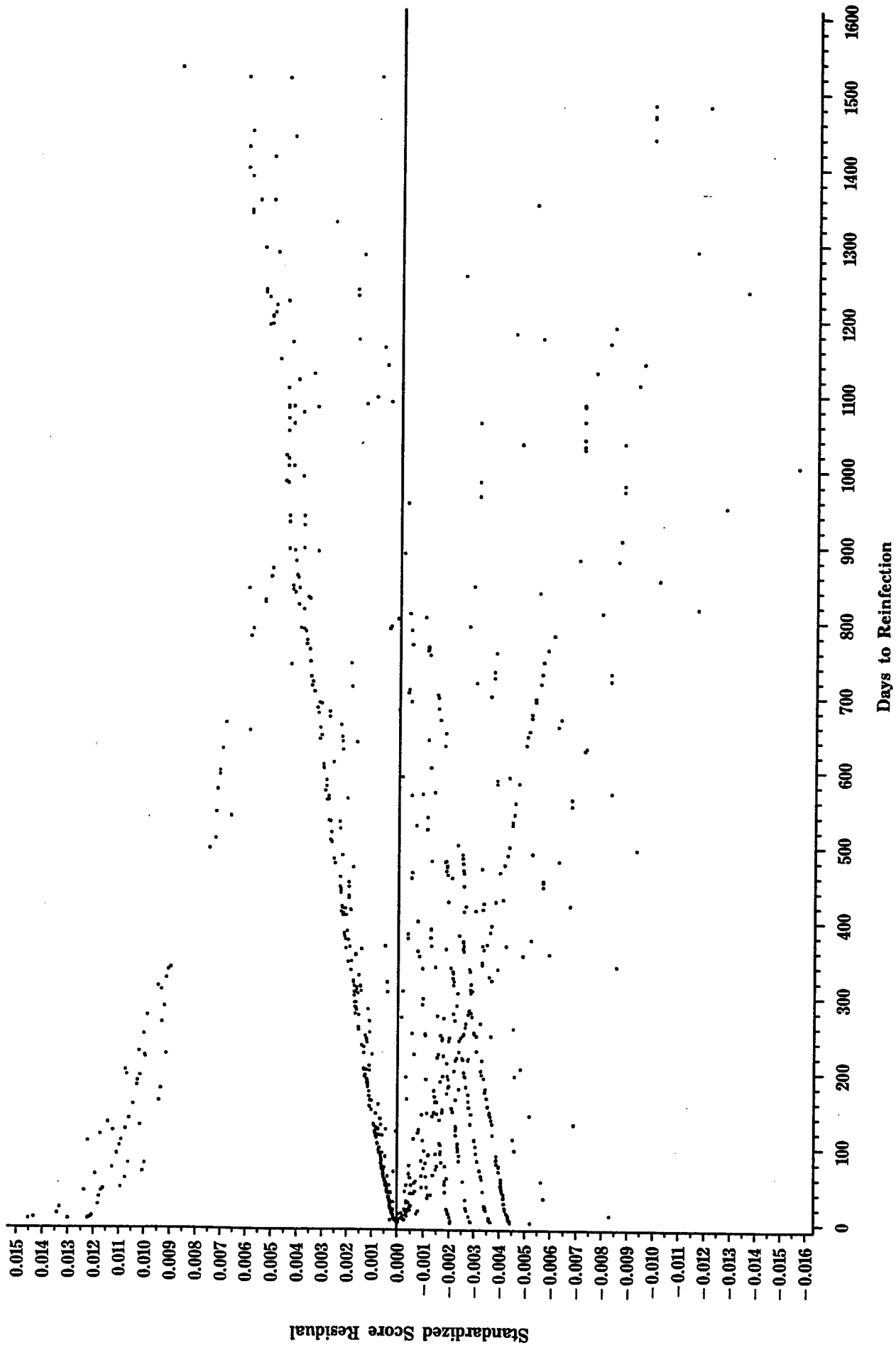




**Figure 6**  
**Standardized Score Residuals for Years of Schooling**



**Figure 7**  
**Standardized Score Residuals for Oral Sex in Last Year**



**Figure 8**  
**Estimate of Cumulative Baseline Hazard**  
**and 95% Confidence Interval**

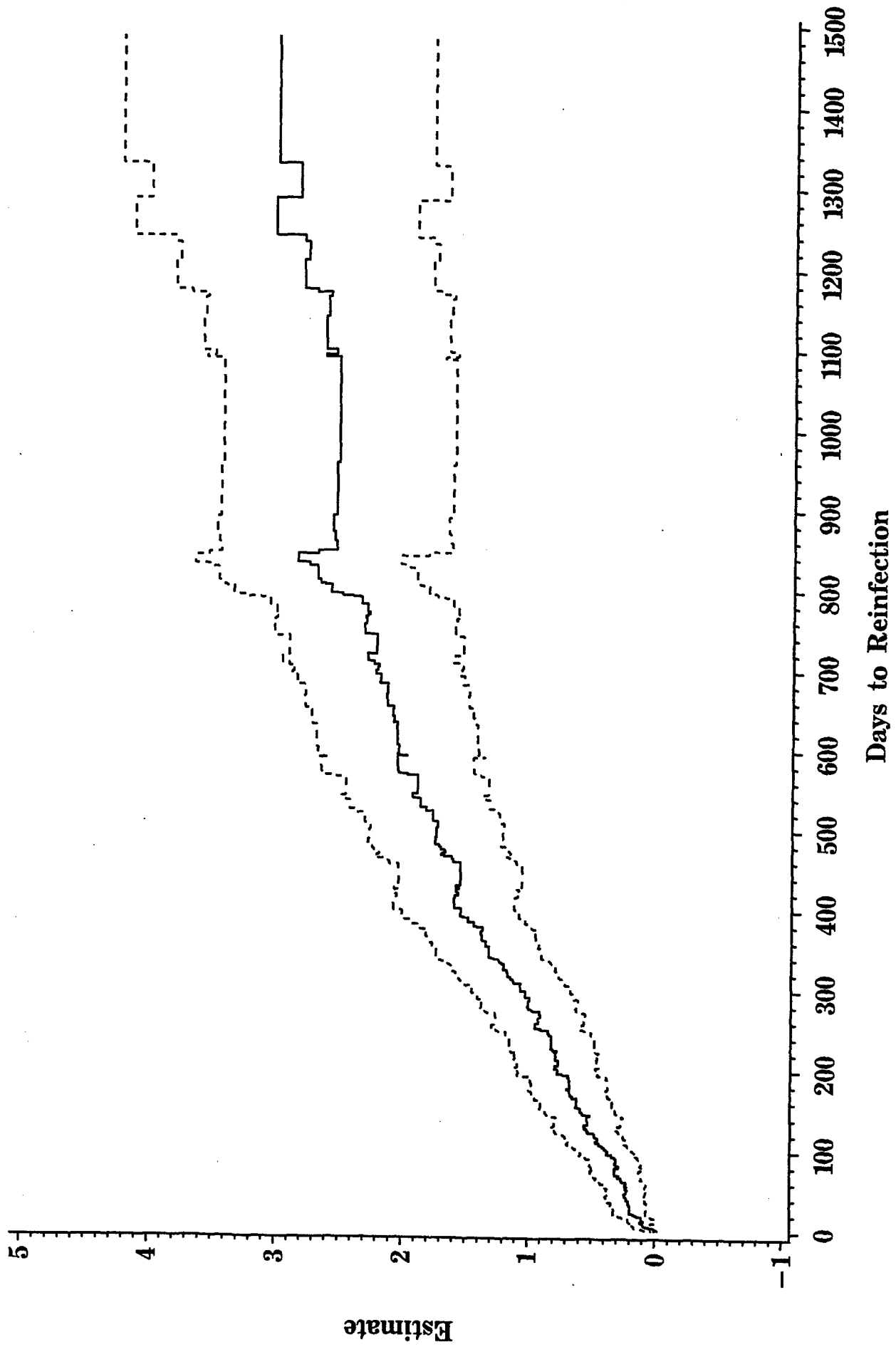
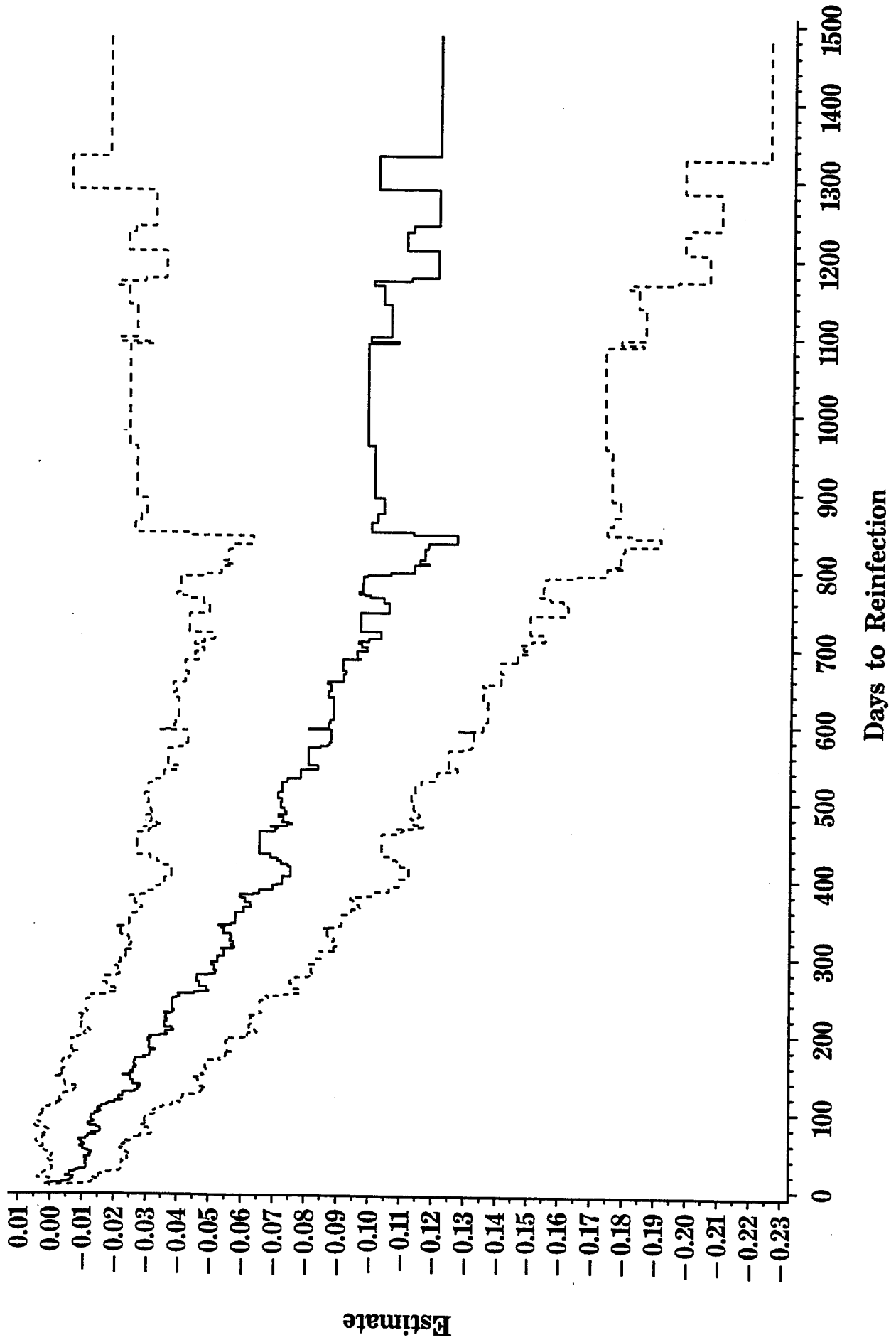
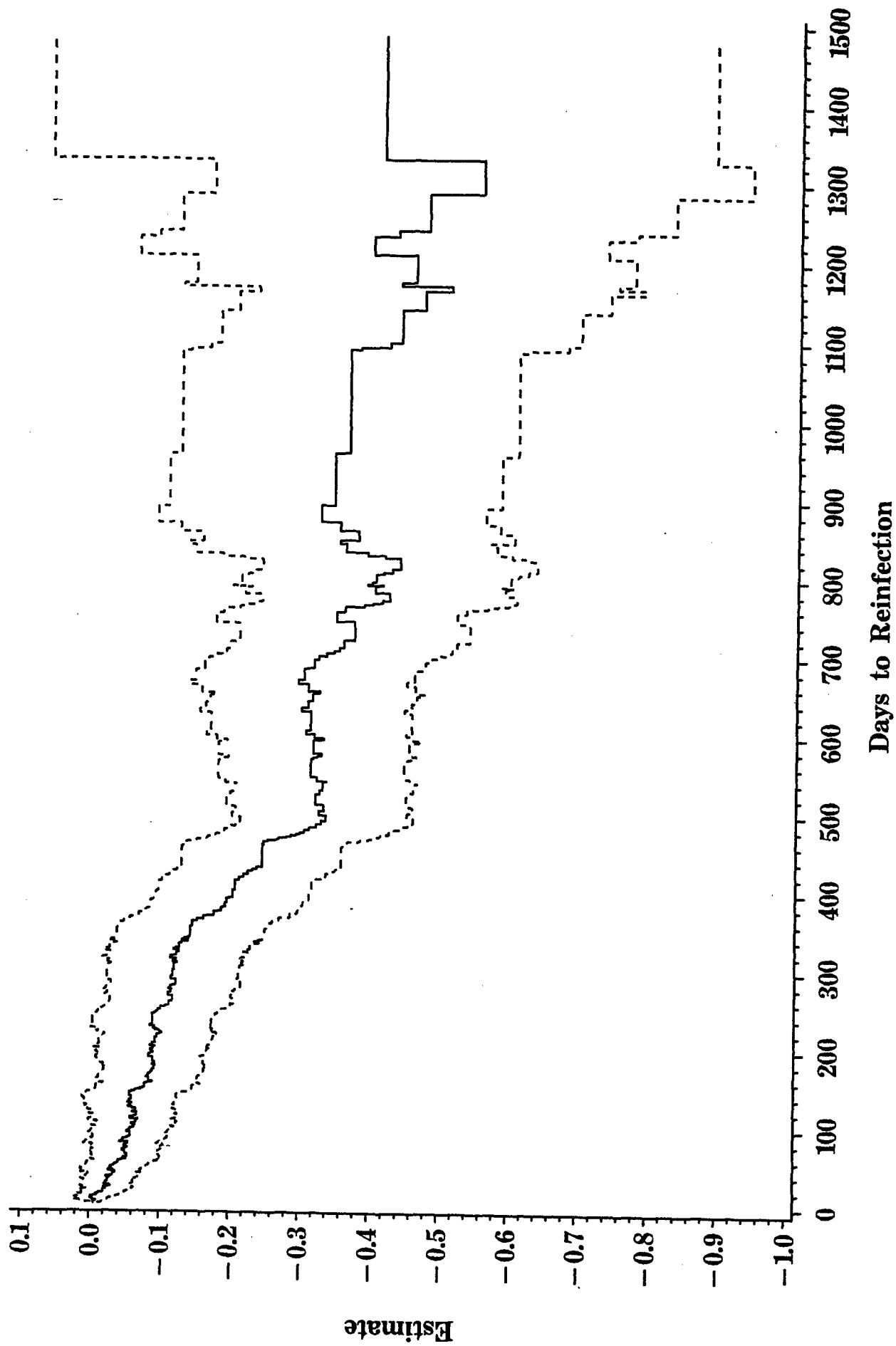


Figure 9  
Estimate of Cumulative Excess Risk of Years of Schooling  
and 95% Confidence Interval



**Figure 10**  
**Estimate of Cumulative Excess Risk of Oral Sex in Last Year**  
**and 95% Confidence Interval**



**Figure 11**  
**Estimate of Cumulative Excess Risk of Sometimes Using Condom**  
**Compared to Always and 95% Confidence Interval**

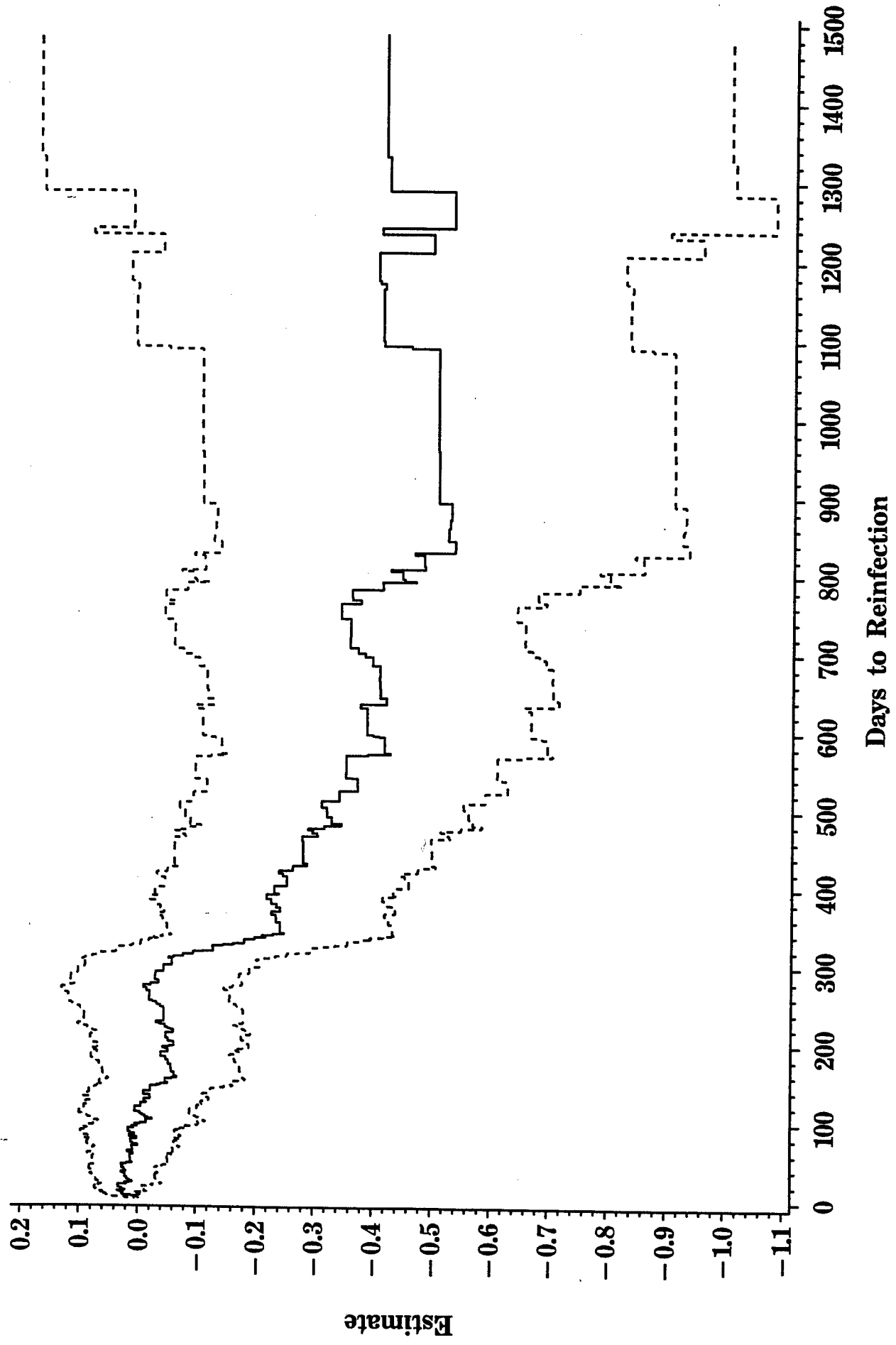
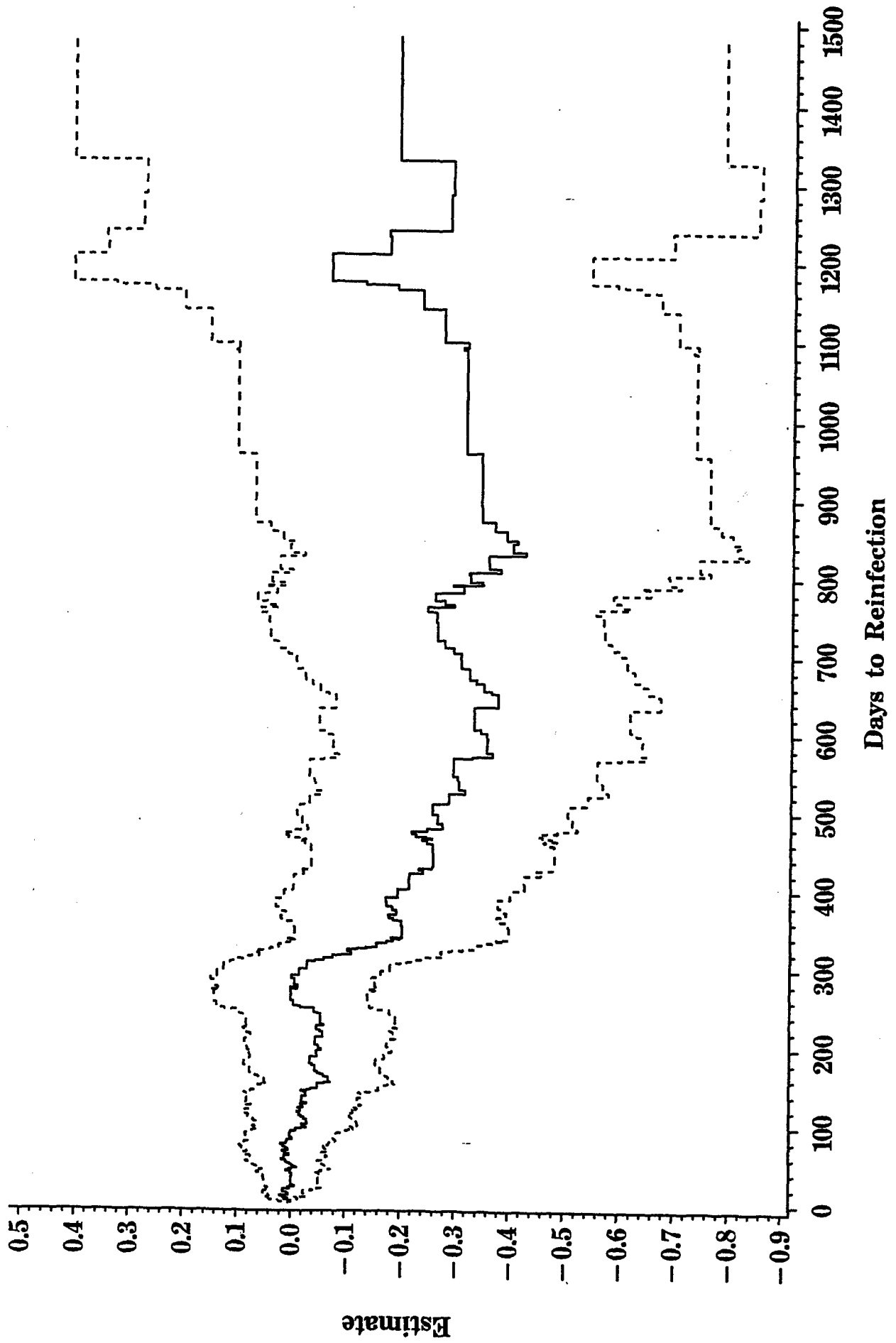


Figure 12  
Estimate of Cumulative Excess Risk of Never Using Condom  
Compared to Always and 95% Confidence Interval





## High-Dose Chemotherapy With Autologous Hematopoietic Stem-Cell Support for Breast Cancer in North America

By Karen H. Antman, Philip A. Rowlings, William P. Vaughan, Corey J. Pelz, Joseph W. Fay, Karen K. Fields, Cesar O. Freytes, Robert Peter Gale, Bruce E. Hillner, H. Kent Holland, M. John Kennedy, John P. Klein, Hillard M. Lazarus, Philip L. McCarthy, Jr, Ruben Saez, Gary Spitzer, Edward A. Stadtmauer, Stephanie F. Williams, Steven Wolff, Kathleen A. Sobocinski, James O. Armitage, and Mary M. Horowitz

**Purpose:** To identify trends in high-dose therapy with autologous hematopoietic stem-cell support (autotransplants) for breast cancer (1989 to 1995).

**Patients and Methods:** Analysis of patients who received autotransplants and were reported to the Autologous Blood and Marrow Transplant Registry. Between January 1, 1989 and June 30, 1995, 19,291 autotransplants were reviewed; 5,886 were for breast cancer. Main outcomes were progression-free survival (PFS) and survival.

**Results:** Between 1989 and 1995, autotransplants for breast cancer increased sixfold. After 1992, breast cancer was the most common indication for autotransplant. Significant trends included increasing use for locally advanced rather than metastatic disease ( $P < .00001$ ) and use of blood-derived rather than marrow-derived stem cells ( $P < .00001$ ). One-hundred-day mortality decreased from 22% to 5% ( $P < .0001$ ). Three-year

PFS probabilities were 65% (95% confidence intervals [CIs], 59 to 71) for stage 2 disease, and 60% (95% CI, 53 to 67) for stage 3 disease. In metastatic breast cancer, 3-year probabilities of PFS were 7% (95% CI, 4 to 10) for women with no response to conventional dose chemotherapy; 13% (95% CI, 9 to 17) for those with partial response; and 32% (95% CI, 27 to 37) for those with complete response. Eleven percent of women with stage 2/3 disease and less than 1% of those with stage 4 disease participated in national cooperative group randomized trials.

**Conclusion:** Autotransplants increasingly are used to treat breast cancer. One-hundred-day mortality has decreased substantially. Three-year survival is better in women with earlier stage disease and in those who respond to pretransplant chemotherapy.

*J Clin Oncol* 15:1870-1879. © 1997 by American Society of Clinical Oncology.

From the Breast Cancer Working Committee of the Autologous Blood and Marrow Transplant Registry of North America, Health Policy Institute, Medical College of Wisconsin, Milwaukee, WI; Division of Medical Oncology, Columbia University, New York, NY; Department of Medicine, University of Alabama, Birmingham, AL; Department of Medicine, Baylor University Medical Center, Dallas, TX; Department of Medicine, University of South Florida, Tampa, FL; Department of Medicine, University of Texas Health Sciences Center at San Antonio, San Antonio, TX; Division of Bone Marrow and Stem Cell Transplantation, Salick Health Care, Inc, Los Angeles, CA; Department of Medicine, Virginia Commonwealth University, Richmond, VA; Department of Medicine, Emory Clinic, Atlanta, GA; Division of Medical Oncology, Johns Hopkins Oncology Center, Baltimore, MD; Department of Biostatistics, Health Policy Institute, Medical College of Wisconsin, Milwaukee, WI; Department of Medicine, Ireland Cancer Center, Cleveland, OH; Department of Medicine, Baylor College of Medicine, Methodist Hospital, Houston, TX; Department of Medicine, University of Oklahoma, Oklahoma City, OK; Department of Medicine, LDS Hospital, Salt Lake City, UT; Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, PA; Department of Medicine, University of Chicago Health Sciences Center, Chicago, IL; Department of Medicine, Vanderbilt University, Nashville, TN; and Department of Medicine, University of Nebraska, Omaha, NE.

Submitted September 23, 1996; accepted January 31, 1997.

Supported by Public Health Service grant no. PO1-CA-40053 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung and Blood Institute of the US Department of Health and Human Services, Bethesda, MD; grant no. DAMD17-95-1-5002 from the Department

of the US Army Medical Research and Development Command; and grants from Alpha Therapeutic Corporation; Amgen, Inc, Thousand Oaks, CA; Astra Pharmaceutical; Baxter Healthcare Corporation; Bayer Corporation; Biogen; Blue Cross and Blue Shield Association; Lynde and Harry Bradley Foundation; Bristol-Myers Squibb Company; Frank G. Brotz Family Foundation; Cancer Center, Medical College of Wisconsin; Caremark, Inc; Centeon; Center for Advanced Studies in Leukemia; Chiron Therapeutics, Inc; COBE BCT, Inc; Charles E. Culpeper Foundation; Eleanor Naylor Dana Charitable Trust; Eppley Foundation for Research; Genentech, Inc; Glaxo Wellcome Company; Hoechst Marion Roussel, Inc; Immunex Corporation; Janssen Pharmaceutica; Kettering Family Foundation; Kirin Brewery Company; Robert J. Kleberg, Jr, and Helen C. Kleberg Foundation; Herbert H. Kohl Charities; Lederle Laboratories; Eli Lilly Company Foundation; Nada and Herbert P. Mahler Charities; MGI Pharma, Inc; Milstein Family Foundation; Milwaukee Foundation/Elsa Schoeneich Research Fund; Samuel Roberts Noble Foundation; Ortho Biotech Corporation; John Oster Family Foundation; Elsa U. Pardee Foundation; Jane and Lloyd Pettit Foundation; Alirio Pfiffer Bone Marrow Transplant Support Association; Pfizer, Inc; Pharmacia and Upjohn; RGK Foundation; Sandoz Oncology; Schering-Plough International; Walter Schroeder Foundation; Searle; Stackner Family Foundation; Starr Foundation; Joan and Jack Stein Charities; and Wyeth-Ayerst Laboratories.

Address reprint requests to Karen Antman, MD, Division of Medical Oncology, MHB 6N 435, 177 Ft. Washington Ave, New York, NY 10032; Email KHA4@columbia.edu.

© 1997 by American Society of Clinical Oncology.

0732-183X/97/1505-0028\$3.00/0

**B**REAST CANCER is the most common cancer and the second most common cause of cancer deaths in American women.<sup>1</sup> Survival of women with breast cancer correlates with extent of disease. Ten-year survival is 65% to 80% for women with disease confined to the breast.<sup>2-4</sup> Ten-year survival is 35% to 65% for those with one to three involved axillary lymph nodes, 30% to 40% for those with four to nine involved axillary nodes, and 15% to 30% in those with more than nine involved axillary nodes.<sup>5-7</sup> Recurrent disease tends to develop earlier in patients with multiple involved nodes and relapse risk persists for at least 20 years after mastectomy. Women with metastatic breast cancer have a median survival rate of approximately 2 years and a 2% to 5% probability of 5-year disease-free survival.<sup>8-11</sup>

Intensive therapy (high-dose chemotherapy with or without radiation therapy) with autologous hematopoietic stem-cell support (autotransplant) is increasingly used to treat breast cancer in women at high risk of persistent or recurrent disease. However, most reports of autotransplants include relatively few subjects and there are likely to be substantial reporting biases. One small randomized study of women with metastatic breast cancer shows a statistically significant advantage in both survival and disease-free survival for high-dose chemotherapy with bone marrow transplant versus conventional-dose chemotherapy.<sup>12</sup> Here we report results of autotransplants in more than 5,800 consecutive women receiving autotransplants at over 130 centers between 1989 and 1995.

## METHODS

### Patients

The Autologous Blood and Marrow Transplant Registry of North America (ABMTR) is a voluntary organization of more than 170 transplant institutions in the United States, Canada, and Central and South America that report data on consecutive autotransplants to a Statistical Center at the Medical College of Wisconsin. An autotransplant is defined as treatment with a sufficiently high dose of chemotherapy to require autologous bone marrow or blood-derived hematopoietic stem-cell support. The Statistical Center also collects data for allogeneic blood and bone marrow transplants (allotransplants) from centers that participate in the International Bone Marrow Transplant Registry, a similar but independent organization of allotransplant centers worldwide.

The ABMTR began data collection in 1992. Data were collected retrospectively for patients who received autotransplants between 1989 and 1992 and prospectively thereafter. Participating centers register basic information on consecutive autotransplants for all disease indications. Based on data collected in the Centers for Disease Control Hospital Surveys,<sup>13,14</sup> approximately half of North American autotransplants for all diseases were registered with the ABMTR during the study period. A list of participating centers is shown in the Appendix. Registration data from consecutive women with breast cancer who received an autotransplant at ABMTR centers between January 1, 1989 and June 30, 1995 were the subject of this analysis.

Data regarding disease type, age, sex, and posttransplant survival

were requested for all patients. Questions regarding pretransplant disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow and/or blood-derived stem cells), high-dose conditioning regimen, and posttransplant disease progression were added to registration forms more recently. Although an attempt was made to collect this information for previously registered patients, these data are not available for all patients. Patients with primary (stages 2, 3, and inflammatory) and metastatic breast cancer were considered separately in the analysis. The ABMTR requests data on progression or death in registered patients at 6-month intervals.

### Statistical Methods

Comparisons of patient and treatment characteristics over time used  $\chi^2$  test for categorical and Kruskal-Wallis test for continuous variables.<sup>15</sup> Probabilities of 100-day mortality (death in the first 100 days as a result of toxicity, disease progression, or both), progression-free survival (PFS), and overall survival were calculated using the Kaplan-Meier product limit estimate.<sup>16</sup> The log-rank test was used for comparisons of 100-day mortality, PFS, and survival between groups.<sup>17</sup>

## RESULTS

Between January 1, 1989 and June 30, 1995, 19,291 patients receiving high-dose therapy with autologous hematopoietic stem-cell support were registered with the ABMTR. Of these, 5,886 (31%) had breast cancer. Between 1989 and 1995, autotransplants for breast cancer increased from 16% to 40% ( $P < .00001$ ) of all autotransplants registered (Fig 1, Table 1). Numbers of autotransplants for breast cancer exceeded those for Hodgkin disease and non-Hodgkin lymphoma after 1992. By 1993 to 1994, breast cancer was the most common indication for stem-cell transplants of all types (Fig 1).

Numbers of patients reported per year, age at transplant, pretransplant disease stage, source of stem cells, and 100-day mortality are listed in Table 1. The distribution of disease stage at transplantation changed from 7% local and 93% metastatic disease in 1989 to approxi-

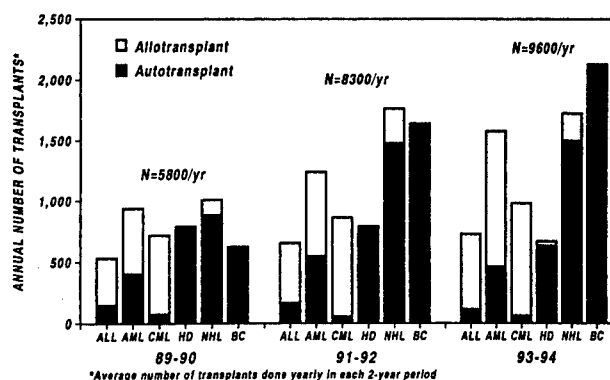


Fig 1. Numbers of allotransplants (hematopoietic stem cells collected from a donor) and autotransplants by year by disease for most common indications.

Table 1. Autotransplants for Breast Cancer Registered With the ABMTR

	1989	1990	1991	1992	1993	1994	January to June 1995	P
No. of patients	272	342	683	1,069	1,189	1,513	818	
Percent of all autotransplants registered	16	16	25	33	33	39	40	< .00001
Autotransplants for breast cancer								
No. of centers reporting	34	45	66	85	99	105	101	
Median transplants per center	3	5	6	7	6	8	5	.005
Range	1-58	1-44	1-44	1-71	1-59	1-86	1-63	
Stage immediately before high-dose chemotherapy and autotransplant								
No. assessable*	213	313	650	1,005	1,088	1,404	721	< .00001
Local disease† (%)	7	16	23	34	31	39	49	
Metastatic (%)	93	83	77	65	68	60	50	
Other‡ (%)	< 1	1	< 1	1	1	1	1	
Age, years								
No. assessable	272	341	678	1,059	1,123	1,461	817	< .00001
Median	41	42	44	44	45	45	45	
Range	23-64	24-66	22-72	25-65	24-66	22-69	22-71	
Interval diagnosis to transplant (years)								
No. assessable	237	299	614	960	1,106	1,392	774	< .00001
< 1 (%)	18	24	31	44	42	49	57	
1-2 (%)	28	19	16	14	12	13	10	
> 2 (%)	54	57	53	42	46	38	33	
Graft type								
No. assessable	162	215	474	813	1,189	1,447	760	< .00001
BM (%)	81	79	58	42	30	19	10	
BM + PBSC (%)	5	7	22	33	30	25	18	
PBSC (%)	14	14	20	25	40	56	72	
Conditioning regimen								
No. assessable	140	183	423	735	870	1,174	587	< .00001
CBP (%)	7	4	11	13	9	14	6	
CT (%)	25	22	23	23	21	21	21	
CTCb (%)	18	16	15	28	37	39	44	
CTM (%)	6	2	6	4	4	2	1	
ICE (%)	3	10	8	7	6	4	4	
CTHu (%)	8	4	5	4	3	3	4	
CEP (%)	3	3	5	3	2	1	2	
Other (%)	30	37	27	18	18	16	18	
100-day mortality								
No. assessable	265	340	679	1,034	1,153	1,366	784	< .00001
%	22	15	11	6	6	4	5	

Abbreviations: BM, bone marrow; PBSC, peripheral-blood stem cells; C, cyclophosphamide; B, carmustine; P, cisplatin; T, thiotepa; Cb, carboplatin; M, mitoxantrone; I, ifosfamide; E, etoposide; Hu, hydroxyurea.

\*Information for all variables not available for all patients; registration forms were revised in 1992 and 1993 to capture additional information.

†Local disease = stage 2, 3; and inflammatory breast cancer.

‡Patients with locally persistent or recurrent disease post-conventional therapy.

mately 50% local and 50% metastatic disease in 1995 ( $P < .00001$ ). This is reflected in the interval from diagnosis to transplant, which decreased over the study period. By 1995, 57% of transplants for breast cancer were performed within 1 year of diagnosis.

Use of blood-derived cells alone or in combination with bone marrow increased from 19% to 90% ( $P < .00001$ ) in these 6 years. Various preparatory regimens were used, with only the combination of cyclophosphamide, thiotepa, and carboplatin (CTCb) used in more than 25% of all

patients. An important finding was decreasing 100-day mortality, from 22% in 1989 to 5% in 1995 ( $P < .00001$ ).

#### High-Risk Primary Breast Cancer

Characteristics of women who received autotransplants for stage 2, 3, and inflammatory breast cancer are listed in Table 2. Eleven percent were treated as part of randomized cooperative group trials. Although most patients had stage 2 or 3 breast cancer and  $\geq 10$  involved axillary nodes, some transplants were performed for inflammatory

Table 2. Autotransplants for Stage 2, 3, or Inflammatory Breast Cancer

	No. assessable*	No.	%
No. registered	1,747		—
Median age, years	1,731	44	
Range		22-69	
Stage pretransplant			
2	1,613†	750	46
3		603	37
Inflammatory		260	17
Months from diagnosis to transplant	1,636	7	
Range		2-16	
No. of nodes positive	542		
< 10		150	28
≥ 10		392	72
ER positive	479	298	62
Principal adjuvant chemotherapy			
CAF	491	314	64
Graft type	1,527		
BM		502	32
BM + PBSC		450	30
PBSC		555	38
High-dose chemotherapy regimen used	1,370		
CT		432	32
CTCb		403	29
CBP		220	16
CTM		52	4
ICE		78	6
CEP		26	2
Other		156	11
100-day mortality (%)	1,668		3

Abbreviations: ER, estrogen receptor; C, cyclophosphamide; A, doxorubicin; F, fluorouracil; BM, bone marrow; PBSC, peripheral-blood stem cells; B, carmustine; P, cisplatin; T, thiotepa; Cb, carboplatin; M, mitoxantrone; E, etoposide; Hu, hydroxyurea.

\*Information for all variables not available for all patients. Registration forms were revised in 1992 and 1993 to capture additional information.

†One hundred thirty-four additional patients stage 2 v 3 v inflammatory not specified.

breast cancer (17%) or for women with less than 10 involved axillary nodes (28%). Kaplan-Meier estimates of survival and PFS by disease stage are shown in Fig 2; 3-year probabilities are listed in Table 3.

#### Metastatic Breast Cancer

Characteristics of women who received autotransplants for metastatic breast cancer are listed in Table 4. Fewer than 1% were treated on randomized cooperative group trials. Most patients had chemotherapy-sensitive disease (complete or partial response before transplant) and either visceral or bone disease. Median survival was 19 months (Fig 2). Three-year PFS and survival probabilities are listed in Table 3. Women with a complete response to chemotherapy pretransplant had higher survival and PFS than those with either a partial response or resistant disease (Fig 3).

#### Second Malignancies

Data regarding second malignancies were available for 2,045 women. There were 13 cancers reported: four myelodysplastic syndromes, two endometrial carcinomas, one ovarian carcinoma, one squamous cell carcinoma, one transitional cell carcinoma of the bladder, one Hurthle cell tumor of the thyroid, one lung carcinoma, one glioblastoma, and one cervical cancer.

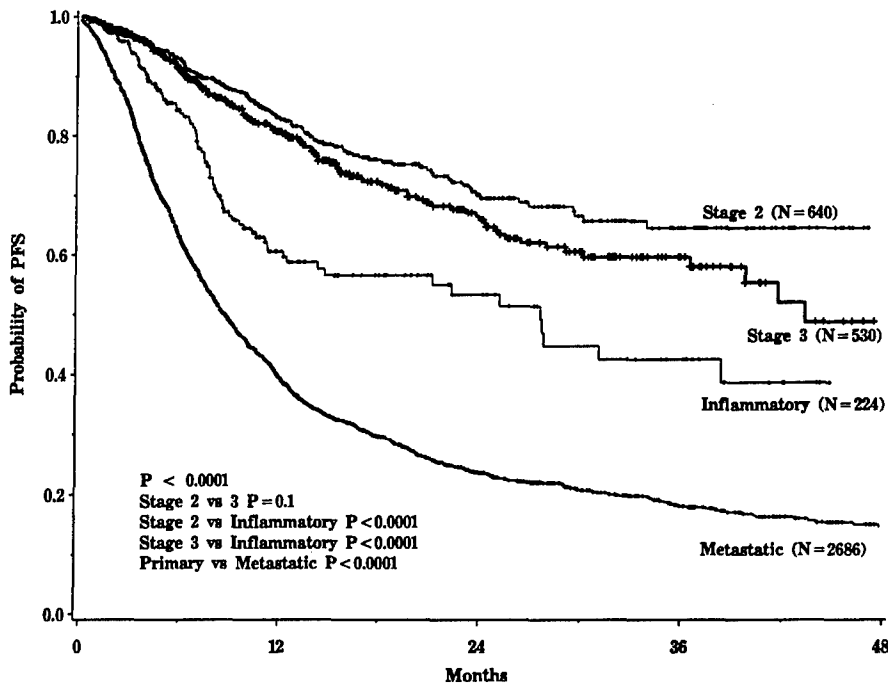
#### DISCUSSION

These data indicate several interesting aspects of autotransplants for breast cancer. First, the annual frequency of autotransplants has increased substantially, from fewer than 300 reported to the ABMTR in 1989 to approximately 1,500 presently. Second, an increasing proportion are for women with locally advanced disease: less than 10% in 1989 versus approximately 50% presently. As a correlate, the interval from diagnosis to transplant has decreased substantially; less than 20% of transplants were performed within 1 year of diagnosis in 1989 versus more than 50% presently. A third trend is increasing use of blood-derived rather than bone marrow-derived grafts: 14% in 1989 versus more than 70% presently. Finally, 100-day mortality also decreased substantially, from more than 20% in 1989 versus 5% presently. This probably reflects several factors, including selection of patients with less advanced disease and better performance status.

Women with locally advanced (stage 2 and 3) breast cancer who receive autotransplants differ from the general population of women presenting with breast cancer. Median age was 44 years and more than 70% had more than nine involved lymph nodes. These data contrast with typical women with breast cancer, whose median age is approximately 60 years, of whom approximately 5% have more than nine involved lymph nodes.<sup>6,7</sup> These differences reflect the substantial selection factors for transplant and underscore the importance of comparing autotransplants and chemotherapy in comparable subjects. A Toronto study reported that 28% of patients referred for one randomized trial of high- versus lower-dose therapy were ineligible because of occult metastatic disease identified by the required pretransplant evaluation.<sup>18</sup> Thus, differences observed between patients who received autotransplants and those who received conventional-dose chemotherapy in historical data bases may result from selection of patients without occult metastases.

Women with metastatic (stage 4) disease who received autotransplants were also somewhat atypical. Median age was 44 years and 58% had cancers with estrogen receptors. Approximately 28% had a complete response to chemotherapy, but 24% had disease progression. These data contrast with typical women with stage 4 breast cancer

A



B

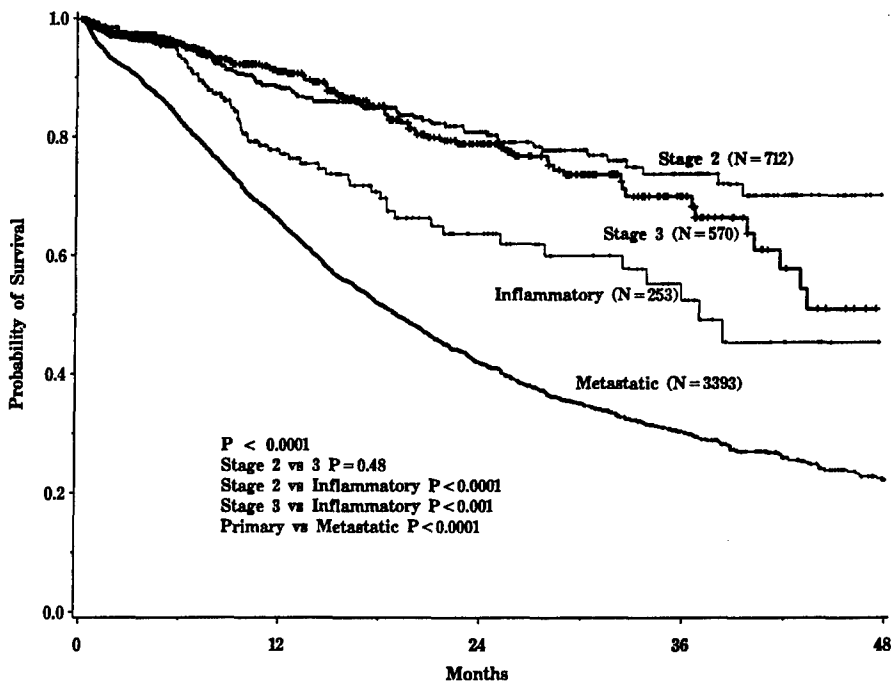


Fig 2. Kaplan-Meier estimates of PFS (A) and survival (B) after auto-transplants for primary (stage 2, 3, or inflammatory) and metastatic breast cancer.

**Table 3. Three-year Kaplan-Meier Estimates of PFS and Overall Survival After Autotransplants for Breast Cancer**

Stage	PFS (%)	95% CI	Survival (%)	95% CI
2 (2 to 5 cm or involved lymph nodes)	65	59-71	74	68-80
3 (> 5 cm or fixed to the chest wall)	60	53-67	70	63-77
Inflammatory	42	31-53	52	40-64
Metastatic	18	16-20	30	28-32
Response to chemotherapy				
In complete remission	32	27-37	46	40-52
In partial remission	13	9-17	29	25-33
Not responding	7	4-10	16	12-20

whose median age is approximately 60 years, of whom 60% to 70% have cancers with estrogen receptors. These differences again underscore the importance of comparing autotransplants and chemotherapy in comparable subjects. Nevertheless, one small randomized study showed a statistically significant advantage in both survival and disease-free survival for high-dose chemotherapy with bone marrow transplant versus conventional-dose chemotherapy in women with metastatic disease.<sup>12</sup>

Results of autotransplants correlated with disease stage. Women with stage 2 or 3 disease had better PFS and survival than those with stage 4 disease. However, there was no difference in PFS or survival between women with stage 2 versus 3 disease. Among women with metastatic (stage 4) disease, those with a complete response to pretransplant chemotherapy fared better than those with a partial response. The latter fared better than those with stable disease or progression. Women with tumors unresponsive to lower-dose treatment are very unlikely to achieve long-term disease-free survival after autotransplant.

The correlation between stage and chemotherapy response and outcome is not surprising. Similar results are reported for conventional treatments. Better transplant outcome in "better" subjects does not mean that transplants should be performed earlier or indicate whether transplants are better than conventional therapy. These questions are best addressed in prospective studies, several of which are underway (Table 5). In this survey, only 11% of women with stage 2 or 3 disease and fewer than 1% of those with stage 4 disease participated in national cooperative group randomized trials. During the time covered by this survey, three cooperative group trials were open for enrollment in the United States, one for metastatic disease and two for adjuvant therapy. Additionally, randomized trials, including the one published study<sup>12</sup> and those listed in Table 5, are not designed to answer other important questions such as relative efficacy of various high-dose regimens, supportive care technologies, or even patient-, disease-, and treatment-related factors important

for transplant outcome. The ABMTR is an important resource for addressing such issues. Data collected by the Centers for Disease Control hospital survey<sup>13,14</sup> suggest that approximately half of all autotransplants in North America are reported to the ABMTR. We believe that reporting of autotransplants for breast cancer is similar, making available a substantial proportion of cases for study. Registry audits ensure that this sample is unselected and that data are accurate. Because participation in the ABMTR is voluntary, it is possible that participating centers differ from nonparticipating centers. For example, nonacademic centers may be less likely to participate than academic centers, although the ABMTR includes many

**Table 4. Autotransplants for Metastatic Breast Cancer**

	No. assessable*	No.	%
No. registered	3,451		
Median age, years	3,398	44	
Range		22-72	
Sensitivity to chemotherapy pretransplant	3,411		
Complete or partial response		2,134	63
Stable or progressive disease		595	17
Undetermined		682	20
Sites of metastatic disease	1,212		
Viscera (no CNS)†		593	49
Bone or bone marrow ± soft tissue‡		328	27
Soft tissue alone		273	23
CNS§		18	1
ER positive	1,203	700	58
Interval, diagnosis to transplant (years)	3,298		
< 1		687	21
1-2		568	17
> 2		2,038	62
Graft type	3,018		
BM		993	33
PBSC		1,373	46
BM + PBSC		652	21
Conditioning regimen	2,522		
CTCb		899	36
CT		416	17
ICE		132	5
CTHu		146	6
CTM		71	3
CBP		202	8
CEP		60	2
Other		596	23
100-day mortality (%)	3,395		10

Abbreviations: ER, estrogen receptor; BM, bone marrow; PBSC, peripheral-blood stem cells; C, cyclophosphamide; B, carmustine; P, cisplatin, T, thiotepa; Cb, carboplatin; M, mitoxantrone; E, etoposide; Hu, hydroxyurea.

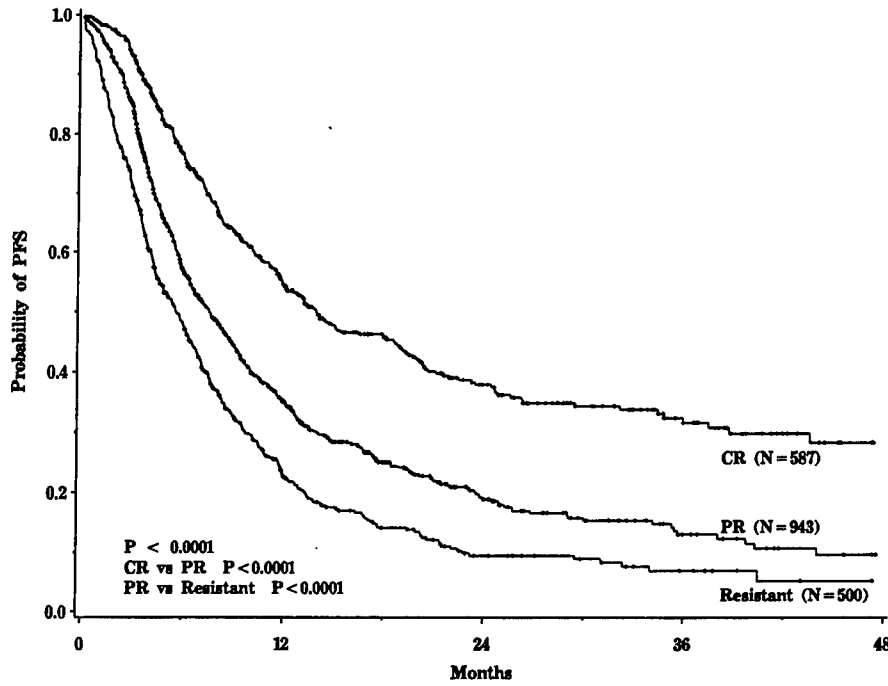
\*Information for all variables not available for all patients. Registration forms were revised in 1992 and 1993 to capture additional information.

†Includes patients with or without bone, bone marrow, or soft tissue involvement.

‡Excludes patients with visceral or CNS involvement.

§Includes patients with or without visceral, bone, bone marrow, or soft tissue involvement.

A



B

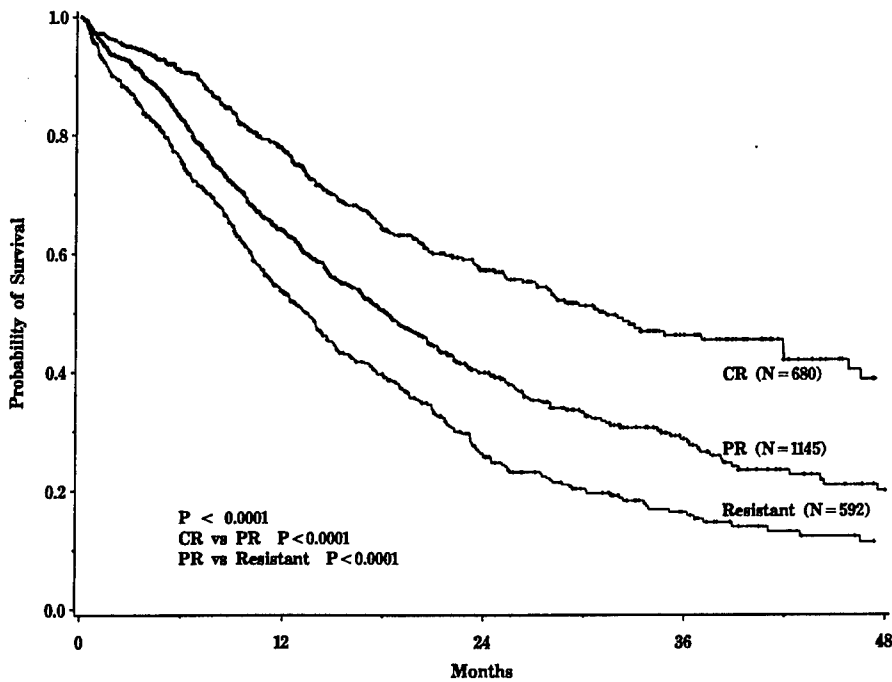


Fig 3. Kaplan-Meier estimates of PFS (A) and survival (B) after autotransplant for metastatic breast cancer by responsiveness to chemotherapy pretransplant. CR, complete response to conventional-dose chemotherapy pretransplant; PR, partial response; resistant, stable or progressive disease pretransplant.

Table 5. Ongoing Randomized Trials of Autotransplants in Breast Cancer by Stage

Eligible Stage	Study Sponsor	Standard Initial Therapy	High-dose Regimen	Control
<b>Stage 2</b>				
No. of involved lymph nodes				
≤ 4	Milan/Italy	None	HDS	E × 3, CMF × 6
≤ 4	Inter-Scandinavian	CEF × 4	CTCb	CEF × 4
≤ 4	Italian	CEF × 4	CEL	CEF × 2
≤ 4	Dutch	CEF × 4	CTCb	CEF × 1
4-9	Duke	AF	CBP	No more therapy v CBP alone
≤ 6	ICG (Manchester)	CE × 4	CTCb	CE × 4
≤ 8	SFGM/FNCCC	CEF × 4	CMitoxL	No further therapy
≤ 10 or > 4 high risk	IBCSG		CE × 3	AC or EC × 4, then CMF × 3
≤ 10	CALGB	CAF × 4	CBP	Conventional-dose CBP
≤ 10	German Multicenter	CE × 4	CTMitox	CMF × 3
≤ 10	ECOG	CAF × 4	CT	No further therapy
<b>Stage 3</b>				
	Milan/Italy	None	HDS	E × 3, then CMF × 6
	SFGM/FNCCC	Chemotherapy × 4	CMitoxL	Conventional chemotherapy
	IBCSG		CE × 3	AC or EC × 4, then CMF × 3
	CALGB	A × 4	CTCb	Continuous CMF × 16 weeks
	German Multicenter	CE × 4	CTMitox	CMF × 3
<b>Stage 4</b>				
	Duke (CRs only)	AFM × 4	CBP	CBP at relapse
	Duke (bone only)	AFM × 4, radiation	CBP	CBP at relapse
	Philadelphia Intergroup	CAF × 6	CTCb	CMF × 2 years
	SFGM/FNCCC	Chemotherapy × 4	CMitoxL	Conventional chemotherapy

Abbreviations: ICG, International Collaborative Group (Manchester); SFGM, Societe Francaise de Greffe du Muelle; FNCCC, Federation Nationale des Centres de Lutte Contra le Cancer; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; SWOG, Southwest Oncology Group; IBCSG, International Breast Cancer Study Group; C, cyclophosphamide; E, epirubicin; A, doxorubicin; F, fluorouracil; Cb, carboplatin; M, methotrexate; P, cisplatin; L, melphalan; Mitox, mitoxantrone; T, thiotepa; HDS, high-dose sequential therapy.

nonacademic centers. It is also possible that centers with poorer results do not report their data, although outcomes in our analyses are similar to those of large nonparticipating centers. Of interest, prior surveys of worldwide allogeneic transplant activity<sup>19-21</sup> suggest that centers in the IBMTR are similar to nonparticipating centers in characteristics and outcome. Finally, analyses of differences among centers are difficult for centers that perform fewer than 30 autotransplants. However, small centers, considered as a group, did not perform worse than large centers

in this study. The ABMTR provides an important observational data base that will complement data from randomized trials and with which one can monitor trends and assess new technology in blood and marrow transplantation. Registry data will be critical for extrapolating results of these trials, which tend to be applied in restricted populations, to other patients, and for evaluating the impact of preparative regimens, demographic factors, prior treatment, and other variables on transplant outcome.

## APPENDIX

## Institutions That Report Breast Cancer Cases to the ABMTR

Country/Institution	City	Country/Institution	City
<b>Argentina</b>			
Alexander Fleming Institute	Buenos Aires	Baptist Regional Cancer Center	Jacksonville, FL
Centro de Internacion e Investigation	Buenos Aires	University of Kansas Medical Center	Kansas City, KS
Hospital Privado de Oncologia	Buenos Aires	Scripps Clinic & Research Foundation	La Jolla, CA
Navy Hospital "Pedro Mallo"	Buenos Aires	Dartmouth-Hitchcock Medical Center	Lebanon, NH
Hospital Privado de Cordoba	Cordoba	University of Kentucky Medical Center	Lexington, KY
<b>Austria</b>			
Donauspital	Vienna	University of Arkansas for Health Sciences	Little Rock, AR
<b>Brazil</b>			
Hospital de Clinicas	Curitiba	UCLA Center for Health Sciences	Los Angeles, CA
Hospital Nossa Senhora das Gracias	Curitiba	USC/Norris Cancer Hospital	Los Angeles, CA
		James Graham Brown Cancer Center	Louisville, KY
		University of Wisconsin	Madison, WI



Canada			
University of Calgary	Calgary	M.D. Anderson Cancer Center	Houston, TX
Royal Victoria Hospital	Montreal	Indiana University Hospital & Outpatient Center	Indianapolis, IN
Sacré Coeur Hospital	Montreal	Methodist Hospital of Indiana	Indianapolis, IN
Northeastern Ontario Regional Cancer Centre	Sudbury	St. Vincent Hospital & Health Care Ctr.	Indianapolis, IN
Toronto Hospital	Toronto	North Shore University Hospital	Manhasset, NY
Vancouver General Hospital	Vancouver	Marshfield Clinic	Marshfield, WI
Manitoba Cancer Treatment Center	Winnipeg	Loyola University Medical Center	Maywood, IL
Cuba		Methodist Hospital Central	Memphis, TN
Hermanos Ameijeiras Hospital	Havana	Baptist Hospital of Miami	Miami, FL
Mexico		Froedtert Memorial Lutheran	Milwaukee, WI
Instituto Nacional de Cancerologia	Mexico City	St. Luke's Medical Center	Milwaukee, WI
Centro de Hematologia y Medicina Interna	Puebla	Abbott Northwestern Hospital	Minneapolis, MN
Russia		University of Minnesota	Minneapolis, MN
Petrov Research Institute of Oncology	St. Petersburg	West Virginia University	Morgantown, WV
United States		Vanderbilt University Medical Center	Nashville, TN
Presbyterian Health Care Services	Albuquerque, NM	Columbia Presbyterian Medical Center	New York, NY
University of Michigan Medical Center	Ann Arbor, MI	Mount Sinai Medical Center	New York, NY
Arlington Cancer Center	Arlington, TX	Medical Center of Delaware	Newark, DE
Emory Clinic	Atlanta, GA	Hoag Cancer Center	Newport Beach, CA
Southwest Regional Cancer Center	Austin, TX	University of Oklahoma Health Sciences Center	Oklahoma City, OK
Johns Hopkins Hospital	Baltimore, MD	University of Nebraska Medical Center	Omaha, NE
University of Maryland Cancer Center	Baltimore, MD	Saint Joseph Hospital	Orange, CA
Mary Bird Perkins Cancer Center	Baton Rouge, LA	Lutheran General Hospital	Park Ridge, IL
Alta Bates Hospital	Berkeley, CA	Hematology Associates	Peoria, IL
University of Alabama at Birmingham	Birmingham, AL	Hahnemann University Hospital	Philadelphia, PA
Dana-Farber Cancer Institute	Boston, MA	Temple University Comprehensive Cancer Center	Philadelphia, PA
Montefiore Medical Center	Bronx, NY	University of Pennsylvania Hospital	Philadelphia, PA
Roswell Park Cancer Institute	Buffalo, NY	Shadyside Hospital	Pittsburgh, PA
University of North Carolina Chapel Hill	Chapel Hill, NC	University of Pittsburgh	Pittsburgh, PA
Medical University of South Carolina	Charleston, SC	Cancer Center of Boston	Plymouth, MA
University of Virginia Medical Center	Charlottesville, VA	North Shore Hem/Onc Assoc	East Setauket, NY
Rush Presbyterian/St. Luke's Medical Center	Chicago, IL	Oregon Health Sciences Univ.	Portland, OR
University of Chicago Medical Center	Chicago, IL	Roger Williams Medical Center	Providence, RI
Jewish Hospital of Cincinnati	Cincinnati, OH	Cancer & Blood Institute of the Desert	Rancho Mirage, CA
University Hospital Cincinnati	Cincinnati, OH	Washow Regional Cancer Center	Reno, NV
Case Western Reserve University Hospital	Cleveland, OH	Mayo Clinic Rochester	Rochester, NY
Cleveland Clinic Foundation	Cleveland, OH	University of Rochester	Rochester, NY
University of South Carolina	Columbia, SC	Sutter Memorial Hospital	Sacramento, CA
Ohio State University Hospital	Columbus, OH	University of California Davis Cancer Center	Sacramento, CA
Baylor University Medical Center	Dallas, TX	Latter Day Saints Hospital	Salt Lake City, UT
Miami Valley Hospital	Dayton, OH	University of Utah Medical Center	Salt Lake City, UT
Presbyterian/St. Luke's Hospital	Denver, CO	South Texas Cancer Institute	San Antonio, TX
Wayne State University	Detroit, MI	University of Texas Health Sciences Center	San Antonio, TX
City of Hope National Medical Center	Duarte, CA	University of CA, San Diego	San Diego, CA
University of Connecticut Health Center	Farmington, CT	University of CA, San Francisco Medical Center	San Francisco, CA
Bone Marrow & Stem Cell Institute of Florida	Fort Lauderdale, FL	Mayo Clinic Scottsdale	Scottsdale, AZ
Harris Methodist Oncology Program	Fort Worth, TX	LSU Medical Center-Shreveport	Shreveport, LA
University of Florida, Shands Hospital	Gainesville, FL	Memorial Medical Center	Springfield, IL
East Carolina University School of Medicine	Greenville, NC	Tufts University School of Medicine	Springfield, MA
Hackensack Medical Center	Hackensack, NJ	Methodist Hospital/Nicollet Cancer Center	St. Louis Park, MN
Hinsdale Hematology-Oncology Associates	Hinsdale, IL	St. Louis University Medical Center	St. Louis, MO
Queen's Cancer Center	Honolulu, HI	Bennett Cancer Center	Stanford, CT
St. Francis Medical Center	Honolulu, HI	Stanford University Hospital	Stanford, CA
Baylor College of Medicine	Houston, TX	SUNY-Health Science Center	Syracuse, NY

H. Lee Moffitt Cancer Center	Tampa, FL	Walter Reed Army Medical Center	Washington, DC
Arizona Cancer Center	Tucson, AZ	Westlake Comprehensive Cancer Center	Westlake Village, CA
St. Francis Hospital	Tulsa, OK	St. Francis Hospital	Wichita, KS
New York Medical College	Valhalla, NY	Wake Forest University	Winston-Salem, NC
George Washington University Medical Center	Washington, DC	University of Massachusetts Medical Center	Worcester, MA

## REFERENCES

1. Wingo P, Tong T, Bolden S: Cancer Statistics, 1995. *CA Cancer J Clin* 45:8-30, 1995
2. Fisher B, Bauer M, Margolese R, et al: Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 312:665-673, 1985
3. Fisher B, Redmond C, Poisson R, et al: Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 320:822-828, 1989
4. Veronesi U, Saccozzi R, Del Vecchio M, et al: Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancer of the breast. *N Engl J Med* 305:6-11, 1981
5. Valagussa P, Bonadonna G, Veronesi U: Patterns of relapse and survival following radical mastectomy: Analysis of 716 consecutive patients. *Cancer* 41:1170-1178, 1978
6. Fisher E, Sass R, Fisher B: Pathologic findings from the national surgical adjuvant project for breast cancers (protocol no. 4). *Cancer* 53:712-723, 1984
7. Nemoto T, Vana J, Bedwani RN, et al: Management and survival of female breast cancer: Results of a national survey by the American College of Surgeons. *Cancer* 45:2917-2924, 1980
8. Clark G, Sledge GW, Osborne CK, et al: Survival from first recurrence: Relative importance of prognostic factors in 1,015 breast cancer patients. *J Clin Oncol* 5:55-61, 1987
9. Mick R, Begg CB, Antman K, et al: Diverse prognosis in metastatic breast cancer: Who should be offered alternative initial therapies? *Breast Cancer Res Treat* 13:33-38, 1989
10. Henderson IC: Chemotherapy for advanced disease, in Harris JR, Hellman S, Henderson IC, et al (eds): *Breast Diseases*. Philadelphia, PA, Lippincott, 1987, pp 428-479
11. Hortobagyi GN, Buzdar AU, Bodey GP, et al: High-dose induction chemotherapy of metastatic breast cancer in protected environment: A prospective randomized study. *J Clin Oncol* 5:178-184, 1987
12. Bezwoda WR, Seymour L, Dansey RD: High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: A randomized trial. *J Clin Oncol* 13:2483-2489, 1995
13. National Hospital Discharge Survey for 1990 and 1991. US Department of Health and Human Services, Public Health Service, Center for Disease Control. National Center for Health Statistics. Hospital Care Statistics Branch, Hyattsville, MD
14. Graves EJ: Detailed diagnoses and procedures, National Hospital Discharge Survey, 1989. *Vital & Health Statistics-Series 13: Data From the National Health Survey*. 108:1-236, 1991
15. Kruskal WH, Wallis WA: Use of ranks in one-criterion variance analysis. *J Am Stat Assoc* 47:583-621, 1952
16. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
17. Cox DR: Regression models and life tables. *J R Stat Soc B* 34:187-202, 1972
18. Crump M, Prince M, Goss P: Outcome of extensive evaluation of women with > 10 positive axillary lymph nodes prior to adjuvant therapy for breast cancer. *Anti Cancer Drugs* 6:71, 1995 (abstr)
19. Bortin MM, Rimm AA: Increasing utilization of bone marrow transplantation. II. Results of 1985-1987 survey. *Transplantation* 48:453-458, 1989
20. Bortin MM, Horowitz MM, Rimm AA: Increasing utilization of allogeneic bone marrow transplantation. III. Results of the 1988-1990 survey. *Ann Intern Med* 116:505-512, 1992
21. Silberman G, Crosse MG, Peterson EA, et al: Availability and appropriateness of allogeneic bone marrow transplantation for chronic myeloid leukemia in 10 countries. *N Engl J Med* 331:1063-1067, 1994

F:\BMTR-UND\DATA\BREAST\METSTUDY\MS\DRAFT.9  
April 23, 1998 (1:03pm)

**FACTORS CORRELATED WITH PROGRESSION-FREE SURVIVAL AFTER  
HIGH-DOSE THERAPY AND HEMATOPOIETIC STEM CELL  
TRANSPLANTATION FOR METASTATIC BREAST CANCER**

Philip A. Rowlings, MBBS, MS; Stephanie F. Williams, MD; Karen H. Antman, MD; Karen K. Fields, MD; Joseph W. Fay, MD; Elizabeth Reed, MD; Corey J. Pelz, MS; John P. Klein, PhD; Kathleen A. Sobocinski, MS; M. John Kennedy, MD; Cesar O. Freytes, MD; Philip L. McCarthy, Jr., MD; Roger H. Herzig, MD; Edward A. Stadtmaier, MD; Hillard M. Lazarus, MD; Andrew L. Pecora, MD; Jacob D. Bitran, MD; Steven N. Wolff, MD; Robert Peter Gale, MD, PhD; James O. Armitage, MD; William P. Vaughan, MD; Gary Spitzer, MD and Mary M. Horowitz, MD, MS

From the Breast Cancer Working Committee of the Autologous Blood and Marrow Transplant Registry, Health Policy Institute, Medical College of Wisconsin, Milwaukee, Wisconsin, USA (PAR, CJP, JPK, KAS, MMH); and Section of Hematology/Oncology, University of Chicago Medical Center, Chicago, Illinois, USA (SFW); Division of Medical Oncology, Columbia University, New York, New York, USA (KHA); Division of Bone Marrow Transplantation, H. Lee Moffitt Cancer Center, Tampa, Florida, USA (KKF); Sammons Cancer Center, Baylor University, Dallas, Texas, USA (JWF); Division of Oncology-Hematology, University of Nebraska Medical Center, Omaha, Nebraska, USA (ER, JOA); Oncology Center, Johns Hopkins Hospital, Baltimore, Maryland, USA (MJK); Adult Bone Marrow Transplant Program, University of Texas Health Science Center, San Antonio, Texas, USA (COF); Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York, USA (PLM); James Graham Brown Cancer

Center, University of Louisville, Louisville, Kentucky, USA (RHH); Bone Marrow Transplant Program, University of Pennsylvania, Philadelphia, Pennsylvania, USA (EAS); Ireland Cancer Center, Case Western Reserve University, Cleveland, Ohio, USA (HML); Hackensack University Medical Center, Hackensack, New Jersey, USA (ALP); Division of Hematology/ Oncology, Lutheran General Hospital Cancer Care Center, Park Ridge, Illinois, USA (JDB); Department of Medicine, Vanderbilt University, Nashville, Tennessee, USA (SNW); Division of Bone Marrow and Stem Cell Transplantation, Salick Health Care, Inc., Los Angeles, California, USA (RPG); Bone Marrow Transplant Program, University of Alabama, Birmingham, Alabama, USA (WPV); Bone Marrow Transplant Division, Georgetown University Hospital, Washington, DC, USA (GS).

## ABSTRACT

**Context.**-Women with breast cancer are the most frequent recipients of high-dose therapy followed by autologous hematopoietic stem cell transplantation (autotransplants) in North America. Despite widespread use there remains controversy about who are most appropriate candidates.

**Objective.**-To determine factors correlated with progression-free survival after autotransplant in women with metastatic breast cancer.

**Design.**-Cohort study; Cox regression analysis of observational database.

**Setting.**-63 North American hospitals between 1989 and 1995.

**Participants.**-1188 consecutive women aged 18 to 79 years receiving autotransplants for metastatic or locally recurrent breast cancer.

**Main Outcome Measures.**-Time to treatment failure (progression or death) from time of autotransplant.

**Results.**-Three-year probabilities of survival and progression-free survival were 31 (28-34)% and 13 (10-16)%. Factors associated with significantly ( $p < 0.05$ ) increased risk of treatment failure were: age  $> 45$  yrs; Karnofsky performance score  $< 90\%$ ; absence of hormone receptors; prior use of adjuvant chemotherapy; initial disease-free survival interval with adjuvant treatment  $\leq 18$  months; metastases in the liver or central nervous system (compared to soft tissue, bone or lung); 3 or more sites of metastatic disease; and incomplete or no response (compared to a complete response) to standard dose chemotherapy. Receiving hormonal therapy posttransplant was associated with a reduced risk of treatment failure in women with hormone receptor positive tumors ( $p=0.0001$ ).

**Conclusion.**-These data indicate some women are very unlikely to benefit from autotransplant and should only receive this treatment in the context of clinical trials attempting to improve outcome.

~~CONFIDENTIAL~~

## INTRODUCTION

Metastatic or locally recurrent breast cancer is generally an incurable disease (1). High-dose therapy followed by autologous hematopoietic stem cell transplantation (autotransplant) is an increasingly used treatment approach for this disorder. Breast cancer is the most common indication for hematopoietic stem cell transplantation in North America and most women receiving autotransplants have advanced disease (2). Despite widespread use, its appropriateness and benefits are still debated (3-5). Many phase I and II studies report outcomes of autotransplants in women with advanced breast cancer (6-17) and one published randomized trial compares standard to high-dose therapy (18). Inclusion criteria for these studies differ and numbers of subjects are usually small. We recently reported data from 3,500 women with advanced breast cancer treated at centers reporting to the Autologous Blood and Marrow Transplant Registry (ABMTR) (2). Three-year progression-free survival (PFS) ranged from 7-32% depending on response to conventional dose chemotherapy prior to autotransplant.

Identifying women most likely to benefit from autotransplants for advanced breast cancer is important for women and doctors deciding treatment options and for investigators developing new trials. Factors predicting treatment failure after conventional therapy are reasonably well-established (19-25). Few multivariate analyses of such factors are published for women receiving autotransplants (13, 15, 16). We studied 1188 women with advanced (metastatic or locally recurrent) breast cancer receiving autotransplants at 63 centers to determine factors associated with progression or death (treatment failure).

## METHODS

### Data Collection

The ABMTR is a voluntary organization of more than 200 institutions performing autotransplants, primarily in the United States, Canada, and Central and South America. Centers report data on consecutive autotransplants to a Statistical Center at the Medical College of Wisconsin. The ABMTR defines autotransplant as treatment with a sufficiently high dose of chemotherapy to warrant autologous bone marrow- or blood-derived hematopoietic stem cell support.

The ABMTR began data collection in 1992. Data were collected retrospectively for women receiving autotransplants between 1989 and 1992 and prospectively thereafter. Participating centers register consecutive autotransplants for all disease indications. Based on data collected in the Centers for Disease Control Hospital Surveys (26,27), about half of autotransplants in North America are registered with the ABMTR.

The ABMTR collects data at two levels: Registration and Research. Registration data include disease type, age, sex, pretransplant disease stage and chemotherapy-responsiveness, date of diagnosis, graft type (bone marrow- and/or blood-derived stem cells), high-dose conditioning regimen, posttransplant disease progression and survival, development of a new malignancy and cause of death. Requests for data on progression or death for registered patients are at six month intervals. All ABMTR teams contribute Registration data. Research data is collected on subsets of registered patients, including comprehensive pre- and posttransplant clinical information such as tumor size and pathology, sites of disease, menopausal status, hormone receptor status, all breast cancer treatments before and after transplant, clinical status (including cardiac, pulmonary, renal and liver function) before and after transplant, doses of high-dose therapy, and blood or



marrow graft treatment and sites of posttransplant progression.

### Patients

This analysis uses ABMTR Research data reported for 1188 women with metastatic and locally recurrent breast cancer consecutively transplanted by 63 teams between January 1, 1989 and January 31, 1995 (Participating centers listed in Appendix.). Women with disease recurrence solely in the contralateral breast were excluded because of difficulty in distinguishing recurrence from a new primary site of disease. One hundred and seven women were excluded because of incomplete data for sites of metastases or date of diagnosis of metastatic disease. The survival of women excluded was not different from the 1188 included in the analysis (log-rank test for difference in survival probability  $p=0.58$ ). Women were considered to have hormone receptor positive tumors if either estrogen receptor (ER) or progesterone receptor (PR) assays were positive; those reported as having borderline receptor levels were grouped with the receptor-negative patients. Women in whom metastases were found within one month of diagnosis of breast cancer were considered in the same group as women with metastases at first presentation. Women with pleural or parenchymal lung disease were considered as a single group.

### Statistical Methods

The primary outcome was treatment failure, the inverse of PFS. Events were death, progression, and, in women with a complete response, breast cancer recurrence. Women alive without progression or recurrence were censored at last follow-up. Univariate probabilities of survival and PFS were calculated using the Kaplan-Meier estimator. Variables were tested in univariate analysis for their association with treatment failure using Cox proportional hazards regression; these analyses also examined whether the proportional hazards assumption was met, using the time-dependent covariate method. Optimal cut points for categorizing continuous

variables were determined using Martingale residual plots (28). A forward stepwise selection method with a significance level of 0.05 was used to select variables for the multivariate model. All analyses were performed using PROC PHREG in SAS<sup>®</sup> version 6.12. Covariates in the final multivariate model were tested for proportional hazards, using the time-dependent covariate method, and for first order interactions. Tests for “center effects” (inter-center differences unexplained by known covariates) were not statistically significant (29).

*Posttransplant hormone and radiation therapy:* Studying effects of posttransplant maneuvers on outcome, such as posttransplant hormone therapy and radiation therapy, must account for bias introduced by early deaths occurring before intended treatments were administered. This bias artificially increases the proportion of adverse events in the non-treatment group if all patients are considered from the time of transplant. This bias was overcome by only studying effects of posttransplant hormone and radiation therapy in women already surviving without disease recurrence more than 6 months posttransplant. Hormone therapy was analyzed in 4 groups; women who were hormone receptor positive and received therapy pretransplant only, posttransplant only, both pre- and posttransplant and those receiving hormone therapy neither pre- or posttransplant. These 4 groups were compared simultaneously against women with hormone receptor negative tumors while adjusting for other variables found to be significant in the multivariate analyses. Prophylactic posttransplant radiation therapy was similarly studied in women surviving > 6 months posttransplant.

## RESULTS

The distribution of patient-, disease- and transplant-related characteristics of the 1188 women are presented in Table 1. Median follow-up after transplant was 29.5 months. The three-year probabilities of survival and PFS were 31 (28-34)% and PFS 13 (10-16)%, respectively (Figure 1).

### Univariate analyses

Eight factors were significant ( $p < 0.001$ ) and four marginally significant ( $p < 0.05-0.01$ ) in univariate analyses of association with treatment failure. Significant variables were breast cancer stage at diagnosis, hormone receptor status, use of adjuvant chemotherapy, initial disease-free interval, response to pretransplant chemotherapy, pretransplant Karnofsky performance score, and number and sites of metastases. Marginally significant variables were age, use of radiation therapy prior to transplant, type of high-dose therapy used and year of transplant.

### Multivariate analysis

Factors significant in the final multivariate model of risk of treatment failure are shown in Table 2. All highly significant variables from the univariate analyses remained significant in the final model (see Methods). Of the marginally significant variables only age remained in the model. Women older than 45 years at time of transplant had relative risk (RR) of treatment failure of 1.17 (95% confidence interval, 1.02, 1.33) compared with younger women ( $p = 0.02$ ). A low Karnofsky performance score pretransplant ( $< 90\%$ ) was associated with an increased risk of treatment failure 1.27 (1.07, 1.51), ( $p < 0.005$ ). Absence of hormone receptors was associated with a RR of treatment failure of 1.31 (1.15, 1.51) compared to women with hormone receptor positive tumors ( $p < 0.0001$ ).

A complex interaction was found between prior use of adjuvant chemotherapy and initial disease-free interval (interval from diagnosis of breast cancer to detection of metastatic disease). First, women whose first presentation was with metastatic disease were not eligible for adjuvant therapy. Additionally, the effect of prior adjuvant therapy on posttransplant treatment failure differed in women with initial disease-free intervals  $\leq$  and  $>$  18 months. These two variables were therefore combined in the final model into a single covariate with the following categories: metastatic breast cancer at diagnosis, no adjuvant therapy, adjuvant therapy and disease-free interval  $\leq$  18 months, adjuvant therapy and disease-free interval  $>$  18 months. Women not receiving adjuvant therapy had the same risk of treatment failure as women with metastases at diagnosis. Disease-free interval was not significant in women not receiving adjuvant chemotherapy. Women receiving adjuvant chemotherapy with a disease-free interval  $\leq$  18 months had a high risk of treatment failure (RR 1.99 [1.62, 2.43],  $p < 0.0001$ ) as did women receiving adjuvant chemotherapy with a disease-free interval  $>$  18 months (RR 1.31 [1.10, 1.56],  $p = 0.002$ ). The latter two groups were also significantly different from each other ( $p < 0.001$ ).

Number and sites of metastases were also important. Four important prognostic groups were determined in the final model. Women with one or two sites of metastases, providing neither were viscera (other than lung) or central nervous system (CNS), had similar risks of treatment failure and were used as the reference group. Women with CNS or liver metastases or metastases in three or more organs of any kind had a poor prognosis.

Risk of treatment failure correlated strongly with pretransplant response to chemotherapy. Women with a partial response to chemotherapy had a RR of 1.65 (1.36, 1.99) ( $p < 0.0001$ ), and women with resistant disease a RR of 1.87 (1.54, 2.27) ( $p < 0.0001$ ) compared to women in complete remission, but were not significantly different from each other ( $p = 0.09$ ). Women with

indeterminant sensitivity (due to bone only disease, single site disease excised or irradiated pretransplant, or response to chemotherapy untested) had a RR of treatment failure similar to the reference group. Figures 2-4 present Kaplan-Meier estimates of PFS according to chemotherapy sensitivity pretransplant, number and sites of metastases, adjuvant chemotherapy and disease-free interval.

#### Posttransplant Hormone and Radiation Therapy

Effect of posttransplant hormone therapy was only analyzed in women surviving without progression six months posttransplant. After adjustment for other variables in the final model described above, posttransplant hormone therapy was associated with decreased treatment failure in women with hormone receptor positive disease. Use of pretransplant hormone therapy did not influence posttransplant PFS regardless of whether posttransplant hormones were given. The use of radiation as part of the planned posttransplant treatment was not associated with improved outcome (Table 3).

### **DISCUSSION**

In this study of 1188 women receiving autotransplants for advanced breast cancer, use of posttransplant hormonal therapy in women with hormone receptor positive tumors significantly reduced risk of treatment failure. Eight other factors were significant predictors of treatment failure in multivariate analysis, including age >45 years; Karnofsky performance score <90; CNS or liver metastases or metastases involving three or more sites; hormone receptor negative tumors; use of adjuvant chemotherapy; initial disease-free interval  $\leq$  18 months in women receiving adjuvant chemotherapy; and poor response to chemotherapy pretransplant.

Surprisingly, there was little difference in risk of treatment failure between women with partial and no response to chemotherapy pretransplant. From this study it is not possible to state

whether conventional dose therapy affected the natural history of the disease or just identified women who would do poorly with autotransplant.

The survival of women with advanced breast cancer varies widely, regardless of treatment given. Prior studies attempting to define patient, disease and treatment factors predicting progression or death following therapy are summarized in Table 4 (8,13,15,16,19-25,30). Interpretation of these studies and their sometimes conflicting results is difficult. Variations among studies likely relate to small sizes of study populations and differing selection criteria. Additionally, in most studies statistical techniques did not attempt to adjust for important interactions between factors and changes in effect of factors over time as was done in the current analysis (28). This study analyzed a large population of women consecutively transplanted, examined interactions among factors under study and considered changing effects of factors on treatment failure over time. Women receiving autotransplants are no doubt a selected group of women with advanced breast cancer, however we believe this study accurately determines factors affecting outcome of women receiving this therapy.

There are several important negative findings from this study. Interval from diagnosis of metastases to transplant, prior hormonal therapy, prior anthracycline therapy, use of growth factors to enhance marrow recovery, and source of stem cells did not affect progression-free survival. Several factors were significantly correlated with treatment failure in univariate analysis but not after adjustment for other prognostic factors in multivariate analysis. These included stage of breast cancer at diagnosis, prior radiation therapy, high-dose therapy regimen and calendar year. Correlations among variables may account for some differences in published studies. Outcomes were similar among the 63 teams contributing data, after adjustment for patient characteristics.

The only intervention found to reduce treatment failure after autotransplant was the use of hormone therapy after transplant. This should therefore be recommended in all hormone receptor positive women. Failure to determine a superior high-dose chemotherapy regimen suggests that women should be treated with the least toxic transplant regimens (unless volunteering to be part of a clinical trial). Absence of an effect on treatment failure of interval from diagnosis of metastases to transplant in this study may indirectly support a recently reported benefit on survival of delaying autotransplant until progression of disease in women achieving a complete remission after standard dose chemotherapy (30).

The question of superiority of high-dose compared with standard dose therapy for advanced breast cancer is not addressed by this study. However, the data suggest that some women are very unlikely to benefit from this approach: women with resistant disease, CNS metastases, three or more metastatic sites and those who relapsed early after adjuvant chemotherapy for early stage disease all had PFS rates of <10% at three years (Figures 2-4). Such women should probably not be considered for autotransplants except in the context of clinical trials designed to test regimens that might improve this very poor prognosis.

In this study of a large number of women consecutively treated with autotransplants for advanced breast cancer, we determined patient-, disease- and transplant-related factors associated with treatment failure. The large number and complex interaction of prognostic factors determined in this study highlight the need for careful statistical analyses on large numbers of patients to determine prognostic factors and impact of new therapies in treating women with advanced breast cancer. The design of new clinical trials should consider data available in information resources such as the ABMTR and similar organizations.

## ACKNOWLEDGEMENTS

We would like to thank Ms. Patty Vespalec and Ms. Diane Knutson for assistance in data coordination.

Supported by Public Health Service Grant No. P01-CA-40053 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung and Blood Institute of the U.S. Department of Health and Human Services; Grant No. DAMD17-95-I-5002 from the Department of the U.S. Army Medical Research and Development Command; and by grants from Alpha Therapeutic Corporation; Amgen Inc.; Anonymous; Baxter Healthcare Corporation; Bayer Corporation; Berlex Laboratories; Blue Cross and Blue Shield Association; Bristol-Myers Squibb Company; CellPro, Inc.; Cell Therapeutics, Inc.; Centeon; Center for Advanced Studies in Leukemia; Chimeric Therapies, Inc.; Chiron Therapeutics; COBE BCT, Inc.; The Eppley Foundation for Research; Genentech, Inc.; ICN Pharmaceuticals; Immunex Corporation; The Kettering Family Foundation; Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation; MGI Pharma, Inc.; Milstein Family Foundation; Milwaukee Foundation/Elsa Schoeneich Research Fund; Novartis Pharmaceuticals; Ortho Biotech, Inc.; Pharmacia and Upjohn; Pfizer, Inc; Principal Mutual Life Insurance Company; Roche Laboratories; SangStat Medical Corporation; Searle; SyStemix; and United Resource Networks.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.



## REFERENCES

1. Harris JR, Morrow M, Bonadonna G. Cancer of the breast. In: DeVita VT Jr., Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 4th ed. Philadelphia, PA: J.B. Lippincott Co; 1993:1264-1332.
2. Antman KH, Rowlings PA, Vaughan WP, et al. High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in North America. *Journal of Clinical Oncology*. 1997;15:1870-1879.
3. Gradishar WJ, Tallman MS, Abrams JS. High-dose chemotherapy for breast cancer. *Annals of Internal Medicine*. 1996;125:599-604.
4. United States General Accounting Office. Report to the Honorable Ron Wyden, U.S. Senate. Health Insurance: Coverage of Autologous Bone Marrow Transplantation for Breast Cancer. GAO/HEHS-96-83, 1996.
5. Peters WP, Rogers MC. Variation in approval by insurance companies of coverage for autologous bone marrow transplantation for breast cancer. *New England Journal of Medicine*. 1994;330:473-477.
6. Peters WP, Shpall EJ, Jones RB, et al. High-dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. *Journal of Clinical Oncology*. 1988;6:1368-1376.
7. Williams SF, Mick R, Desser R, Golick J, Beschorner J, Bitran JD. High-dose consolidation therapy with autologous stem cell rescue in stage IV breast cancer. *Journal of Clinical Oncology*. 1989;7:1824-1830.

8. Dunphy FR, Spitzer G, Buzdar AU, et al. Treatment of estrogen receptor-negative or hormonally refractory breast cancer with double high-dose chemotherapy intensification and bone marrow support. *Journal of Clinical Oncology*. 1990;8:1207-1216.
9. Wallerstein R Jr, Spitzer G, Dunphy F, et al. A phase II study of mitoxantrone, etoposide, and thiotepa with autologous marrow support for patients with relapsed breast cancer. *Journal of Clinical Oncology*. 1990;8:1782-1788.
10. Kennedy MJ, Beveridge RA, Rowley SD, Gordon GB, Abeloff MD, Davidson NE. High-dose chemotherapy with reinfusion of purged autologous bone marrow following dose-intensive induction as initial therapy for metastatic breast cancer. *Journal of the National Cancer Institute*. 1991;83:920-926.
11. Antman K, Elias A, Wheeler C, et al. A phase II study of high-dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. *Journal of Clinical Oncology*. 1992;10:102-110.
12. Ayash LJ, Elias A, Wheeler C, et al. Double dose-intensive chemotherapy with autologous marrow and peripheral-blood progenitor-cell support for metastatic breast cancer: A feasibility study. *Journal of Clinical Oncology*. 1994;12:37-44.
13. Dunphy FR, Spitzer G, Rossiter Fornoff JE, et al. Factors predicting long-term survival for metastatic breast cancer patients treated with high-dose chemotherapy and bone marrow support. *Cancer*. 1994;73:2157-2167.

14. Vaughan WP, Reed EC, Edwards B, Kessinger A. High-dose cyclophosphamide, thiotepa and hydroxyurea with autologous hematopoietic stem cell rescue: an effective consolidation chemotherapy regimen for early metastatic breast cancer. *Bone Marrow Transplantation*. 1994;13:619-624.
15. Ayash LJ, Wheeler C, Fairclough D, et al. Prognostic factors for prolonged progression-free survival with high-dose chemotherapy with autologous stem-cell support for advanced breast cancer. *Journal of Clinical Oncology*. 1995;13:2043-2049.
16. Weaver CH, West WH, Schwartzberg LS, et al. Induction, mobilization of peripheral blood stem cells, high-dose chemotherapy and PBSC infusion in patients with untreated stage IV breast cancer: outcomes by intent to treat analyses. *Bone Marrow Transplantation*. 1997;19:661-670.
17. Bensinger WI, Schiffman KS, Holmberg L, et al. High-dose busulfan, melphalan, thiotepa and peripheral blood stem cell infusion for the treatment of metastatic breast cancer. *Bone Marrow Transplantation*. 1997;19:1183-1189.
18. Bezwoda WR, Seymour L, Dansey RD. High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: A randomized trial. *Journal of Clinical Oncology*. 1995;13:2483-2489.
19. Swenerton KD, Legha SS, Smith T, et al. Prognostic factors in metastatic breast cancer treated with combination chemotherapy. *Cancer Research*. 1979;39:1552-1562.
20. Nash CH III, Jones SE, Moon TE, Davis SL, Salmon SE. Prediction of outcome in metastatic breast cancer treated with adriamycin combination chemotherapy. *Cancer*. 1980;46:2380-2388.

21. Ahmann FR, Jones SE, Moon TE. The effect of prior adjuvant chemotherapy on survival in metastatic breast cancer. *Journal of Surgical Oncology*. 1988;37:116-122.
22. Falkson G, Gelman RS, Leone L, Falkson CI. Survival of premenopausal women with metastatic breast cancer. *Cancer*. 1990;66:1621-1629.
23. Falkson G, Gelman R, Falkson CI, Glick J, Harris J. Factors predicting for response, time to treatment failure, and survival in women with metastatic breast cancer treated with DAVTH: A prospective Eastern Cooperative Oncology Group study. *Journal of Clinical Oncology*. 1991;9:2153-2161.
24. Greenberg PAC, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Buzdar AU. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *Journal of Clinical Oncology*. 1996;14:2197-2205.
25. Henderson IC, Harris JR, Kinne DW, Hellman S. Cancer of the breast. In: DeVita VT Jr., Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 3rd ed. Philadelphia, PA: J.B. Lippincott Co; 1989:1197-1268.
26. National Hospital Discharge Survey for 1990 and 1991. U.S. Department of Health and Human Services, Public Health Service, Center for Disease Control. National Center for Health Statistics. Hospital Care Statistics Branch; 6525 Belcrest Road: Hyattsville, MD, 20782.
27. Graves EJ. Detailed diagnoses and procedures, National Hospital Discharge Survey, 1989. Vital & Health Statistics-Series 13: Data from the National Health Survey. 1991;108:1-236.
28. Klein JP, Moeschberger ML. *Survival Analysis: Techniques for Censored and Truncated Data*. New York, NY: Springer-Verlag; 1997.

29. Commenges D, Andersen PK. Score test of homogeneity for survival data. *Lifetime Data Analysis*. 1995;1:145-160.
30. Peters WP, Jones RB, Vredenburgh J, et al. A large, prospective, randomized trial of high-dose combination alkylating agents with autologous cellular support as consolidation for patients with metastatic breast cancer achieving complete remission after intensive doxorubicin-based induction therapy (abstract). *Proceedings of the American Society of Clinical Oncology*. 1996;15:121.

Table 1. Patient-, disease- and treatment-related factors and their association with risk of treatment failure (progression or death) in univariate analyses.

Variable	N (%)	RR (95% CI)	P-value
<b>Age at transplant</b>			
Median (range), years	44 (18-70)		
≤ 45 years	658 (55%)	1.00	---
> 45 years	530 (45%)	1.15 (1.01,1.31)	0.036
<b>Stage at diagnosis</b>			
Metastatic	221 (19%)	1.00	---
Stage I <sup>a</sup>	98 ( 8%)	1.02 (0.76,1.36)	0.91
Stage II <sup>a</sup>	377 (32%)	1.26 (1.03,1.55)	0.02
Stage III (includes inflammatory) <sup>a</sup>	94 ( 8%)	1.63 (1.23,2.16)	0.0006
Not metastatic, initial stage unknown <sup>a</sup>	398 (33%)	1.42 (1.17,1.73)	0.0004
<b>Initial surgery type</b>			
Lumpectomy	269 (23%)	0.91 (0.77,1.08)	0.26
Mastectomy	835 (70%)	1.00	---
None <sup>b</sup> (N=63) or unknown (N=21)	84 ( 7%)	1.08 (0.84,1.39)	0.56
<b>Hormone receptor status</b>			
Positive	676 (57%)	1.00	---
Not tested (N=60) or unknown (N=42)	102 ( 9%)	1.14 (0.79,1.64)	0.47
Negative / borderline	410 (35%)	1.28 (1.12,1.47)	0.0003
<b>Interval from diagnosis to metastases</b>			
Median (range), months	21 (0-238)		
Metastatic disease at diagnosis	221 (19%)	1.00	---
≤ 18 months <sup>a</sup>	312 (26%)	1.72 (1.40,1.32)	<0.0001
> 18 months <sup>a</sup>	655 (55%)	1.32 (1.10,1.58)	0.003
<b>Response to pretransplant chemotherapy</b>			
Complete response	263 (23%)	1.00	---
Partial response	375 (33%)	1.71 (1.42,2.06)	<0.0001
Resistant	330 (29%)	2.07 (1.72,2.05)	<0.0001
Indeterminant / untested	169 (15%)	1.18 (0.94,1.49)	0.16
Missing	51	1.13 (0.92,1.94)	0.12
<b>Karnofsky score pretransplant</b>			
90-100%	895 (75%)	1.00	---
< 90%	214 (18%)	1.44 (1.22,1.69)	0.0001
Unknown	79 ( 7%)	1.48 (1.15,1.91)	0.003

*Table 1, continued*

Variable	N (%)	RR (95% CI)	P-value
<b>Interval from metastases to transplant</b>			
Median (range), months	8 (<1-138)	1.00 (0.99,1.01)	0.11
<b>Sites of metastases pretransplant</b>			
Bone/Bone marrow only	207 (17%)	1.00	---
Lung only	76 ( 6%)	1.25 (0.92,1.69)	0.16
Liver only	62 ( 5%)	1.66 (1.21,2.28)	0.002
Soft tissue only	262 (22%)	1.22 (0.98,1.51)	0.07
CNS ± other	21 ( 2%)	2.25 (1.41,3.39)	0.0007
Bone + lung	50 ( 4%)	1.54 (1.09,2.16)	0.01
Bone + liver	34 ( 3%)	1.88 (1.25,2.82)	0.002
Bone + soft tissue	96 ( 8%)	1.18 (0.89,1.56)	0.25
Lung + soft tissue	59 ( 5%)	1.44 (1.08,2.07)	0.016
Other 2 sites <sup>c</sup>	40 ( 3%)	2.52 (1.26,3.60)	<0.0001
Bone + lung + soft tissue	35 ( 3%)	3.00 (2.03,4.37)	<0.0001
Other 3 sites <sup>d</sup>	45 ( 4%)	2.13 (1.50,3.03)	<0.0001
4 or more sites + other visceral <sup>e</sup>	201 (17%)	1.44 (1.15,1.79)	0.0014
<b>Radiation therapy pretransplant</b>			
No	574 (48%)	1.00	---
Yes	614 (52%)	1.18 (1.04,1.36)	0.01
<b>Hormone therapy pretransplant</b>			
No	609 (51%)	1.00	---
Yes	579 (49%)	0.99 (0.88,1.13)	0.96
<b>Anthracyclines pretransplant<sup>f,g</sup></b>			
No	203 (17%)	1.00	---
Yes	985 (83%)	1.02 (0.86,1.21)	0.80
<b>Adjuvant chemotherapy given</b>			
No adjuvant chemotherapy <sup>h</sup>	220 (19%)	1.00	---
Metastases at diagnosis <sup>i</sup>	221 (19%)	0.94 (0.76,1.16)	0.55
CMF ± other <sup>j</sup>	357 (31%)	1.46 (1.22,1.75)	<0.0001
CAF ± other <sup>k</sup>	197 (18%)	1.55 (1.26,1.90)	<0.0001
Other chemotherapy	143 (13%)	1.70 (1.34,2.17)	<0.0001

Table 1, continued

Variable	N (%)	RR (95% CI)	P-value
Conditioning regimen, N evaluable	1184		0.04
CyTCb	311 (26%)	1.00	---
CyT	143 (12%)	1.16 (0.93,1.44)	0.20
CyTM	48 ( 4%)	0.92 (0.63,1.34)	0.67
ICE	70 ( 6%)	1.19 (0.89,1.57)	0.24
CyCbM	30 ( 3%)	1.24 (0.83,1.87)	0.29
CyTHu	106 ( 9%)	1.01 (0.79,1.30)	0.93
CyCbE	67 ( 6%)	1.16 (0.86,1.56)	0.33
CyCisE	45 ( 4%)	1.64 (1.17,2.29)	0.004
MT	63 ( 5%)	1.57 (1.17,2.29)	0.003
CyMVnb	30 ( 3%)	1.33 (0.88,2.00)	0.18
Other with BCNU	36 ( 3%)	0.89 (0.59,1.33)	0.56
Other no BCNU	235 (20%)	1.20 (0.89,1.46)	0.06
G/GM - CSF in first 7 days, N evaluable	1155		
No	278 (24%)	1.00	---
Yes	877 (76%)	0.90 (0.78,1.05)	0.19
Source of graft			0.30
Bone marrow	463 (39%)	1.00	---
PBSC	507 (43%)	0.98 (0.85,1.13)	0.78
Bone marrow + PBSC	218 (18%)	0.13 (0.94,1.35)	0.20
Year of transplant			0.08
1989-1990	201 (17%)	1.00	---
1991-1992	475 (40%)	0.88 (0.74,1.05)	0.16
1993-1995	512 (43%)	0.81 (0.68,0.97)	0.02

**Abbreviations:** RR = relative risk; CI = confidence interval; CNS=central nervous system; C = cyclophosphamide; M = methotrexate; F = 5-fluorouracil; A = adriamycin; Cy = cyclophosphamide; T = thiotepa; Cb = carboplatin; M=Mitoxantrone; ICE = ifosfamide, carboplatin and etoposide; Hu = hydroxurea; E = etoposide; Cis =cisplatin; Vnb = vinblastine; BCNU = carmustine; G = granulocyte; GM = granulocyte-macrophage; CSF = colony-stimulating factor; PBSC = peripheral blood stem cells

**Footnotes**

- <sup>a</sup> These women had Stage I, II or III disease at diagnosis, may or may not have received adjuvant therapy, and subsequently developed metastases.
- <sup>b</sup> These women received chemotherapy prior to surgery.
- <sup>c</sup> Other 2 sites include: lung + liver; liver + soft tissue.
- <sup>d</sup> Other 3 sites include: bone + lung + liver; bone + liver + soft tissue; lung + liver + soft tissue.
- <sup>e</sup> Other viscera includes visceral sites other than lung, liver or CNS.
- <sup>f</sup> Includes adriamycin, mitoxantrone, and epirubicin.



Table 1, Footnotes, ~~CONFIDENTIAL~~ continued.

- <sup>g</sup> Dose of anthracycline also tested and not significant (p=0.86)
- <sup>h</sup> Refers only to women with Stage I-III disease at diagnosis.
- <sup>i</sup> These women not eligible for adjuvant chemotherapy.
- <sup>j</sup> Excludes anthracyclines
- <sup>k</sup> Excludes methotrexate

Table 2. Multivariate analysis of treatment failure in 1188 women with metastatic breast cancer receiving autologous transplants between January 1, 1989, and January 31, 1995, at 63 centers in North America and reported to the ABMTR.

Covariates	RR	95% CI	P-value
<b>Age at transplant</b>			
≤ 45 years	1.00		---
> 45 years	1.17	(1.02, 1.33)	0.02
<b>Karnofsky score, pretransplant</b>			
90-100%	1.00		---
< 90%	1.27	(1.07, 1.51)	0.005
<b>Hormone receptor status</b>			
Positive	1.00		---
Negative	1.31	(1.15, 1.51)	0.0001 <sup>b</sup>
<b>Adjuvant chemotherapy and DFI</b>			
None given <sup>c</sup>	1.00		---
Metastatic disease at diagnosis	0.96	(0.78, 1.19)	0.71 <sup>b</sup>
Chemotherapy given and DFI ≤ 18 months <sup>c</sup>	1.99	(1.62, 2.43)	0.0001 <sup>b</sup>
Chemotherapy given and DFI > 18 months <sup>c</sup>	1.31	(1.10, 1.56)	0.002 <sup>b</sup>
<b>Sites of metastatic disease, pretransplant</b>			
Not liver or CNS, 1-2 sites <sup>d</sup>	1.00		---
CNS ± other	1.56	(0.99, 2.46)	0.05 <sup>b</sup>
Liver, 1-2 sites <sup>e</sup>	1.47	(1.20, 1.80)	0.0002 <sup>b</sup>
3+ sites <sup>f</sup>	1.32	(1.13, 1.54)	0.0005 <sup>b</sup>
<b>Chemotherapy sensitivity pretransplant</b>			
Complete remission	1.00		---
Partial remission	1.65	(1.36, 1.99)	0.0001 <sup>b</sup>
Resistant	1.87	(1.54, 2.27)	0.0001 <sup>b</sup>
Indeterminant / unknown	1.20	(0.97, 1.50)	0.10 <sup>b</sup>

Abbreviations: RR = relative risk; CI = confidence interval; DFI = disease-free interval; CNS = central nervous system

<sup>a</sup> Overall p-value for effect of the categorical covariate using the Wald test.

<sup>b</sup> P-value for pairwise comparisons of specific category with the reference (baseline) group

<sup>c</sup> Refers to women with Stage I-III disease at diagnosis, who subsequently developed metastases.

<sup>d</sup> Not liver or CNS (1-2 sites) includes: bone; bone marrow; soft tissue; lung; bone + lung; bone + soft tissue; lung + soft tissue.

<sup>e</sup> Liver (1-2 sites) includes: liver, bone + liver; lung + liver; liver + soft tissue

<sup>f</sup> 3+ sites includes: bone + lung + liver; bone + liver + soft tissue; bone + lung + soft tissue; lung + liver + soft tissue; 4+ sites; other viscera (excluding liver, lung and CNS)

Table 3. Effect of posttransplant hormonal therapy and radiation in 999 patients surviving 6 months after autotransplant for advanced breast cancer.

Covariate	N	RR	P
Hormone receptor status		-	0.0004
Negative	358	1.00	--
Positive-no hormone therapy <sup>a</sup>	517	0.87 (0.74, 1.01)	0.07
Positive-hormone therapy <sup>a</sup>	124	0.60 (0.47, 0.87)	0.0001
No planned posttransplant radiation	832	1.00	--
Planned posttransplant radiation	167	0.94 (0.77, 1.16)	0.59

Abbreviations: RR = relative risk

<sup>a</sup> Pairwise comparison p=0.003

Table 4. Factors associated with increased risk of progression or death in prior studies of women with advanced breast cancer treated with standard dose chemotherapy or autotransplant.

Chemotherapy Studies	Autotransplant studies	ABMTR multivariate analysis
Age < 45 yrs (22) Age < 50 yrs (20) Age > 50 yrs (24)	Age < 40 years (15)	Age > 45 years
ER-negative status (22,23)	ER-positive status (15)	Hormone receptor status-negative
DFI < 2 years (25)	DFI < 1 year (13) DFI < 2 years (15)	DFI ≤ 18 months if received adjuvant therapy
Adjuvant therapy (21,23) Prior radiation therapy (19) Failure of hormonal therapy (19) Delay of chemotherapy following oophorectomy (22)	Prior adjuvant therapy (13) Prior adriamycin therapy (16)	Adjuvant therapy
Extent of disease (19) Number of different sites >2 (20) Lung involvement (20) Liver involvement (20, 23) Visceral involvement (22) Soft tissue involvement (22)	Number of different sites > 1 (15) Number of different sites > 2 (8, 13) Liver involvement (8, 13) Soft tissue involvement (8, 13) Lung and/or liver metastases (16)	Number of different sites >2, if not liver or CNS Liver or CNS metastases
Poorer performance status (19)	-----	Karnofsky performance score < 90
-----	Not achieving prior CR (15)	PR or Resistant disease
-----	Early transplant after CR (30)	-----
-----	-----	No posttransplant hormonal therapy

Abbreviations: ER = estrogen receptor; DFI = disease-free interval; PR = partial response; CR = complete response

Appendix. Institutions reporting breast cancer cases to the ABMTR.

USA

Emory Clinic	Atlanta
Johns Hopkins Oncology Center	Baltimore
University of Maryland Cancer Center	Baltimore
Alta Bates Medical Center, Comprehensive Cancer Center	Berkeley
University of Alabama at Birmingham (UAB)	Birmingham
Dana-Farber Cancer Institute	Boston
Roswell Park Cancer Institute	Buffalo
University of North Carolina, Chapel Hill	Chapel Hill
Medical University of South Carolina	Charleston
St. Luke's Medical Center	Chicago
University of Chicago Medical Center	Chicago
The Jewish Hospital of Cincinnati	Cincinnati
University Hosp of Cleveland, Ireland Cancer Center	Cleveland
Baylor University Medical Center	Dallas
Miami Valley Hospital	Dayton
Presbyterian St. Lukes Hospital	Denver
Klabzuba Cancer Center	Fort Worth
University of Florida, Shands Hospital	Gainesville
Hackensack Medical Center	Hackensack
Baylor College of Medicine	Houston

~~CONFIDENTIAL~~

Appendix, continued.

Indiana University Medical Center & Outpatient Center	Indianapolis
Methodist Hospital of Indiana	Indianapolis
University of Kansas Medical Center	Kansas City
University of California, San Diego	La Jolla
Dartmouth-Hitchcock Medical Center	Lebanon
UCLA Center for Health Sciences	Los Angeles
University of Louisville	Louisville
University of Wisconsin Hospital & Clinics	Madison
Methodist Hospital Central	Memphis
Baptist Hospital of Miami	Miami
Medical College of Wisconsin	Milwaukee
St. Luke's Medical Center	Milwaukee
Abbott Northwestern Hospital	Minneapolis
University of Minnesota Hospitals and Clinics	Minneapolis
West Virginia University Hospitals	Morgantown
Vanderbilt University Medical Center	Nashville
Medical Center of Delaware	Newark
University of Oklahoma Health Sciences Center	Oklahoma
CityUniversity of Nebraska Medical Center	Omaha
Lutheran General Hospital	Park Ridge
University of Pittsburgh Medical Center	Pittsburgh

~~CONFIDENTIAL~~

Appendix, continued.

Cancer Center of Boston	Plymouth
Sutter Cancer Center	Sacramento
University of California, Davis Cancer Center	Sacramento
University of Utah Medical Center	Salt Lake City
University of Texas, Health Science Center at San Antonio	San Antonio
University of California, San Francisco	San Francisco
Louisiana State University Medical Center-Shreveport	Shreveport
Memorial Medical Center	Springfield
St. Louis University	St. Louis
Methodist Hospital & Park Nicollet Cancer Center	St. Louis Park
University Hospital-SUNY Health Sciences Center	Syracuse
H. Lee Moffitt Cancer Center	Tampa
St. Francis Hospital	Tulsa
Walter Reed Army Medical Center	Washington
St. Francis Hospital	Wichita
North Carolina Baptist Hospital/Bowman Gray School of Medicine	Winston-Salem

**CANADA**

Royal Victoria Hospital	Montreal
Sacre Coeur Hospital	Montreal
Northeastern Ontario Regional Cancer Center	Sudbury

~~CONFIDENTIAL~~

Appendix, continued.

**OTHER COUNTRIES**

Hospital de Clinicas  
Centro de Hematologia y Medicina Interna  
Petrov Research Institute of Oncology

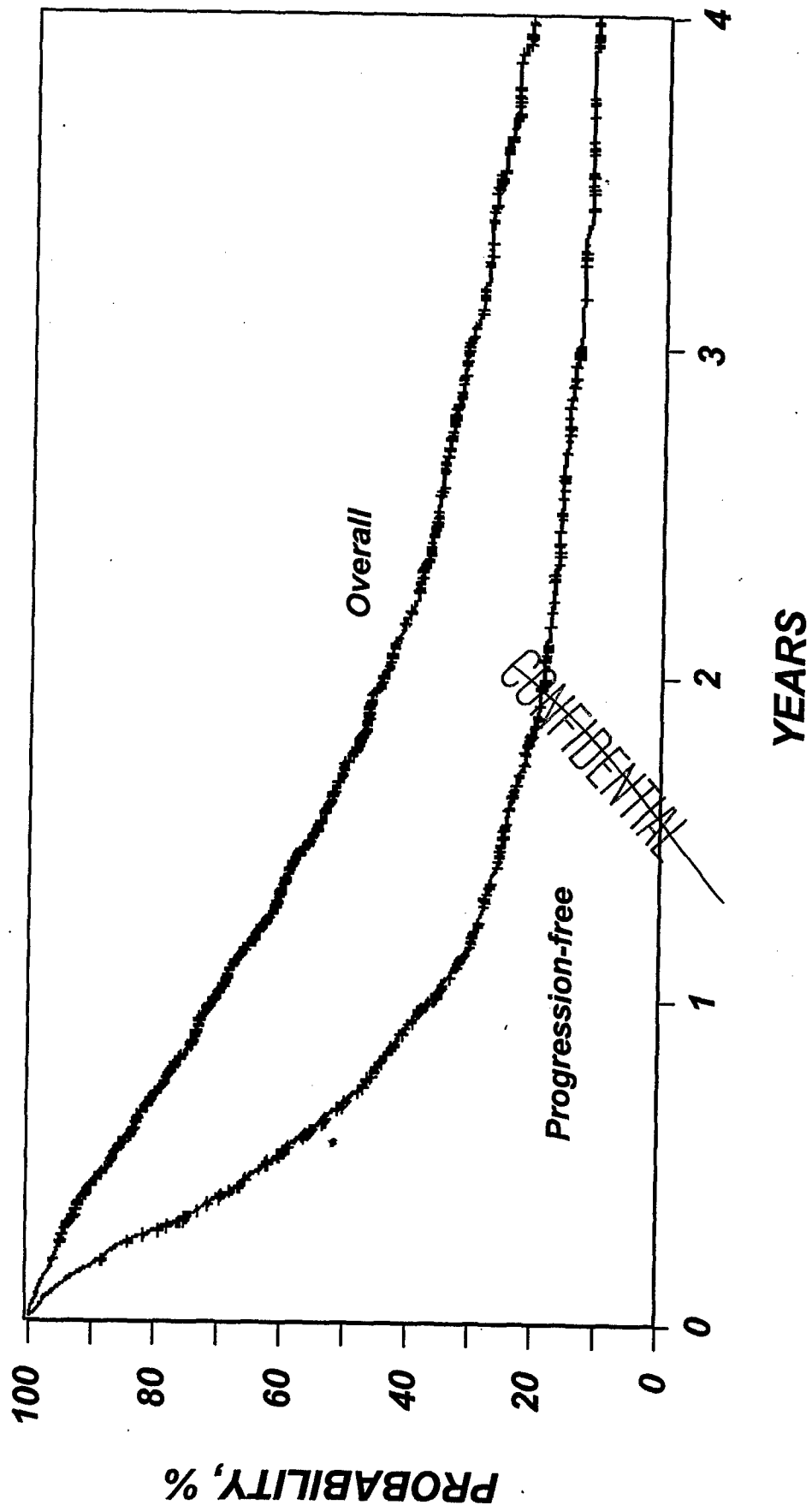
Curitiba, Brazil  
Puebla, Mexico  
St. Petersburg, Russia

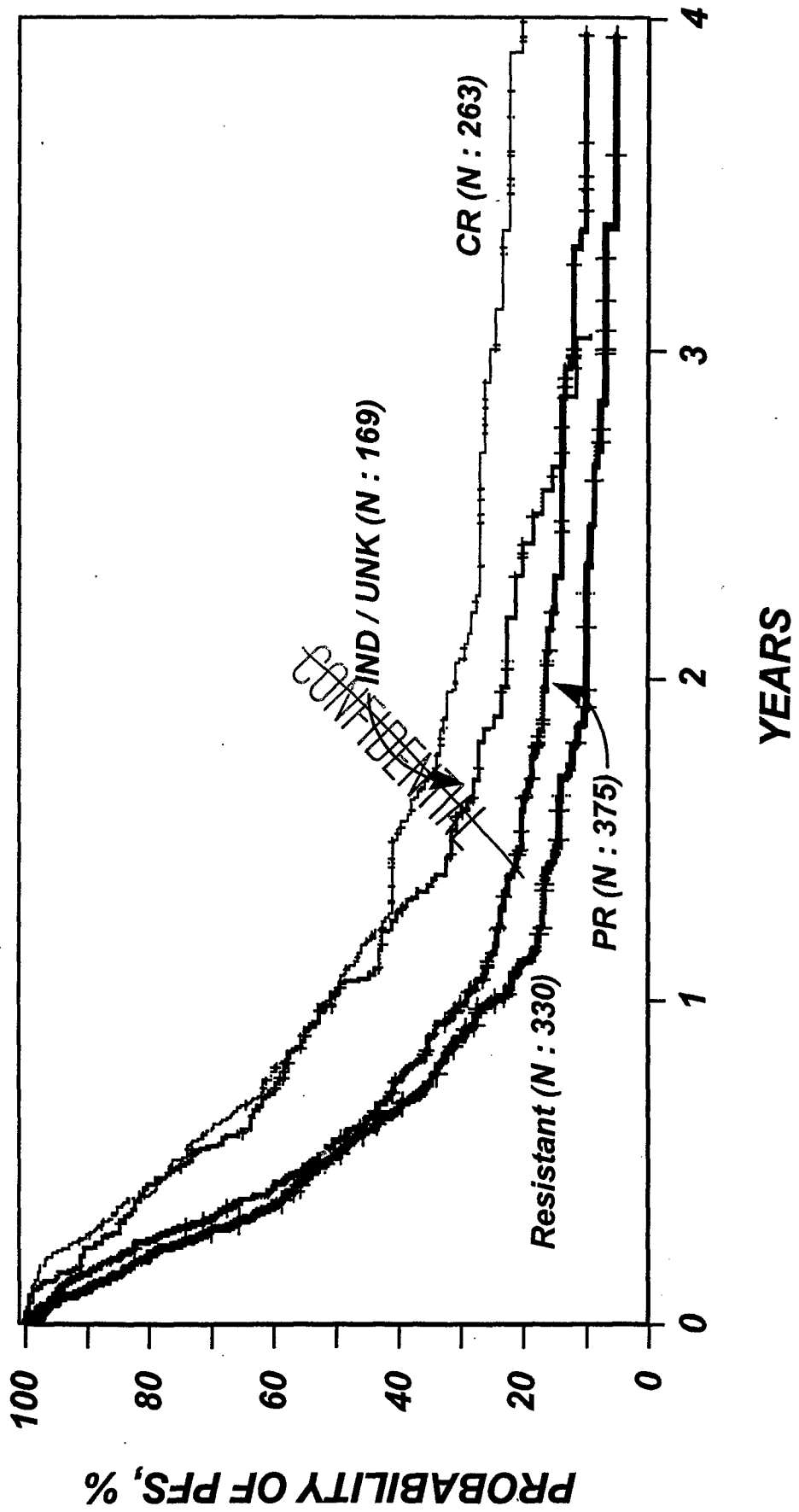
~~CONFIDENTIAL~~

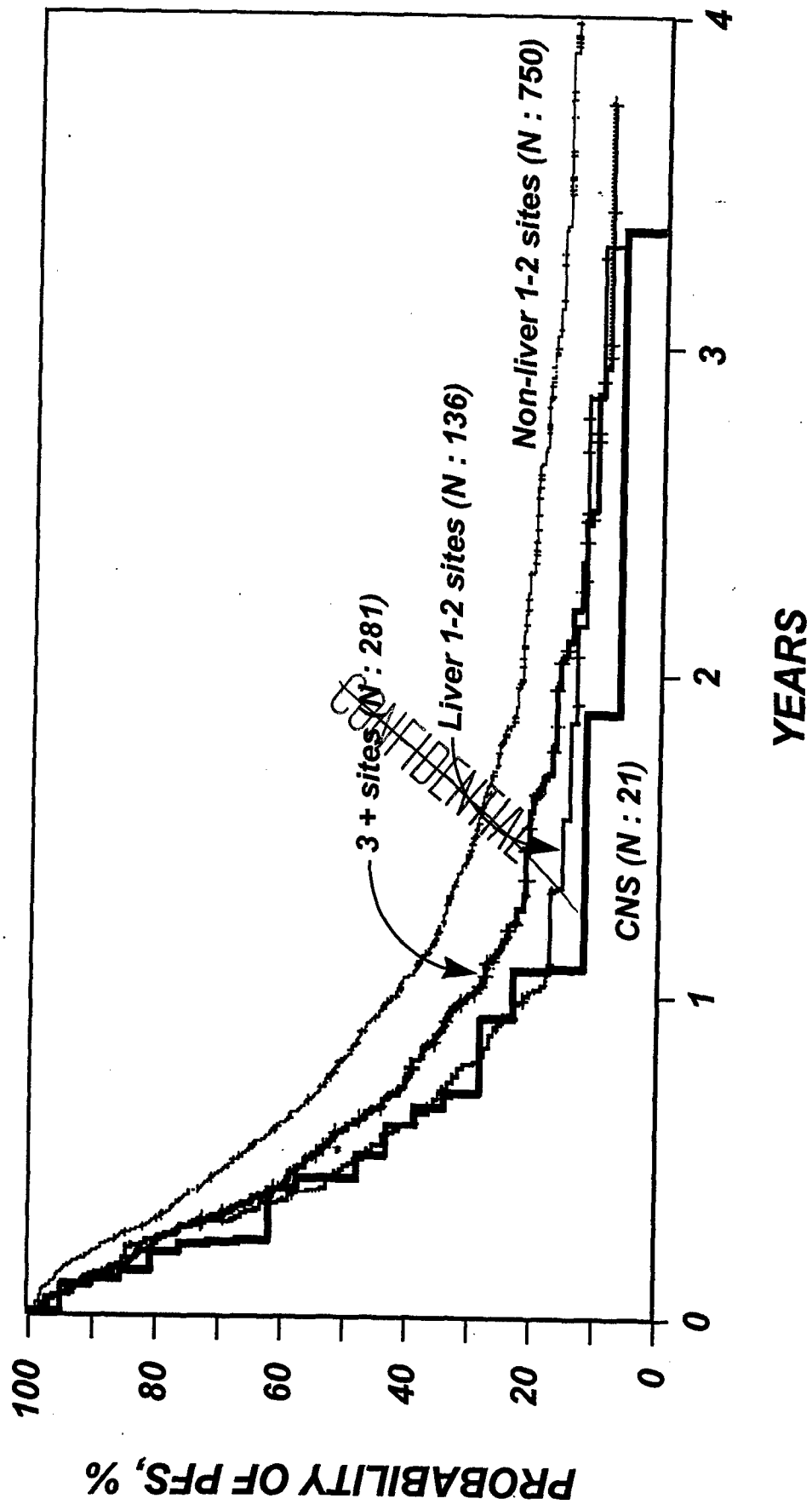


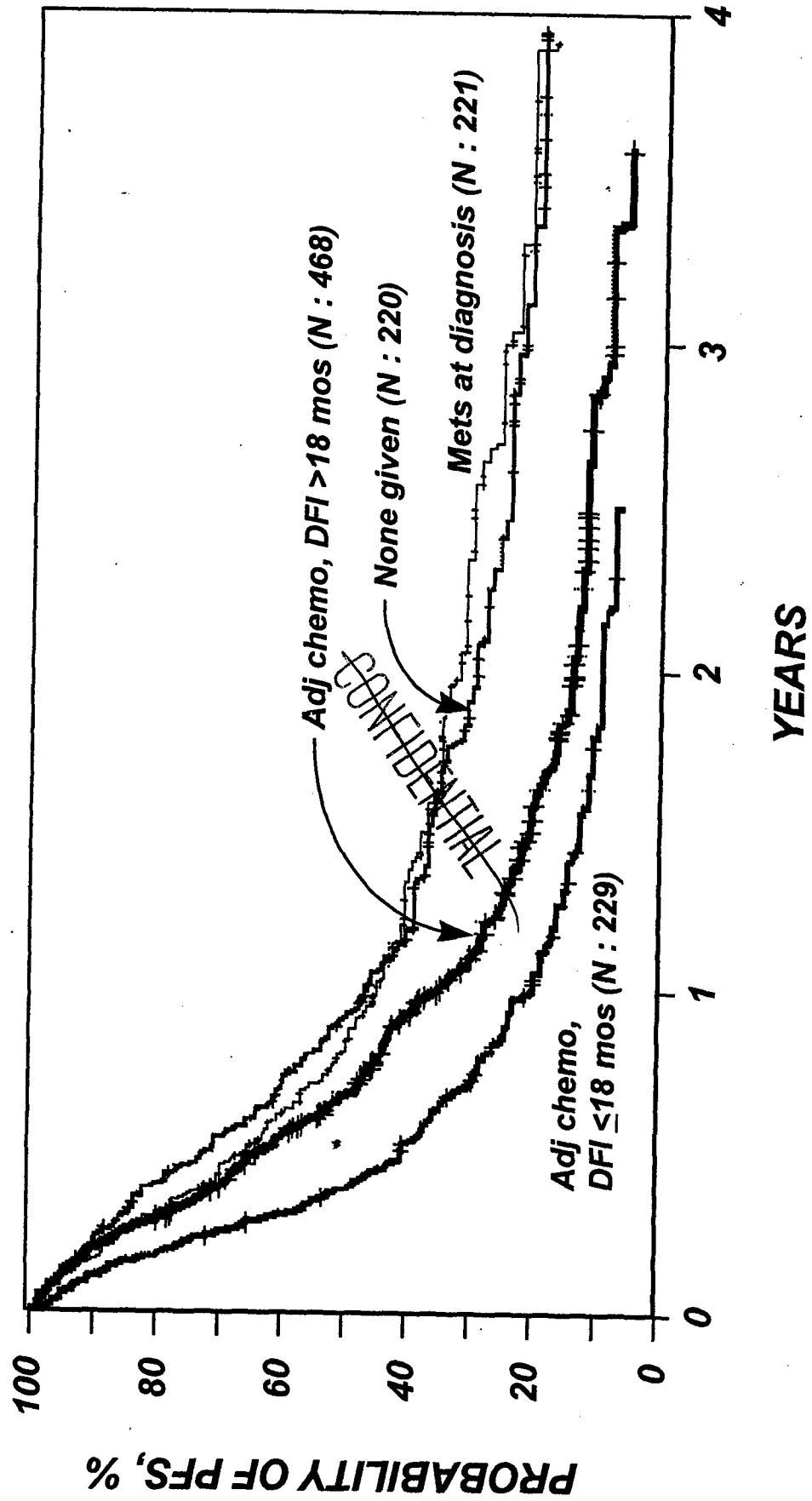
## LEGENDS FOR FIGURES

- Figure 1. Kaplan-Meier estimate of overall survival and progression-free survival following autotransplant for 1188 women with metastatic breast cancer transplanted at 63 centers reporting to the ABMTR, from 1989 to 1995.
- Figure 2. Kaplan-Meier estimates of progression-free survival by chemotherapy sensitivity pretransplant. CR = complete remission; PR = partial remission; IND/UNK = indeterminate/unknown.
- Figure 3. Kaplan-Meier estimates of progression-free survival women with central nervous system (CNS), liver metastases or any disease at 3 or more sites.
- Figure 4. Kaplan-Meier estimates of progression-free survival for women receiving no adjuvant chemotherapy (Adj chemo), receiving adjuvant chemotherapy with a disease-free interval (DFI)  $\leq$  18 months and with a DFI  $>$  18 months. Mets = metastases.









## Appendix 4.13

**BRS: Systemic**  
**Berry, Donald**

**1999 Annual Meeting of the American Society of  
Clinical Oncology**

**Presenting Author:** Donald A Berry  
**Institution:** Duke University, Durham, NC, 27708-0251.  
**Address:** 223 Old Chemistry Bldg, Box 90251, Durham, NC, 27708-0251  
**Phone:** 919-684-3063 **Fax:** 919-684-8594 **E-Mail:** db@stat.duke.edu

**Abstract Categories:** BRS. Systemic

**Format Preference:** Slide or Poster presentation **Awards:**

**Audio/Visual:** Yes

**Sponsor:** Mary M Horowitz **Sponsor Fax:** 414-456-6530

**CONVENTIONAL- VS HIGH-DOSE THERAPY FOR METASTATIC BREAST CANCER: COMPARISON OF CANCER AND LEUKEMIA GROUP B (CALGB) AND BLOOD AND MARROW TRANSPLANT REGISTRY (ABMTR) PATIENTS.** D A Berry, G Broadwater<sup>2</sup>, M C Perry<sup>2</sup>, J Aisner<sup>2</sup>, M Costanza<sup>2</sup>, H Parnes<sup>2</sup>, I C Henderson<sup>2</sup>, L Norton<sup>2</sup>, K Antman<sup>3,4</sup>, J P Klein<sup>4</sup> and M M Horowitz<sup>4</sup>. <sup>1</sup>Institute of Statistics and Decision Sciences, Duke University, Durham, NC; <sup>2</sup>Cancer and Leukemia Group B (CALGB), Chicago, IL; <sup>3</sup>Columbia University, New York, NY and <sup>4</sup>Blood and Marrow Transplant (ABMTR) Registry, Milwaukee, WI.

We compared survival of women with metastatic breast cancer registered on 4 CALGB conventional-dose chemotherapy trials versus women registered with the ABMTR. The initial data set included 1621 CALGB patients treated in 1980-92 and 1188 ABMTR patients treated in 1989-95. CALGB protocols were: CALGB 8081 (cyclophosphamide [Cy], doxorubicin, and fluorouracil [CAF] vs Tamoxifen +CAF, n=458), CALGB 8281 (CAF vs vinblastine, doxorubicin, thiotepa [T], and halotestin [VATH] followed by Cy, methotrexate, fluorouracil, vincristine, and prednisone [CMFVP] at failure vs VATH alternating with CMFVP, n=484), CALGB 8642 (CAF vs phase II agent followed by CAF, n=452), CALGB 9140 (CAF vs CAF+ Leucovorin, n=227); there were no significant differences in outcomes between study arms or trials. 51% of ABMTR cases received high-dose CyT ± other drugs; various other regimens were used. Survival did not differ across regimens. We excluded 196 women with missing prognostic factor data. To minimize selection biases we focused on women with chemotherapy-sensitive disease and not more than 60 y of age. The study sample included 1217 women: 657 from CALGB, 560 from ABMTR. To minimize time to treatment bias, we used left-truncation; to adjust for potentially confounding prognostic factor differences we used Cox regression. A left-truncated univariate model showed significant survival benefit for autotransplant (relative risk of death [RR] 0.86, p=0.011); however, a multivariate model including disease-free interval after primary treatment, performance score, number of metastases and ER status showed no significant difference with high- vs conventional-dose therapy (RR=0.91, p=0.19). We conclude that some of the encouraging results of high-dose therapy in breast cancer may be due to patient selection and that careful controlled comparisons in large groups of women are needed to evaluate relative efficacy of these approaches.

Table 2: Patient, disease and transplant characteristics of 689 high-risk primary breast cancer patients (excludes stage III inflammatory) reported to the ABMTR from 1989 to 1996 by 70 teams worldwide.

Variable	N (%)
Number of Patients, N evaluable	689
Stage, N evaluable	689
Stage II	387 (56%)
Stage III	302 (44%)
Number of Reporting Centers	70
Year of Transplant, N evaluable	689
1989-1990	15 (2%)
1991-1992	156 (22%)
1993-1994	288 (42%)
1995-1996	230 (33%)
Age at Transplant, N evaluable	680
Median (range), years	44 (24-65)
Performance score pretransplant, N evaluable	668
< 90	46 (7%)
90-100	622 (93%)
Pathological Tumor Size, in cm, N evaluable*	486
Median (range)	3.5 (<1-16)
≤ 2	135 (28%)
2 to 5	234 (48%)
> 5	117 (24%)
Number of Positive Axillary Nodes, N evaluable*	556
Median (range)	12 (0-46)
≤ 9	171 (31%)
> 9	385 (69%)

\* Excludes 86 patients receiving neoadjuvant chemotherapy

<b>Variable</b>	<b>N (%)</b>
Estrogen receptor status, N evaluable	661
Negative	231 (35%)
Borderline	22 (3%)
Positive	394 (60%)
None performed	14 (2%)
Adjuvant Therapy, N evaluable	658
CAF/FAC	443 (67%)
Other Anthracycline Regimens	151 (23%)
Other	64 (10%)
Surgery pretransplant, N evaluable	649
Mastectomy	558 (86%)
Lumpectomy	91 (14%)
Chemotherapy for initial management, N evaluable	676
Adjuvant	590
Stage II	362 (61%)
Stage III	228 (39%)
Neoadjuvant	86
Stage II	21 (24%)
Stage III	65 (76%)
Pretransplant hormonal therapy, N evaluable	650
Total receiving	75 (12%)
Estrogen Receptor positive	57/394 (14%)
Estrogen Receptor negative	11/231 (5%)
Estrogen Receptor borderline/not tested	3/22 (14%)

~~CONFIDENTIAL~~



<b>Variable</b>	<b>N (%)</b>
Radiation Treatment, N evaluable	681
Pretransplant	90 (13%)
Post transplant	392 (58%)
Pre and post transplant	11 (2%)
None	188 (28%)
Conditioning Regimen, N evaluable	688
CBP	57 (8%)
CT	277 (40%)
CTCb	140 (20%)
CTM	26 (4%)
ICbE	38 (5%)
Other	142 (21%)
Source of Graft, N evaluable	689
Bone Marrow	234 (34%)
PBSC	291 (42%)
Bone Marrow + PBSC	164 (24%)
Interval from Diagnosis to Transplant, N evaluable	685
Median (Range)	7 (1-18)
Treatment to enhance PBSC collection, N evaluable**	436
Growth Factor Only	291 (67%)
Growth Factor and Chemotherapy	140 (32%)
Growth Factor in First 7 Days, N evaluable	665
None	51 (8%)
G-CSF	417 (63%)
GM-CSF	116 (17%)
G- and GM-CSF	81 (12%)

~~CONFIDENTIAL~~

\*\*Excludes 231 patients receiving bone marrow alone.

Variable	N (%)
Tamoxifen Treatment Post Transplant, N evaluable	680
Total Receiving	275 (40%)
Estrogen receptor positive	229/394 (58%)
Estrogen receptor negative	27/231 (12%)
Estrogen receptor borderline/not tested	9/22 (40%)

PBSC = peripheral blood stem cells, C = cyclophosphamide, B = BCNU, P=cisplatin, T = thiotepa, Cb = carboplatin, M=mitoxantrone, I = ifosfamide, E = etposide

~~CONFIDENTIAL~~

~~CONFIDENTIAL~~

Table 3. Univariate analysis of survival and progressive-free survival (95% confidence interval) after autotransplant for high-risk primary breast cancer (excluding inflammatory) between 1989 and 1996.

Variable	N(%)	3yr Survival	P*	3yr DFS	P*	3yr TRM	P*
All Patients	689	72 (67-76)%	-	60 (56-64)%	-	5 (3-7)%	-
Disease status	689		0.94		0.72		0.79
Stage II	387 (56%)	72 (66-78)%		61 (55-67)%		4 (2-6)%	
Stage III	302 (44%)	72 (65-78)%		59 (52-66)%		6 (3-10)%	
Age at dx	680		0.85		0.18		0.02
≤ 45	389 (57%)	72 (66-77)%		63 (57-68)%		3 (1-5)%	
> 45	291 (43%)	73 (66-79)%		57 (49-64)%		8 (4-13)%	
Year of transplant	689		0.06		0.47		0.08
1989-1991	60 (9%)	62 (49-74)%		53 (40-66)%		0	
1992-1996	629 (91%)	73 (68-78)%		61 (56-66)%		5 (3,8)%	
Performance score	668		0.15		0.048		0.66
<90	46 (7%)	66 (48-82)%		51 (32-70)%		6 (0-22)%	
≥ 90	622 (93%)	72 (68-77)%		61 (56-66)%		5 (3-8)%	
Tumor size	496		0.35		0.34		0.06
≤ 2	138 (28%)	67 (57-76)%		57 (47-67)%		10 (4-17)%	
2 to 5	236 (48%)	76 (69-82)%		64 (57-72)%		3 (1-6)%	
> 5	122 (25%)	75 (65-83)%		65(54-75)%		4 (1-9)%	
Number of positive axillary nodes	568		0.07		0.15		0.24
≤ 9	173 (31%)	67 (57-75)%		59 (50-68)%		8 (3-15)%	
> 9	395 (69%)	76 (70-81)%		63 (57-69)%		4 (2-7)%	
ER status pretx	625		0.0001		0.0001		0.23
Negative	231 (37%)	61 (53-69)%		48 (40-56)%		7 (3-12)%	
Positive	394 (63%)	79 (74-83)%		67 (61-73)%		4 (2-7)%	
Surgery pretx	649		0.87		0.87		0.09
Mastectomy	558 (86%)	72 (67-76)%		61 (56-66)%		4 (2-7)%	
Lumpectomy	91 (14%)	71 (59-82)%		61 (48-73)%		10 (4-20)%	
Radiation therapy	681		0.0001		0.0001		0.03
Pretx	90 (13%)	69 (57-79)%		54 (42-66)%		8 (2-16)%	
Posttx	403 (59%)	80 (76-84)%		67 (62-73)%		3 (1-6)%	
None	188 (28%)	56 (47-66)%		46 (37-55)%		7 (3-14)%	
Adjuvant Therapy	677		0.0001		0.0001		0.59
CAF/FAC	443 (65%)	74 (69-79)%		63 (58-69)%		4 (2-6)%	
Other Anthracycline	172 (25%)	71 (62-80)%		57 (47-66)%		8 (3-15)%	
Other	62 (10%)	66 (50-80)%		51 (35-66)%		3 (3-9)%	
Graft Type	689		0.66		0.67		0.7
BM	234 (34%)	71 (64-77)%		61 (54-68)%		6 (3-10)%	
PBSC	291 (42%)	73 (65-80)%		61 (52-69)%		3 (1-7)%	
BM+PBSC	164 (24%)	72 (64-80)%		60 (51-68)%		5 (2-9)%	

Variable	N(%)	3yr Survival	3yr DFS	P*	3yr TRM	P*
Mobilization	418					
GF only	272 (65%)	67 (60-74)%	60 (52-67)%		5 (3-9)%	
GF and Chemo	146 (35%)	84 (75-91)%	59 (48-70)%		2 (0-6)%	
Conditioning Regimen	687					
CBP	57 (8%)	74 (61-85)%	69 (60-82)%		4 (0-12)%	
CT	277 (40%)	75 (69-81)%	63 (56-70)%		5 (2-9)%	
CTCb	140 (20%)	73 (61-83)%	55 (43-67)%		5 (1-13)%	
CTM	26 (4%)	85 (69-96)%	81 (64-93)%		4 (0-16)%	
ICE	46 (7%)	72 (57-84)%	57 (42-72)%		4 (0-12)%	
Other	141 (21%)	58 (47-69)%	48 (38-59)%		5 (2-11)%	
GF in first 7 days	662					
None	51 (8%)	66 (48-83)%	51 (34-68)%		0	
G	417 (63%)	74 (69-80)%	63 (57-69)%		6 (3-10)%	
GM	116 (18%)	77 (66-85)%	56 (45-66)%		2 (0-7)%	
G and GM	78 (12%)	64 (52-75)%	61 (49-72)%		7 (2-16)%	
Interval dx to tx	685					
≤ 9 months	539 (79%)	75 (71-80)%	65 (60-70)%		4 (2-6)%	
> 9 months	146 (21%)	58 (47-68)%	43 (33-53)%		11 (5-20)%	

\*P-value computed using the log-rank test.

Table 4: Variables tested in multivariate analysis

---

Stage at transplant (stage II, stage III)
Age at transplant (<45, ≥45)
Year of transplant (1989-1991, 1992-1996)
Performance score pretransplant (10 to 80, ≥ 90)
Pathological tumor size (≤ 2 cm, >2 and ≤ 5 cm, >5 cm)
Number of positive axillary nodes (≤9, >9)
Estrogen receptor status/tamoxifen posttransplant (ER positive with tamoxifen, ER positive without tamoxifen, ER negative with or without tamoxifen)
Surgery pretransplant (mastectomy, lumpectomy, missing)
Neoadjuvant treatment (yes, no)
Hormone treatment pretransplant (yes, no)
Radiation treatment (none, radiation pretransplant, radiation posttransplant)
Adjuvant therapy (FAC, other anthrocycline, other)
Conditioning Regimen (CBP, CT, CTCb, CTM, ICE, other)
Months from diagnosis to transplant (≤9, >9)
Graft type (bone marrow, peripheral blood, bone marrow and peripheral blood)
Growth factors - started up to 7 days post transplant (None, G only, GM only, G and GM)
Treatment to enhance PBSC collection (growth factors only, growth factors and chemo)

---

Table 5: Multivariate analysis of survival for recipients of autologous transplants for high risk primary breast cancer (excludes stage III inflammatory) reported to the ABMTR by 70 centers worldwide.

Covariate	N (%)	RR	95% CI	P value
Estrogen Receptor	669			0.0001
Status/Tamoxifen Posttransplant				
ER negative with or without tamoxifen posttransplant	222 (32%)	1.00	---	---
ER positive with tamoxifen posttransplant	227 (34%)	0.42	(0.27,0.63)	0.0001
ER positive without tamoxifen posttransplant	159 (24%)	0.72	(0.48,1.07)	0.11
ER unknown with/without tamoxifen posttransplant	61 (10%)	1.15	(0.67, 1.98)	0.60
Radiation Treatment	669			0.0005
None	183 (27%)	1.00	---	---
Pretransplant	88 (13%)	0.65	(0.40,1.04)	0.08
Posttransplant				
First 7 months	92 (14%)	0.14	(0.005, 0.37)	0.0001
>7 months posttransplant	306 (46%)	0.80	(0.53, 1.21)	0.20
Time From Diagnosis to Transplant	669			0.005
> 9 months	145 (22%)	1.00	---	---
≤ 9 months	524 (78%)	0.57	(0.38,0.84)	0.005

**AUTOTRANSPLANTS IN MEN WITH BREAST CANCER**

Philip L. McCarthy, Jr., MD; David D. Hurd, MD; Philip A. Rowlings, MD, MS; Sandra C. Murphy, MS; Karen H. Antman, MD; James O. Armitage, MD; Emanuel Cirenza, MD; Michael Crump, MD, James Doroshower, MD, Cesar O. Freytes, MD; Robert Peter Gale, MD, PhD; Leonard A. Kalman, MD; Hillard M. Lazarus, MD; William P. Vaughan, MD; B. Barry Weinberger, DO, MPH; Michael C. Wiemann, MD; and Mary M. Horowitz, MD, MS.

From the Breast Cancer Working Committee of the Autologous Blood and Marrow Transplant Registry, Health Policy Institute, Medical College of Wisconsin, Milwaukee, Wisconsin, USA (PAR, SCM, MMH); and Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York, USA (PLM); Comprehensive Cancer Center, Bowman Gray School of Medicine, Winston-Salem, North Carolina, USA (DDH); Division of Medical Oncology, Columbia University, New York, New York, USA (KHA); Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA (JOA); Division of Hematology, Albany Medical Center, Albany, New York, USA (EC); Adult Bone Marrow Transplant Program, University of Texas Health Science Center, San Antonio, Texas, USA (COF); Division of Bone Marrow and Stem Cell Transplantation, Salick Health Care, Inc., Los Angeles, California, USA (RPG); Autologous Bone Marrow Transplant Program, Baptist Hospital of Miami, Miami, Florida, USA (LAK); Autologous Bone Marrow Transplant Program, The Toronto Hospital, General Division, Toronto, Ontario, Canada (MC); Department of Medicine, Ireland Cancer Center, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio, USA (HML); Bone Marrow Transplant Program, University of Alabama, Birmingham, Alabama, USA (WPV);

~~CONFIDENTIAL~~

Louisiana State Medical Center, Shreveport, Louisiana, USA (BW); and St. Vincent Hospital and Health Care Center, Indianapolis, Indiana, USA (MCW).

Supported by the Ontario Cancer Research and Treatment Foundation; Public Health Service Grants No. P01-CA40053 and U24-CA76518 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung and Blood Institute of the U.S. Department of Health and Human Services; Grant No. DAMD17-95-I-5002 from the Department of the U.S. Army Medical Research and Development Command; and by grants from Alpha Therapeutic Corporation; Amgen Inc.; Anonymous; Baxter Healthcare Corporation; Bayer Corporation; Berlex Laboratories; BioWhittaker, Inc.; Blue Cross and Blue Shield Association; Bristol-Myers Squibb Company; CellPro, Inc.; Cell Therapeutics, Inc.; Centeon; Center for Advanced Studies in Leukemia; Chimeric Therapies, Inc.; Chiron Therapeutics; COBE BCT, Inc.; The Eppley Foundation for Research; Genentech, Inc.; Human Genome Sciences; ICN Pharmaceuticals; Immunex Corporation; The Kettering Family Foundation; Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation; MGI Pharma, Inc.; Milstein Family Foundation; Milwaukee Foundation/Elsa Schoeneich Research Fund; NeXstar Pharmaceuticals, Inc.; Novartis Pharmaceuticals; Orphan Medical; Ortho Biotech, Inc.; Pharmacia and Upjohn; Pfizer, Inc.; Principal Mutual Insurance Company; Roche Laboratories; SangStat Medical Corporation; Schering Oncology; Searle; SmithKline Beecham Pharmaceutical; SyStemix; and United Resource Networks.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.



Address correspondence and reprint requests to: Philip L. McCarthy, Jr., MD, Department of  
Medicine, Roswell Park Cancer Institute, 666 Elm & Carlton Sts., Buffalo, NY, 14263, USA.  
Telephone: 716-845-8412; Fax: 716-845-3423.

Running Head: Autotransplants for male breast cancer

## ABSTRACT

Purpose: To determine the outcome of high-dose therapy with autologous hematopoietic stem cell support (autotransplants) in men with breast cancer.

Patients and Methods: We studied 13 men receiving autotransplants for breast cancer and reported to the Autologous Blood & Marrow Transplant Registry (ABMTR) by 10 centers. Six men had Stage 2 breast cancer, four had Stage 3, and three had metastatic breast cancer. Of twelve tumors tested, all were estrogen receptor positive. Median age at transplant was 50 years. The most common conditioning regimen was cyclophosphamide, thiotepa and carboplatin (n=5); the remaining eight men received other alkylator-based regimens. Three men received bone marrow, eight received blood stem cells, and two received both for hematopoietic support.

Results: All patients had hematopoietic recovery. There were no unexpected regimen-related toxicities. Of ten men receiving autotransplants as adjuvant therapy, three relapsed three, five and 50 months posttransplant and died 16, 19 and 67 months posttransplant. Seven of ten are disease-free with median follow-up of 23 months (range, 6-50 months). Of three men treated for metastatic breast cancer, one had progressive disease and two recurrent disease at six, seven and 16 months posttransplant.

Conclusions: Results of autotransplants for male breast cancer appear similar to those reported for women receiving autotransplants for breast cancer.

## INTRODUCTION

Male breast cancer accounts for fewer than 1% of all breast cancers. The annual incidence is <1 per 100,000 males (1,2). Stage at diagnosis is generally more advanced than in women, possibly a result of delays in diagnosis. Anatomic factors may also contribute (3). The median age of men with breast cancer is five to ten years older than women with breast cancer (1-7). While, 64% of premenopausal and 75% of post-menopausal women have estrogen receptor (ER) positive cancers and 58% and 53%, respectively, have progesterone receptor (PR) positive tumors, according to a large study by Clark and colleagues (8), 80-90% of men have ER and PR positive breast cancer (1-7). Recent advances in the molecular biology of breast cancer have allowed detection of differences in the BRCA1 and BRCA2 mutations in hereditary and spontaneously occurring female and male breast cancers (reviewed in 9,10).

The standard therapy of breast cancer in men is similar to treatment in women, including surgery, radiation, hormone therapy and chemotherapy (1-7). Some investigators report outcomes in men to be the same as in women, when patients are matched for histopathology, receptor state and disease stage (3-6). Others suggest that men have poorer outcomes than women despite lower histologic grade, high ER content and small size (6).

Increasing numbers of women now receive high-dose chemotherapy with autologous hematopoietic stem cell support (autotransplant) for both metastatic and high-risk Stage 2/3 breast cancer (11). We studied 13 men receiving high-dose chemotherapy with an autotransplant and reported to the Autologous Blood and Marrow Transplant Registry (ABMTR).

## METHODS

Thirteen men were identified among 3,254 autotransplants for breast cancer reported to the ABMTR between January, 1989 and January, 1996 by 107 centers. Detailed patient-, disease-, treatment- and outcome-related data were obtained on standard ABMTR Report Forms.

The ABMTR is a voluntary working group of more than 120 transplant centers primarily in North and South America that contribute detailed data on their autologous blood and bone marrow transplants to the Statistical Center at the Medical College of Wisconsin. Participants are required to report all consecutive autotransplants; compliance is monitored by on-site audits. The ABMTR database includes data on about 50% of the autotransplants done in North and South America since 1989. Patients are followed longitudinally. Computerized error checks, physician review of submitted data, and on-site audits of participating centers ensure data quality.

## RESULTS

Thirteen subjects were treated at eleven centers. Table 1 lists features at diagnosis. Median age was 49 years (range, 32-60 years). Of twelve cancers tested, twelve were ER positive and ten were PR positive. Twelve men had a mastectomy. One received pre-surgery chemotherapy. Ten men received autotransplants as adjuvant treatment, six for Stage 2 disease (all with greater than ten positive ipsilateral axillary lymph nodes) and four for Stage 3 disease (one with inflammatory breast cancer). All had received prior standard-dose adjuvant chemotherapy with an anthracycline-containing regimen. Three men had autotransplants for metastatic disease. One presented with Stage 4 disease; two developed metastases after presenting with Stage 1 and Stage 2 disease. All three men with metastatic disease had received

chemotherapy treatment for their metastases with an anthracycline-containing regimen. One had a complete response, one a partial response and one stable disease prior to autotransplant.

Twelve of 13 men had Karnofsky performance scores of 90% or 100% at the time of autotransplant. One patient with metastatic disease had a Karnofsky score of 80%. The one patient receiving two autotransplants had a Karnofsky score of 70% prior to the second transplant. Median interval from diagnosis to autotransplant was six months (range, 4-9 months) for men with stage 2 or 3 disease and 12, 31, and 32 months for the three with metastatic disease.

Table 1 also lists types of graft, mobilizing agents, and high-dose therapy regimens. One patient (#13) received a planned second autotransplant. Mobilized peripheral blood (n=9), bone marrow (n=3) or both (n=2) were used for hematopoietic stem cell support. Five peripheral blood collections were mobilized with hematopoietic growth factors alone and six with growth factors and chemotherapy. High-dose therapy regimens consisted primarily of alkylating drugs. The most common regimen was cyclophosphamide, thiotepa and carboplatin (n=5). Twelve of 13 men received hematopoietic growth factors after graft infusion. Nine of the ten men with Stage 2 or 3 disease received primary chest wall radiation, two before, and seven after autotransplant. Six of ten received hormonal therapy (tamoxifen) after autotransplant. One of the men with metastatic disease received local radiation therapy to the chest wall after autotransplant.

Median day to absolute neutrophil count  $>1.0 \times 10^9/L$  was 12 days (range, 8-22 days). Median day to platelet count  $>25 \times 10^9/L$  was 14 days (range, 6-20 days). In three autotransplants, the exact day of achieving absolute neutrophil count  $>1.0 \text{ cells} \times 10^9/L$  was not reported and in four, the day to platelet count  $>25 \times 10^9/L$  was not available. However, all patients had evidence of hematopoietic recovery and became transfusion-independent. No

patient developed myelodysplasia or other bone marrow disorder. No grade 4 (World Health Organization) non-hematologic toxicities were reported.

Table 2 lists patient outcomes. Seven of ten men receiving autotransplants as adjuvant therapy are disease-free with median follow-up of 23 months (range, 6-50 months). Three men relapsed at three, five and 50 months posttransplant and subsequently died 16, 19 and 67 months posttransplant. All three men treated for metastatic breast cancer had evidence of progressive or recurrent disease after autotransplant. The patient who achieved a complete response to standard-dose chemotherapy received two autotransplants and relapsed five months after his second autotransplant. The patient transplanted after a partial response to standard-dose chemotherapy failed to achieve a complete response and progressed seven months posttransplant. The patient transplanted with stable disease achieved a complete response after autotransplant but relapsed 16 months later. Two subsequently died 12 and 23 months posttransplant. One is alive with progressive breast cancer 27 months posttransplant.

## DISCUSSION

This ABMTR report is the only study of men receiving autotransplants for breast cancer. The treatment was well tolerated with no regimen-related deaths and no unexpected non-hematologic toxicities. The toxicity appears equivalent to previously published reports in women receiving autotransplants for breast cancer (11-14).

Although the number of subjects is small, the efficacy of autotransplant in these 13 men with high-risk breast cancer appear similar to results reported in women (11,12). Outcomes of the patients with metastatic disease were disappointing, however only three patients were available for analysis. Seven of 10 men receiving autotransplants as adjuvant therapy are alive

and disease-free. These results are encouraging when compared to historic results of treatment with standard chemo-, radiation and hormonal therapy for patients with locally-advanced disease (1-7). However, evaluation of more cases and longer follow-up will be necessary to determine the incidence of late recurrence and possibility for cure in this population. The relative efficacy of standard and high-dose chemotherapy in men with breast cancer is probably not evaluable given the rarity of this disease. However, these data suggest that indications for high-dose therapy developed in the ongoing randomized studies in women will be applicable to men. Additionally, it seems reasonable to recommend inclusion of men in randomized studies that examine the role of autotransplant for breast cancer.

## REFERENCES

1. Williams WL Jr, Powers M, Wagman LD. Cancer of the male breast: a review. *J Natl Med Assoc* 1996; **88**: 439-443.
2. Moore MP. Special therapeutic problems: male breast cancer. In: Harris JR, Lippman ME, Morrow M, Hellman S (eds.). *Diseases of the Breast*. Lippincott-Raven: Philadelphia, 1996, pp 859-863.
3. Willsher PC, Leach IH, Ellis IO *et al*. A comparison outcome of male breast cancer with female breast cancer. *Am J Surg* 1997; **173**: 185-188.
4. Cutuli B, Lacroze M, Dilhuydy JM *et al*. Male breast cancer: results of the treatments and prognostic factors in 397 cases. *Eur J Cancer* 1995; **31A**: 1960-1964.
5. Donegan WL, Redlich PN. Breast cancer in men. *Surg Clin N Amer* 1996; **76**: 434-463.
6. Borgen PI, Senie RT, McKinnon WM, Rosen PP. Carcinoma of the breast: analysis of prognosis compared with matched female patients. *Ann Surg Oncol* 1997; **4**: 385-388.
7. Joshi MG, Lee AK, Loda M *et al*. Male breast carcinoma: an evaluation of prognostic factors contributing to a poorer outcome. *Cancer* 1996; **77**: 490-498.
8. Clark GM, Sledge GW Jr, Osborne CK, McGuire W. Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. *J Clin Oncol* 1987; **5**: 55-61.
9. Stratton MR, Wooster R. Hereditary predisposition to breast cancer. *Curr Opin Genet Dev* 1996; **6**: 93-97.
10. Blackwood MA, Weber BL. Recent advances in breast cancer biology. *Curr Opin Oncol* 1996; **8**: 449-454.



11. Antman KH, Rowlings PA, Vaughan WP *et al.* High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in North America. *J Clin Oncol* 1997; **15**: 1870-1879.
12. Peters WP, Ross M, Vredenburgh JJ *et al.* High-dose chemotherapy and autologous bone marrow support as consolidation after standard dose adjuvant chemotherapy for high-risk primary breast cancer. *J Clin Oncol* 1993; **11**: 1132-1143.
13. Holland HK, Dix SP, Geller RB *et al.* Minimal toxicity and mortality in high-risk breast cancer patients receiving high-dose cyclophosphamide, thiotepa, and carboplatin plus autologous marrow/stem-cell transplantation and comprehensive supportive care. *J Clin Oncol* 1996; **14**: 1156-1164.
14. Tomas JF, Perez-Carrion R, Escudero A *et al.* Results of a pilot study of 40 patients using high-dose therapy with hematopoietic rescue after standard-dose adjuvant therapy for high-risk breast cancer. *Bone Marrow Transplant* 1997; **19**: 331-336.

Patient Number	Age at Diagnosis	Disease Stage at Diagnosis	ER/PR Status	Number Positive LNs <sup>3</sup>	Reason for Transplant	Mobilizing Agents	Stem Cell Source	Conditioning Regimen	Posttransplant HGF
1	49	2	+/+	15/33	Adj	C,G	B	CyTCb	G
2	51	3, Inf	+/+	2/14	Adj	G	B	CyTCb	G
3	48	2	+/+	19/23	Adj	G	B	CyTCb	G
4	50	2	+/+	17/24	Adj	None	BM	CyT	G
5	43	2 <sup>2</sup>	NT/NT	11/17	Adj	C,G	B	TCb	GM
6	53	2	+/-	21/28	Adj	C,G	B	TaCbT	G/Epo
7	48	2	+/+	13/20	Adj	C,G	Both	CyBP	G
8	60	3	+/+	9/15	Adj	G	Both	CyTCb	G
9	48	3	+/+	3/22	Adj	C,G, GM	B	CyCb	None
10	53	3	+/+	14/16	Adj	None	BM	ACyE	None
11 <sup>1</sup>	37	4	+/+	Not done	Met	None	BM	CyEI	GM
12	49	1	+/+	0/6	Met	G	B	CyTCb	G
13	32	2	+/+	1/17	Met	C,G	B	MeIT	G

**Abbreviations:** Inf = inflammatory; ER = estrogen receptor; PR = progesterone receptor; NT=not tested; LNs = lymph nodes; Adj = adjuvant; Met = metastatic; C = chemotherapy; G = granulocyte colony stimulating factor; GM = granulocyte macrophage colony stimulating factor; B = blood; BM = bone marrow; Cy = cyclophosphamide; T = thiotepa; Cb = carboplatin; Ta = taxol; B = carmustine; P = cisplatinum; A = adriamycin; E = etoposide; I = ifosfamide; Mel = melphalan; HGF = hematopoietic growth factor; Epo = erythropoietin.

<sup>1</sup> All patients had mastectomies except for this patient who had an excision.

<sup>2</sup> Probably stage 2; tumor size not available.

<sup>3</sup> Lymph nodes at ipsilateral axillary dissection.

Table 2. Patient outcome.

Patient Number	DFI, mos	Relapse	Survival, mos	Alive
1	48	No	48	Yes
2	20	No	20	Yes
3	18	No	18	Yes
4	3	Yes	16	No
5	32	No	32	Yes
6	5	Yes	19	No
7	37	No	37	Yes
8	28	No	28	Yes
9	18	No	18	Yes
10	50	Yes	67	No
11	16	Yes	23	No
12	NA	Yes	12	No
13	6	Yes	27	Yes

Abbreviations: DFI = disease-free interval; NA = not applicable.

period, one sample has been used for a child with thalassemia who now has no evidence of thalassemia. Since all children with sickle cell anemia and thalassemia are diagnosed at birth, TX can be considered before patients become CMV positive, iron overloaded or alloimmunized. The availability of our national resource offers standardized procedures for collection, transportation, storage and testing of UCB units as well as a resource to evaluate the role of UCB TX for patients with hemoglobinopathies. The absence of CMV, the ability to consider a TX without a complete HLA match in a young child, and the successful results of TX using UCB provide strong support for the recommendation that UCB be collected and cryopreserved in all families who have a child with a hemoglobinopathy. A national resource will provide an effective means to accomplish this goal and to collect information regarding efficacy of UCB-TX for patients with hemoglobinopathies. We conclude from our preliminary results that collection of UCB be encouraged in families that have a child with sickle cell anemia or thalassemia.

Abstract# 550

Poster Board#/Session: 550-I

**TRANSPLANTABILITY AND THERAPEUTIC EFFECTS OF BONE MARROW-DERIVED MESENCHYMAL CELLS IN CHILDREN WITH OSTEOGENESIS IMPERFECTA.** E.M. Horwitz, D.J. Prockop\*, W.W. Koo\*, L.A. Fitzpatrick\*, P. Gordon\*, M. Neel\*, R. Pyeritz\*, P. Orchard, M.K. Brenner. *St. Jude Children's Research Hospital, Allegheny University of the Health Sciences, Wayne State University, Mayo Clinic, and University of Minnesota, Memphis, Philadelphia, Detroit, Rochester, Pittsburgh, and Minneapolis, USA.*

Bone marrow stromal cells are mesenchymal progenitor cells that have been shown to differentiate to bone and muscle in vitro and in vivo in murine model systems. In principle, transplantation of these marrow derived mesenchymal progenitor cells would attenuate or possibly correct genetic disorders of bone, muscle, and cartilage in humans, however, clinical data to support this concept is lacking. We present data demonstrating marrow derived mesenchymal cell engraftment in humans and correlate this with clinical benefit. This report describes the results of allogeneic bone marrow transplantation in three children with severe osteogenesis imperfecta, a genetic disorder in which osteoblasts produce defective type I collagen, leading to osteopenia, multiple fractures, severe bony deformities and markedly shortened stature. Donor osteoblast engraftment was documented in cortical bone by biopsy at 1.5-2.0%, even though donor mesenchymal cells remained absent in the adherent fraction of recipient marrow aspirate. Three months later, representative specimens of trabecular bone showed histologic changes indicative of new dense bone formation. All patients had increased total body bone mineral content ranging from 21 to 29 grams (median, 28 grams) as compared with predicted values of 0 to 4 grams (median, 0 grams) for healthy children with similar weights. These improvements were associated with marked increases in growth velocity, up to the median for normal children in two cases and significantly reduced frequencies of bone fracture, up to 80% reduction. Our results demonstrate that marrow derived mesenchymal cells are transplantable and engraft in the osteogenic environment and confirm that these cells do not contribute to the recipient hematopoietic microenvironment. We conclude that allogeneic bone marrow transplantation can lead to engraftment of functional mesenchymal progenitor cells indicating the feasibility of this approach in the treatment of osteogenesis imperfecta and perhaps other mesenchymal stem cell disorders.

Abstract# 551

Poster Board#/Session: 551-I

**ANALYSIS OF SHORT-TERM COSTS OF ALLOGENEIC TRANSPLANTATION: RESULTS FROM THE INTERNATIONAL BLOOD AND MARROW TRANSPLANT REGISTRY/NORTHWESTERN UNIVERSITY ECONOMIC DATA BASE PROJECT.** C.L. Bennett, T.M. Waters\*, T.J. Stinson\*, O. Almagor\*, K.A. Sobocinski\*, J.P. Klein\*, P.A. Rowlings, M. Horowitz. *Northwestern University and VA Chicago Health Care System, Chicago IL; ABMTR/IBMTR, Medical College of Wisconsin, Milwaukee WI, USA.*

Allogeneic peripheral blood stem cell transplantation is an emerging technology, accounting for 22% of the 1997 allotransplants reported to the IBMTR. This study compared costs for patients with hematologic malignancies who received high dose therapy with standard allogeneic bone marrow (alloBMT) versus the new technology, allogeneic peripheral blood stem cell transplantation (alloPBSCT). Utilization and cost data were obtained for 72 patients with acute leukemia, 70 patients with CML, and 26 patients with non-Hodgkin's lymphomas who received care at 4 transplant centers in the U.S., from the time of mobilization through 100 days post transplant (exclusive of the costs of donor searches). Corresponding clinical data were obtained from the IBMTR. Hospital charges were converted to costs using department-specific cost to charge ratios and clinical data were merged with cost data. Median total costs were evaluated by disease and transplant source. For patients undergoing HLA-matched sibling alloPBSCT, median 100-day cost savings associated with the use of peripheral stem cells in comparison to bone marrow were 60% for AML/ALL (\$62,654 versus \$140,850,  $p < 0.01$ ), and 30% for patients with CML (\$70,678 versus \$98,853,  $p < 0.01$ ), or NHL (\$69,379 versus \$106,420,  $p < 0.05$ ). From 33% to 40% of the total transplant costs were for inpatient room care for patients with leukemia. Room costs accounted for 33% of the total costs for alloPBSCT NHL patients, and 22% of the total costs for alloBMT NHL patients. Pharmaceuticals were also costly, accounting for 25% to 33% of the total transplant costs for patients with AML/ALL. For NHL, pharmaceuticals were the single largest expenditure,

accounting for 40% of the total costs for alloBMT and >50% for alloPBSCT. Laboratory and blood bank costs each accounted for 6% to 14% of the total costs for leukemia and lymphoma patients. This study from four large transplant centers provides preliminary evidence of 30% to 60% cost savings in the first 100 days with alloPBSCT. Longer term cost assessments are needed, particularly related to chronic graft versus host disease.

Abstrac

NON-M  
CELL  
TRANS  
Clave\*,  
Transpl  
Nationa

Session: 552-I

OOD STEM  
S REDUCES  
Bahceci\*, E.  
Bone Marrow  
lood Institute,

## Appendix 4.16

The procedure applicable in older adults with hematologic malignancies and as an experimental treatment to induce graft-versus-tumor effects in cancer patients. Between 11/97-8/98 we treated 11 patients with fludarabine 25 mg/m<sup>2</sup> × 5 days and cyclophosphamide 60 mg/kg × 2 days followed by PBSCT from a G-CSF stimulated HLA matched (n = 10), or one HLA-A locus mismatched sibling donor (n = 1). The mismatched patient received additional ATG. Median transplant dose was 8 × 10<sup>6</sup> CD34+ and 2.4 × 10<sup>8</sup> CD3+ cells/kg. Cyclosporine (CSA) was given until day 30 then tapered to induce a graft-versus-malignancy (GMV) effect. Severe mucositis and VOD did not occur. Hematologic nadirs were brief and recovery was rapid, with a median time to platelets ≥20,000 of 6 days (range 0-15) and neutrophils ≥500 of 11 days (range 9-15 days). Transfusion requirements were low (median: 1 red cell and 1 platelet transfusion/transplant). Median hospital stay post transplant was 13 days (range 10-23). At the time of neutrophil recovery, minisatellite chimerism analysis showed donor engraftment in all patients, 10 with mixed chimerism and one 100% donor in myeloid and lymphoid lineages. Of 9 patients evaluable after day 45, 8 progressed to complete donor chimerism, and one had delayed graft failure followed by autologous recovery. Overall risk of TRM was 9%. Four patients developed grade II-III acute GVHD responsive to steroids (one mismatched transplant and 3 following CSA withdrawal). No patient has so far developed chronic GVHD. Only 3 patients developed CMV antigenemia, which resolved with gancyclovir. Five patients over 55 years (median 60, range 56-68) had hematologic malignancies (2 CML, 2 MDS, 1 NHL). Three survive in complete remission and one shows regression of lymphoma. One patient in a second chronic phase of CML relapsed into blast crisis and died. Six patients (median age 44, range 23-50) had metastatic tumors and had failed conventional treatment. Two renal cell carcinoma patients with pulmonary metastases at transplant survive, one in complete remission (day 200), one with stable disease (day 135). Four patients had melanoma: one survives with progressive disease following graft rejection; one, with evidence of tumor regression, died from transplant-related causes and two died from progressive disease. These results show that non-myeloablative transplants are tolerated well and have a low risk of TRM and GVHD. Sufficient donor engraftment was achieved to confer a GVM effect.

Abstract# 553

Poster Board#/Session: 553-I

**SECONDARY ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO SCT) USING A NON-MYELOABLATIVE CONDITIONING REGIMEN FOR PATIENTS WITH HEMATOLOGICAL MALIGNANCIES.** A. Nagler, R. Or, E. Naparstek, G. Varadi\*, R. BenYosef\*, S. Slavin. *BMT Depts., Hadassah, Jerusalem, Israel.*

Therapeutic options for patients (pts) with hematological malignancies following autologous (auto) or allogeneic (allo) SCT is rather limited. Secondary allogeneic transplantation is associated with a high incidence of transplant related mortality (TRM) and toxicity (TRT) due to the mega doses of chemoradiotherapy traditionally used in the conditioning regimens. Recently we reported that it is possible to achieve fast engraftment and elimination of malignant cells with minimal procedure related toxicity by using a non-myeloablative conditioning regimen (Flu/BU/ATG) prior to alloSCT. Based on our experience we decided to use the same strategy for pts with hematological malignancies following auto or allo SCT. Since 12/96 ten very high risk heavily treated pts with hematological malignancies (NHL-4, AML-3 (secondary-2), ALL-1, CML-1, HD-1) have undergone secondary alloSCT (sibling-8, unrelated-2; PBSC-8, BM-2) with non-myeloablative conditioning 29 (6-61) months following their first SCT (auto-8, allo-2). Eight were male and 2 female, of median age 37 (13-63) years. Engraftment was fast, with WBC > 1 × 10<sup>9</sup>/L and ANC > 0.5 × 10<sup>9</sup>/L on day 15 (11-30), plt > 25 × 10<sup>9</sup>/L on day 21 (15-∞) and plt > 50 × 10<sup>9</sup>/L on day 28 (19-∞) post alloSCT. TRT was minimal, with no VOD, renal or pulmonary toxicity. Only one pt (10%) with protracted resistant thrombocytopenia developed grade IV hemorrhagic cystitis and died. Two pts (20%) developed acute GVHD (Grade II) and other 3 (30%) chronic GVHD (moderate-2, mild-1). Two very high risk pts with NHL relapsed 2 and 9 months post alloSCT and died. Seven pts are alive with 100% donor chimerism and no evidence of disease, after a median follow-up of 7 (2-16) months. We suggest that non-myeloablative conditioning significantly reduces transplant related toxicity and thus makes secondary alloSCT feasible. Our preliminary results should be confirmed in a larger group of pts with a longer follow up.



# Safeguarding the administration of high-dose chemotherapy: a national practice survey by the American Society for Blood and Marrow Transplantation

Chien-Shing Chen,<sup>1,2</sup> Kristy Seidel,<sup>1</sup> James O. Armitage,<sup>3</sup> Joseph W. Fay,<sup>4</sup> Frederick R. Appelbaum,<sup>1,2</sup> Mary M. Horowitz,<sup>5</sup> Elizabeth J. Shpall,<sup>6</sup> Paul L. Weiden,<sup>7</sup> Karen S. Antman,<sup>8</sup> Richard E. Champlin,<sup>9</sup> John H. Kersey,<sup>10</sup> Keith M. Sullivan<sup>1,2</sup>

<sup>1</sup>Fred Hutchinson Cancer Research Center and <sup>2</sup>University of Washington, Seattle, WA; <sup>3</sup>University of Nebraska Medical Center, Omaha, NE; <sup>4</sup>Baylor University Medical Center, Dallas, TX; <sup>5</sup>International Bone Marrow Transplant Registry, and Medical College of Wisconsin, Milwaukee, WI; <sup>6</sup>University of Colorado Health Science Center, Denver, CO; <sup>7</sup>Virginia Mason Clinic, Seattle, WA; <sup>8</sup>Columbia Presbyterian Medical Center, New York, NY; <sup>9</sup>M.D. Anderson Cancer Center and University of Texas, Houston, TX; <sup>10</sup>University of Minnesota Cancer Center, Minneapolis, MN

Offprint requests: Keith M. Sullivan, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104

(Received 22 October 1997; accepted 16 December 1997)

## ABSTRACT

Overdoses of high-dose chemotherapy before hematopoietic cell transplantation are serious adverse events, but their frequency and etiology are unknown. The American Society for Blood and Marrow Transplantation (ASBMT) conducted an anonymous national survey to identify errors in safety practices during the administration of high-dose chemotherapy. The questionnaire was returned from 115 (68%) of 170 hematopoietic transplant centers in the United States. Ninety-four of the programs were university or affiliated centers, 19 were community hospitals, and 41 were founded since 1990. A total of 7650 transplants were reported for 1994: 22% of the programs performed 1-20 transplants, 60% performed 21-100 transplants, and 18% performed more than 100 transplants. Fifteen of the 115 responding centers reported a total of 18 patients inadvertently given overdoses of cisplatin (n=3), carboplatin (n=2), busulfan (n=2), cytosine arabinoside (n=2), cyclophosphamide (n=2), interleukin-2 (n=2), or other agents (n=5) between 1989 and 1994. Cumulative drug doses given as a daily dose (six cases) and nursing infusion errors (six cases) were the most common errors. The estimated chemotherapy overdose error rate was 0.06%, or 6 cases/10,000 transplants, with 95% confidence limits of 0.03-0.11%. The overdose rate among more experienced centers in operation before 1990 was lower than that among newer centers ( $p < 0.01$ ). Large centers (>100 transplants performed in 1994) experienced errors at rates lower than those in medium-sized centers (21-100 transplants,  $p = 0.03$ ). Although the number of events was small in this self-reporting survey, overdoses were noted in 13% of the responding centers, especially among more recently established units. Safety practices need to emphasize multidisciplinary checkpoints at the physician, pharmacist, nursing, and institutional levels. Based on these survey results, ASBMT recommendations for further safeguards for high-dose chemotherapy administration are proposed.

## KEY WORDS

Bone marrow transplantation • High-dose chemotherapy • Medication errors • Physician orders

## INTRODUCTION

High-dose chemotherapy followed by marrow or peripheral blood stem cell transplantation is widely used for the treatment of hematologic and malignant disorders [1-3]. Recent episodes of accidental overdose of myeloabla-

Supported in part by grants from the National Institutes of Health (HL36444, CA18029, CA18221) and the Agency for Health Care Policy and Research (HS09407), Department of Health and Human Services.

tive chemotherapy have been widely publicized and call into question the safety of these procedures [4-6]. The frequency and nature of overdoses are poorly understood, however, as are the implementation and reliability of practices designed to prevent their occurrence.

Medical practice errors take many forms. They include mistakes made by physicians, nurses, pharmacists, and ancillary personnel when ordering and administering treatments and medications, or performing procedures such as surgery or blood transfusion [7-10]. The Harvard Medical Practice Study found that in 1984 negligent care caused 28% of iatrogenic injuries, which afflicted 3.7% of all hospitalized patients in New York state [7]. Based on that study, it has been estimated that accidental injuries are likely to affect over a million hospitalized people each year in the United States [11]. The costs associated with such adverse events are substantial, further underscoring the need for investment in prevention [12]. Analysis of causal relationships has shown that many errors could be prevented through the implementation of well-designed regulations and policies; accordingly, several guidelines for preventing medication errors have been proposed as standards of care [13-20].

To enhance the safety of high-dose chemotherapy administration, the Executive and Practice Committees of the American Society for Blood and Marrow Transplantation (ASBMT) designed a questionnaire to evaluate chemotherapy practices in the United States from 1989 to 1994. Our hypothesis was that overdoses were associated with identifiable patterns of practice. The study was designed to meet the following objectives: 1) investigate the nature and frequency of overdose errors; 2) describe current safeguard systems in transplant centers; 3) determine whether the absence of certain safeguards was related to overdose errors; 4) determine whether center characteristics were related to errors or practice policy; and 5) describe planned policy and practice modifications.

## METHODS

### Transplant centers

Pediatric and adult blood and marrow transplant units in the United States were identified from the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry-North American (ABMTR). The IBMTR has collected data from over 300 institutions performing allogeneic marrow transplants worldwide since 1972. In 1991, the ABMTR began collecting data on transplants using autologous marrow or blood stem cells performed in North America. These lists were further updated by members of the Executive and Clinical Practice Committees of ASBMT. A total of 176 centers were identified in 44 states. The eight states with the greatest number of transplant centers were California (24), New York (13), Texas (11), Illinois (11), Florida (9), Ohio (9), Pennsylvania (8), and Massachusetts (7).

### Data collection and survey respondents

A self-reporting anonymous form surveyed center attributes, clinical practices, quality control measures for ordering and delivering chemotherapy, and circumstances and detection of prior overdose errors (Appendix). Areas

surveyed included: center characteristics, chemotherapy ordering practices, pharmacy policies, nursing practices, quality control and review, cause and detection of overdoses, and current safeguard systems and plans for modifications. The anonymous questionnaire was mailed to 176 program directors. Six were returned as incorrect center identification or no longer involved in transplantation. Replies were received from 115 (68%) of the 170 centers after a second survey was facsimiled to all centers.

To assess possible sampling biases among respondents, one of the authors (M.M.H.) compared the reported characteristics of the 115 anonymous centers with those of a larger sample of US centers using the IBMTR or ABMTR database for the same 5 year period. A total of 139 programs were included in the database for comparison. Seventy centers participating in one or both registries at some time over the past 7 years could not be included because of incomplete data for the years of the current survey. Many of these centers either began performing transplants or joined the registry recently.

### Statistical analysis

Statistical comparisons of our samples with the IBMTR or ABMTR database sample were performed with Chi-square test or Fisher's exact test if any categories occurred very infrequently. Logistic regression was used to analyze the occurrence rate of overdose errors. Missing or ambiguous responses complicated some analyses. All 115 centers provided information on cases of chemotherapy errors, however, 17 centers failed to furnish data on the cumulative number of patients transplanted. Due to the anonymous nature of this survey, we were not able to recover omissions or clarify ambiguous data. We used Rubin's multiple imputation method for missing data in conjunction with the logistic regression approach so that cases with partial responses could be included [21,22]. Multiple imputation allows calculation of rate estimates, confidence intervals, and test statistics, which are adjusted for the fraction of missing information. Intermediate predictor variables used to generate the multiple imputation values for the 5-year transplant totals were current number of transplant-dedicated beds, number of transplants in 1994, and years of center operation.

We recognized that the time frame (Appendix, item 1e) requesting the cumulative number of transplanted patients could have been interpreted in several ways. All analyses involving error rates were repeated assuming each of three possible interpretations (i.e., a cumulative total of 4, 5, or 6 years). Rate estimates varied only slightly under the different assumptions (1/10,000). Rate estimates presented in the text are the median values computed under each set of assumptions, and confidence intervals represent the smallest intervals spanning all three computed intervals. *P*-values given for comparisons of error rates in relation to center characteristics are the maximums of the three found under each set of assumptions. All *p*-values presented are two-sided.

## RESULTS

### Transplant center characteristics

The majority (75%) of hematopoietic cell transplant programs are located in university hospitals or academic research centers (Table 1). A minority (17%) of centers

perform only pediatric transplants. Forty-eight (42%) centers conduct only adult and 46 (41%) centers perform both adult and pediatric transplants. Most programs perform both allogeneic and autologous grafts. One hundred eleven (97%) centers are members of national cancer cooperative groups (CALGB, Cancer and Leukemia Group B; SWOG, Southwest Oncology Group; ECOG, Eastern Cooperative Oncology Group; CCG, Children Cancer Groups; POG, Puget Sound Oncology Group) or transplant registries (IBMTR or ABMTR) or both. Sixty-nine (60%) centers, including ten community hospitals and 59 university or research centers, had an external peer review site visit within the preceding 3 years. The characteristics of survey respondents were compared with those of centers in the IBMTR or ABMTR databases. More centers reporting to IBMTR or ABMTR databases performed autologous transplants only (11 vs. 23%,  $p = 0.01$ ) and used peripheral blood stem cells as the only graft source (2 vs. 9%;  $p = 0.02$ ). Otherwise, center characteristics did not differ significantly between the two groups for type of center, age range of patient treated, membership status of cancer cooperative groups, and number of dedicated transplant beds (data not shown).

Among 114 respondents reporting the year the program began, the median inaugural year was 1988. Forty-one (36%) programs were started since 1990. Fourteen (12%) programs were founded before 1980, and 59 (52%) programs were founded between 1980 and 1989 (one not specified). For centers reporting data to IBMTR or ABMTR, 63 (47%) started operations since 1990, which suggests that new centers may be underrepresented in the ASBMT survey ( $p = 0.08$ ).

In the survey group, a total 7650 hematopoietic cell transplants in 109 centers (six nonresponses) were performed in 1994, with the annual number of transplants per center ranging from 2-460 (median 45) (Table 2). Among the 109 reporting centers, 24 (22%) programs performed 1-20 transplants, 65 (60%) performed 21-100 transplants, and 20 (18%) performed more than 100 transplants in 1994. The transplant numbers were compared with those reported to the IBMTR or ABMTR. For the most recent year, the survey sample included fewer small centers and more large centers than the IBMTR/ABMTR sample ( $p = 0.04$ ). Between 1989 and 1994, a total of 22,542 transplants were recorded at the 98 centers responding to this survey (range of 2-2586, median of 121). By considering the 1994 data with the 1989-1994 totals for centers with incomplete responses, however, we estimated that a minimum of 24,255 transplants occurred at the 115 participating centers.

### Safety practices and quality control

As shown in Table 3, 98 (85%) centers used preprinted chemotherapy order sheets. Among the 98 centers, 12 used preprinted orders for some but not all conditioning chemotherapy. A total of 94 centers listed the chemotherapy dose per date in the preprinted orders and 74 centers included the dose per course in the preprinted orders. Reasons given for not using preprinted orders included: treatment off-protocol (seven centers), small accrual protocols (six centers), and new protocols (two centers). Chemotherapy orders were signed by physician's assistant, resident, fellow, and attend-

Table 1. Characteristics of 115 transplant programs

	Number (%)
<b>Type of center (n=113)</b>	
University hospital, affiliated hospital, or research center	85 (75%)
Community hospital, university affiliated	9 (8%)
Community hospital, non-university affiliated	19 (17%)
<b>Type of transplant</b>	
<b>Graft source (n=115)</b>	
Both blood and marrow	109 (95%)
Peripheral blood stem cell only	2 (2%)
Bone marrow only	4 (3%)
<b>Donor (n=114)</b>	
Autologous and allogeneic (no unrelated)	51 (45%)
Autologous, allogeneic, and unrelated	49 (43%)
Autologous only	13 (11%)
Allogeneic only	1 (1%)
<b>Type of patients treated (n=113)</b>	
Both adult and pediatric patients	46 (41%)
Adult patients only	48 (42%)
Pediatric patients only	19 (17%)
<b>Member of cancer cooperative groups<sup>a</sup> or transplant registry (n=115)</b>	
Cooperative groups, ABMTR, and IBMTR	66 (58%)
Cooperative groups and ABMTR	15 (13%)
Cooperative groups and IBMTR	7 (6%)
ABMTR and IBMTR	6 (5%)
Cooperative groups only	10 (9%)
ABMTR	6 (5%)
IBMTR	1 (1%)
None	4 (3%)
<b>Number of dedicated transplant beds (n=112)</b>	
1-5	30 (27%)
6-10	45 (40%)
11-20	23 (21%)
21-30	8 (7%)
31-60	6 (5%)
<b>Peer review site visit within last 3 years (n=115)</b>	
NIH	30 <sup>c</sup>
FDA	10 <sup>c</sup>
Cooperative groups	25 <sup>c</sup>
Others <sup>b</sup>	17 <sup>c</sup>
None	46 (40%)

<sup>a</sup>Cooperative groups include Cancer and Leukemia Group B (CALGB), Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), Puget Sound Oncology Group (POG), and Children Cancer Groups (CCG).

<sup>b</sup>Other mechanisms include by State, National Surgical Adjuvant Breast and Bowel Projects (NSABP), National Marrow Donor Program (NMDP), American Association of Blood Banks (AABB), College of American Pathologists (CAP), American Society for Histocompatibility (ASHI), panel of experts or cancer center review. Eleven centers were reviewed by two or more groups.

<sup>c</sup>Some programs indicated more than one review mechanism; therefore, percentage is not given.

ing in 22, 24, 57, and 107 centers, respectively. Among the eight centers where order sheets were not signed by attendings, four required no mandatory co-signatures.

The chemotherapy dose was recalculated in the pharmacy in 106 (92%) centers. Chemotherapy dose verification was performed by one pharmacist in 66, two pharmacists in 38, or three pharmacists in one center (one not specified). Six centers indicated no dose recalculation by a

Table 2. Number of transplants in 1994 and 1989-1994

Transplants	1994		Transplants	1989-1994	
	ASBMT survey	Center number (%)		ASBMT survey	Center number (%)
1-5	5 (5%)	10 (7%)	1-50	28 (29%)	39 (28%)
6-10	6 (6%)	19 (14%)	51-100	14 (14%)	27 (19%)
11-20	13 (12%)	30 (22%)	101-200	28 (29%)	30 (22%)
21-40	26 (24%)	27 (19%)	201-400	17 (17%)	29 (21%)
41-60	21 (19%)	21 (15%)	>401	11 (11%)	14 (10%)
61-100	18 (16%)	21 (15%)	Not specified	17	—
101-200	13 (12%)	8 (6%)	Total number of centers	115 (100%)	139 (100%)
>201	7 (6%)	3 (2%)			
Not specified	6	—			
Total number of centers	115 (100%)	139 (100%)			

p = 0.04

p = 0.65

pharmacist, but four of the six used computer programs for drug ordering. Sixty-nine (60%) centers operated a computer system for drug ordering and dose limits were set by computer in 22 of the 69 centers. All 115 centers indicated that the chemotherapy dose and drug in bag were identified by nursing staff. Nursing verification of chemotherapy infusions was carried out by two nurses in 66 (57%) centers and one nurse in 42 (37%) centers (seven [6%] not specified). Doses were verified against orders in 111 (97%) centers and against the protocol in 73 (64%) centers by nurses. Patient identification and dose verifica-

tion against orders were not performed in five and three centers, respectively.

Among the 98 centers using preprinted orders, 15 have one, 71 have two to four, and 11 centers have five to six quality control reviews of the order forms (one did not specify). Reviewers included primary investigators (76 centers), medical directors (69 centers), pharmacy directors (33 centers), nursing directors (24 centers), research nurses (43 centers), and others (23 centers). Multidisciplinary standard practice committees (72 centers [63%]) and transplant quality assurance committees (76 centers [66%])

Table 3. Safety practices for high-dose chemotherapy administration in 115 centers

	Routinely used (%)	Not used (%)	Not specified
<b>Chemotherapy orders</b>			
Preprinted chemotherapy orders used	98 <sup>a</sup> (85%)	17 (15%)	0
Preprinted orders used for each drug <sup>b</sup>	84	12 <sup>c</sup>	2
Dates of chemotherapy <sup>b</sup>	96	1	1
Dose per day <sup>b</sup>	94	3	1
Dose per course <sup>b</sup>	74	23	1
Protocol drug dose typed on the orders	93 (81%)	19 (17%)	3
Protocol number specified on the orders	74 (64%)	36 (31%)	5
<b>Chemotherapy infusions</b>			
<b>Pharmacy verification</b>			
Pharmacist recalculates dose	106 (92%)	6 (5%)	3
Dose verified against protocol	87 <sup>d</sup> (76%)	23 (20%)	5
Computerized drug order	69 <sup>e</sup> (60%)	45 (39%)	1
Program sets dose limit <sup>f</sup>	22 <sup>e</sup> (32%)	43 (62%)	3
<b>Nursing verification</b>			
Dose and drug in bag verified	115 (100%)	0 (0%)	0
Dose verified against orders	111 (97%)	3 (2%)	1
Patient identification verified	109 (95%)	5 (4%)	1
Dose verified against protocol	73 (64%)	41 (35%)	1
Patient weight and body surface area verified	90 (78%)	23 (20%)	2

<sup>a</sup>See Results section.

<sup>b</sup>Based on the 98 centers using preprinted orders.

<sup>c</sup>Based on the 69 centers using computerized drug orders.

<sup>d</sup>One program indicated that only some chemotherapy doses were verified against protocol.

<sup>e</sup>One program indicated that only some chemotherapy was computerized and had dose limits set.



were common components of quality control. Other committee or group reviews included medical advisory and staff conferences, policy and procedures, critical care, infection control, and transfusion committees. Eighty-seven centers (78%) had all protocols reviewed by the Institutional Review Board (IRB). Twenty-five centers, including 18 university affiliated centers, six community hospitals, and one of unspecified type, indicated that not all stem cell transplant protocols were reviewed by the IRB. Exemptions included transplants considered as standard treatments (16 centers), non-research protocols (four centers), and other reasons (three centers).

#### Nature and frequency of overdose errors

Fifteen centers reported a total of 18 individuals who received overdoses of high-dose therapy between 1989 and 1994. Twelve centers reported one case each and three reported two cases. The center characteristics, circumstances surrounding the errors, methods of detection and subsequent policy revisions are detailed in Table 4. The overdosed agents included cisplatin ( $n=3$ ), carboplatin ( $n=2$ ), busulfan ( $n=2$ ), cytosine arabinoside ( $n=2$ ), cyclophosphamide ( $n=2$ ), interleukin-2 ( $n=2$ ), doxorubicin, adriamycin, vincristine, methotrexate, and the combination of thiotepa, carboplatin, and etoposide (one each).

Cumulative drug doses given as a daily dose (six cases) and nursing infusion errors (six cases) were the most common types of error, followed by ambiguous orders without attending co-signatures (two cases), new protocols without preprinted orders (two cases), and pharmacy or staff errors (one each). Three centers (cases 14, 15, and 17) using computer programs for dose limitations had errors in physician orders (two cases) or pharmacy verification (one case). The consequences of overdoses were provided for eight cases, including death (case 15), clinical toxicity (cases 2, 13, 14, 16, 17, and 18), and no toxicity (case 6).

Overdose errors prompted policy revisions at ten centers: using preprinted orders; verifying an order against protocol; ordering a list of maximum drug dose; limiting orders to daily dose; verifying all chemotherapy orders by attending physicians, pharmacists and nurses; and increasing education and training. In addition, seven centers (nine cases) described their revision as reinforcing multidisciplinary checkpoints. Of the programs that were not planning to change their policies, six centers (cases 6-12 and 16) reported that multiple safety checkpoints were in place before errors occurred.

The overall rate of chemotherapy overdoses for the 5-year period was 0.06%, or 6 cases in 10,000 transplants, with 95% confidence limits of 0.03-0.11%. Univariate regression analyses detected a lower error rate among large centers (>100 transplants in 1994) than among medium-sized centers (21-100 transplants) ( $p = 0.03$ ); however, there was no evidence that small centers (1-20 transplants) differed from medium-sized programs ( $p = 0.99$ ). Centers in operation before 1990 also had a statistically significant lower error rate ( $p < 0.01$ ). These two findings are closely linked because the older centers are also generally larger. Results also suggest a trend that centers reporting verification by two nurses rather than one might have a lower error rate ( $p = 0.11$ ). Other center characteristics that did not show a statistical association with error rates included

community hospital (university affiliated or non-affiliated) vs. university hospital/research center and the presence of computerized drug ordering ( $p > 0.35$ ).

#### DISCUSSION

This study profiles transplant programs and safety practices for high-dose chemotherapy administration in the United States. Patients were treated in a variety of settings ranging from community hospitals to university research centers throughout the nation. In sampling this broad constituency for reporting overdose errors, we obtained a high proportion of responses. The 68% response rate to this anonymous survey was high given that only one blinded, follow-up reminder was sent to all program directors. This response rate was similar to or higher than return rates in many unblinded surveys [23-25].

Comparison with the IBMTR or ABMTR databases examined the potential for selection bias in the responding sample. Small or new centers may not have responded to this survey as readily as older or larger ones. The registry database consistently comprises about 50% of autotransplants and 40% allotransplants in the United States. Their representations were evaluated and confirmed independently [26; MMH, unpublished data, 1997]. Even though the transplant registries do not receive all the transplant reports, the total number of transplants in the United States can be estimated. About 50,000 transplants (18,000 allogeneic and 32,000 autologous) were performed between 1989 and 1994, and 10,000-12,000 transplants (3-4,000 allogeneic and 7-8,000 autologous) in 1994. Thus, the total number of transplants reported here for 1994 reflects a significant proportion (64-77%) of all hematopoietic cell transplants performed in the United States.

The reported overdose rate, 6 cases/10,000 transplants in a 5-year period, is lower than overall medication error rates reported in the Harvard Medical Practice Study [7]. In that retrospective study with a sample size of 30,195 hospitalized patients, the adverse event rate was 3.7% and drug complications were the most common type of adverse events (19% of the total), which could be translated into a rate of 70 cases/10,000 patients. It should be emphasized that a direct comparison of our results with this reported error rate is problematic. Our survey focused on high-dose chemotherapy overdose, which represents one of the most severe forms of adverse drug events, but did not address the issue of overall drug-related adverse events. It is possible that non-chemotherapy medication errors also occurred, but that information was not provided. Moreover, though the self-reporting survey is a method of error identification frequently used in the literature, errors are not reported unless discovered. Accordingly, self-reported error rates tend to be lower than the actual rates. Despite the limitations of this approach, the purpose of our survey was to provide an opportunity for self-examination of practices. In addition, it provided a method of collecting and analyzing data on chemotherapy errors in settings where treatments were often new and intensive with overdoses potentially resulting in serious consequences.

In this survey, the most common types of errors were cumulative drug doses given as the daily dose and nursing

Table 4. High-dose chemotherapy overdose errors and policy changes

Case	Program starting year	Center type <sup>a</sup>	Transplants in 1994	Type of errors <sup>b</sup>	Drug	Method of detection	Policy change	Reinforced safeguard systems
1	Before 1990	U	21-100	Cumulative dose given for daily dose (3-fold overdose)	Doxorubicin	Nurse recognized errors later	Yes	Pharmacy verify protocols
2	Since 1990	U	21-100	Cumulative dose given for daily dose (4-fold overdose)	Cisplatin	Review of chart/toxicity	Yes	Use preprinted orders; pharmacist verify doses; dedicated nurses on transplant
3	Since 1990	U	>100	Cumulative dose given for daily dose	Cisplatin	Pharmacy detected error later	Yes	Multidisciplinary checkpoints; list maximum drug doses for treatments
4	Since 1990	U	>100	Cumulative dose given for daily dose	Cisplatin	Pharmacy detected error later	Yes	Multidisciplinary checkpoints; list maximum drug doses for treatments
5	Before 1990	U	>100	Cumulative dose given for daily dose	Adriamycin	Pharmacy detected error later	Yes	Limit orders to daily dosing
6	Before 1990	U	>100	Cumulative dose given for daily dose, no attending co-signature (3-fold overdose)	Carboplatin	Pharmacy detected error later	No	Multidisciplinary checkpoints; new protocol orientation; attending co-signs orders
7	Since 1990	C-UA	21-100	Nursing error (b.i.d. dose given concurrently, 2-fold overdose)	Cytosine arabinoside	Physician monitoring	No	Multidisciplinary checkpoints
8	Since 1990	C-UA	21-100	Nursing error (b.i.d. dose given concurrently, 2-fold overdose)	Cytosine arabinoside	Physician monitoring	No	Multidisciplinary checkpoints
9	Before 1990	C	21-100	Nursing error (24-hour infusion given in 6 hours)	Cyclophosphamide	Nurse recognized errors later	No	Multidisciplinary checkpoints
10	Before 1990	U	21-100	Nursing error and pharmacy error	Busulfan	Nurse recognized errors later	No	Multidisciplinary checkpoints
11	Since 1990	C-UA	21-100	Nursing error	Interleukin-2	Pharmacy detected error later	No	Verify orders and doses against protocols by pharmacists
12	Since 1990	C-UA	21-100	Nursing error	Interleukin-2	Pharmacy detected error later	No	Verify orders and doses against protocols by pharmacists
13	Before 1990	U	21-100	Ambiguous orders and no attending co-signature	Carboplatin	Laboratory monitoring, increase creatinine	Yes	Review preprinted orders; attending co-signs orders
14	Since 1990	U	21-100	Ambiguous orders and no attending co-signature	Vincristine	Clinical toxicity	Yes	Attending co-signs orders
15	Before 1990	U	21-100	New protocol and no preprinted orders	Cyclophosphamide	Review of chart	Yes	Use preprinted orders; increase awareness
16	Before 1990	N	>100	New protocol and new fellow	Thiotepa/ carboplatin/ etoposide	Attending detected error	No	Multidisciplinary checkpoints
17	Before 1990	N	21-100	Pharmacy error	Methotrexate	Clinical toxicity	Yes	Multidisciplinary checkpoints; review chemotherapy policies
18	Before 1990	U	>100	Unable to check busulfan blood level	Busulfan	Clinical toxicity	Yes	Centralized incident reports; attending verify all orders

<sup>a</sup>U, university hospital or research center; C-UA, university affiliated community hospital; C, community hospital; N, not specified.

<sup>b</sup>Details varied among centers; all descriptions included.

infusion mistakes; however, overdoses occurred at every step between the processes of ordering and administering. Error rates were higher among newer centers established after 1990, which also tended to be smaller units, suggesting that centers with more experience in high-dose chemotherapy may be more likely to avoid errors. Alternatively, errors may have been recognized in the past and safeguards subsequently strengthened. We did not find individual safeguard measures that were statistically associated with reduced rates of error.

Center variation in marrow or blood stem cell transplantation outcome is more difficult to study, due in part to

wide variations in treatment protocols and patient selection. While data from this survey showed that larger and more experienced centers have lower reported error rates, these findings should be interpreted with caution and should not be used as surrogate markers of hospital performance or outcome since variables associated with voluntary reporting make comparisons between institutions difficult [27].

Safety practices for chemotherapy administration were studied at the physician, pharmacist, and nursing levels. While all centers had procedures in place to prevent chemotherapy errors, the degree of thoroughness differed. Com-

puter programs for drug orders and dose limits may have prevented errors; however, this issue was not addressed by this survey. Importantly, some errors occurred even with computer monitoring in place. Dose verification against protocols as well as confirmation of the patient's weight and body surface area were less commonly performed. Twenty-four centers noted that residents wrote chemotherapy orders which were countersigned by either fellows or attendings.

Our findings are consistent with earlier reports that medication errors frequently occur as a result of multisystem failures. Adverse events and injuries are serious and costly complications of health care and represent a wide range of potential events or errors. Many adverse drug events analyzed in the Harvard study were complex in nature. Episodes were attributed to various problems of process or unique errors caused many categories of adverse drug events. With a systemic approach, errors can be reduced by examining elements and interrelationships of the safety structure [17,18,28,29]. The magnitude of iatrogenic events is probably underestimated since most studies have focused only on injury. Error rates have been distressingly high when errors were specifically audited. For example, autopsy studies indicated high rates (35-40%) of missed diagnosis causing death [30-32]. The annual national cost of such drug-related morbidity and mortality has been estimated at \$76.6 billion, with the majority (\$47 billion) related to hospital admissions associated with drug therapy [12]. Two recent reports have quantified the additional resource utilization associated with these events [33,34]. Data from the prevention study suggested the annual costs attributable to all adverse events and preventable events for a 700-bed teaching hospital were \$5.6 million and \$2.8 million, respectively.

Marrow and peripheral blood stem cell transplants are increasingly used to treat an array of diseases. This factor in turn has led to the establishment of a large number of centers since 1990. It is possible that some newer centers may have less established safeguard systems. More importantly, no standard practice guidelines have been previously formulated for transplantation. To reduce errors in conventional dose chemotherapy, several measures have been suggested, including certification examinations for oncology-trained pharmacists [19,20]. Despite policies in place in many centers, overdose errors did occur, which underscores the need for enhanced guidelines and diligent monitoring.

Based on the published literature and the findings of this survey, ASBMT proposes specific guidelines for high-dose chemotherapy (Table 5). These guidelines emphasize the need for a multidisciplinary approach to standardizing safety practice and apply to all transplant centers regardless of type, size, or experience of the program. Preprinted order sheets should specify the date and daily doses of a drug, which will prevent physicians from prescribing the cumulative drug treatment as the daily dose. Likewise, verifying patient and drug identification against orders and protocols by two nurses will reduce the incidence of nursing infusion errors. On an institutional level, periodic case review and monitoring safeguards and errors will assist in early identification of adverse events. Medication errors should be viewed as system failures that require prompt remedy. Thus, the reporting process should be simple and

**Table 5.** ASBMT guidelines for high-dose chemotherapy administration

**Physician procedures**

- Physician uses preprinted orders that specify protocol number and name of the study
- Preprinted orders specify the daily drug dose and specific dates for all chemotherapy
- Physician verifies that two staff members independently confirm patients' height and weight
- Attending physician verifies the name, protocol number, and recalculates the drug dose
- Attending physician co-signs all chemotherapy orders.

**Pharmacist procedures**

- Pharmacist verifies the patient name, protocol number, and recalculates the drug dose
- Pharmacist recalculates the cumulative dose and compares to the protocol total cumulative dose

**Nursing procedures**

- Two nurses establish the identity of the patient and the drug for administration
- Nurse verifies the drug doses against both the order sheet and the protocol

**Institutional procedures**

- Multidisciplinary group reviews of all new or revised protocols and preprinted orders
- Institution supports ongoing surveillance and reporting process for adverse drug events
- Institution supports continuing staff education of chemotherapy safeguards

confidential. In addition, medication errors or potential errors can be reported in confidence to the Medwatch program of the Food and Drug Administration (phone 1-800-FDA-1088 or facsimile the Medwatch form to 1-800-FDA-0178). Equally important, the ASBMT guidelines are designed to facilitate communication between physicians, nurses, pharmacists, and administrative staff to develop new safeguards and policies. Future efforts at error prevention may be further aided by enhanced monitoring and advances in bioinformatics. Using electronic medical records and computerized physician orders will help to eliminate confusing handwritten records and implementing bar coding of medications and patient identification will accurately identify patients and treatments [35].

In conclusion, this self-reporting survey of the administration of high-dose chemotherapy characterized the current practices and safety measures in a large cohort of blood and marrow transplant centers. Common themes in dose errors were cumulative drug doses given as a daily dose and nursing infusion errors. Guidelines are proposed to reduce system-wide errors and further safeguard the administration of high-dose chemotherapy and hematopoietic cell transplantation.

**ACKNOWLEDGMENTS**

The authors are indebted to the transplant physicians and center staff participating in this survey. We wish to thank Dr. Lucian L. Leape for his comments on an earlier draft of this manuscript.



3. Chemotherapy Infusions: Pharmacy

- a. Is drug ordering computerized? Yes No
- b. If so, does the program set dose limits? Yes No
- c. Does the pharmacist recalculate the dose? Yes No
- d. Does the pharmacist verify against protocol? Yes No
- e. Verification by: one pharmacist two pharmacists

4. Chemotherapy Infusions: Nursing

- a. Does the nurse verify patient ID? Yes No
- b. Does the nurse verify dose and drug in bag? Yes No
- c. Does the nurse verify dose against orders? Yes No
- d. Does the nurse verify dose against protocol? Yes No
- e. Does the nurse verify weight/BSA of patient? Yes No
- f. Verification by: one nurse two nurses

5. Quality Control

- a. Who reviews preprinted orders and revisions? (check all):  
Principal investigator    Medical Director    Research Nurse  
Pharmacy Director    Nursing Director    Other (specify)
- b. Do you have an active, multidisciplinary Standard Practice Committee to update/revise orders and transplant practice? Yes No
- c. Do you have a transplant Quality Assurance Committee? Yes No
- d. Do other committees/groups review transplant practice? (describe)
- e. Does the IRB review all protocols? Yes No  
If no, which are exempt?
- f. Who, how and when do you monitor for regimen-related toxicities?
- g. Over the last 5 years, has there been inadvertent administration of higher than planned doses of chemotherapy? Yes No  
1) How many patients?  
2) Which agents?  
3) Why did it occur (be specific):  
4) How was it detected?

6. Systems Design

- a. What aspects of your system are the strongest safeguards?
- b. What are areas of concern for safety?
- c. Are you planning any change in your policies? Yes No  
If yes, specify:

## REFERENCES

- 1 Thomas ED: Marrow transplantation for malignant diseases. *J Clin Oncol* 9:517, 1983.
- 2 Armitage JO: Bone marrow transplantation. *N Engl J Med* 330:827, 1994.
- 3 Walters MC, Patience M, Leisenring W, Eckman JR, Scott JP, Mentzer WC, Davies SC, Obene-Frempong K, Bernaudin F, Matthews DC, Storb R, Sullivan KM: Bone marrow transplantation for sickle cell disease. *N Engl J Med* 335:369, 1996.
- 4 Roush W: Dana-Farber death sends a warning to research hospitals. *Science* 269:295, 1995.
- 5 Altman LK: Medical errors bring calls for change. *New York Times* 1995 July 18: Sect B:5.
- 6 Erikson J: How safe are the safeguards? A death at Dana-Farber triggers soul searching at cancer centers. *Oncol Times* 17:1, 1995.
- 7 Leape LL, Brennan TA, Laird NM, Lawthers AG, Localio AR, Barnes BA, Hebert L, Newhouse JP, Weiler PC, Hiatt H: The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 324:377, 1991.
- 8 Linden JV, Kaplan HS: Transfusion errors: causes and effects. *Transfus Med Rev* 8:169, 1994.
- 9 Donchin Y, Gopher D, Olin M, Badibi Y, Biesky M, Sprung CL, Cote PR: A look into the nature and causes of human errors in the intensive care unit. *Crit Care Med* 23:294, 1995.
- 10 Lagasse RS, Steinberg ES, Katz RI, Saubermann Af: Defining quality of perioperative care by statistical process control of adverse outcomes. *Anesthesiology* 82:1181, 1995.
- 11 Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, Newhouse JP, Weiler PC, Hiatt HH: Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *N Engl J Med* 324:370, 1991.
- 12 Johnson JA, Bootman JL: Drug-related morbidity and mortality: a cost-of-illness model. *Arch Intern Med* 155:1949, 1995.
- 13 Leape LL, Lawthers AG, Brennan TA, Johnson WG: Preventing medical injury. *Qual Rev Bull* 19:144, 1993.
- 14 American Society of Hospital Pharmacists: ASHP guidelines on preventing medication errors in hospitals. *Am J Hosp Pharm* 50:305, 1993.
- 15 Bradbury K, Wang J, Haskins G, Meh B: Prevention of medication errors. Developing a continuous-quality-improvement approach. *Mt Sinai J Med* 60:379, 1993.
- 16 Cohen MR, Senders J, Davis NM: Twelve ways to prevent medication errors. *Nurs* 24:34, 1994.
- 17 Leape LL, Bates DW, Cullen D, Cooper J, Demonaco H, Gallivan T, Hallisey R, Ives J, Laird N, Laffel G, Nemeskal R, Petersen LA, Porter K, Servi D, Shea BF, Small SD, Sweitzer B, Thompson BT, Vliet MV: Systems analysis of adverse drug events. *JAMA* 274:35, 1995.
- 18 Bates DW, Cullen D, Laird NM, Petersen LA, Small SD, Servi D, Laffel G, Sweitzer B, Shea BF, Hallisey R, Vliet MV, Nemeskal R, Leape LL: Incidence of adverse drug events and potential adverse drug events. Implications for prevention. *JAMA* 274:29, 1995.
- 19 Cohen MR, Anderson RW, Attilio RM, Green L, Muller RJ, Pruemer JM: Preventing medication errors in cancer chemotherapy. *Am J Health Syst Pharm* 53:737, 1996.
- 20 Bates DW, Burrows AM, Grossman DGS, Schneider PJ, Strom BL: Top priority actions for preventing adverse drug events in hospitals. *Am J Health Syst Pharm* 53:747, 1996.
- 21 Rubin DB: *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley & Sons, 1987.
- 22 Rubin DW: Multiple imputation after 18+ years. *J Am Stat Assoc* 91:473, 1996.
- 23 Dillman DA: The design and administration of mail surveys. *Ann Rev Sociol* 17:225, 1991.
- 24 Armstrong BK, White E, Saracci R: Response rates and their maximization. *Monogr Epidemiol Biostat* 21:294, 1992.
- 25 Fischer DS, Alfano S, Knobf MT, Donovan C, Beaulieu N: Improving the cancer chemotherapy use process. *J Clin Oncol* 14:3148, 1996.
- 26 Rowlings PA, Passweg JR, Armitage JO, Gale RP, Sobocinski KA, Klein JP, Zhang M, Horowitz MM: Report from the International Bone Marrow Transplant Registry and the Autologous Blood and Marrow Transplant Registry-North America. *Clin Transplant* 6:87, 1994.
- 27 van Leeuwen DH: Are medication error rates useful as comparative measures of organizational performance? *Jt Comm J Qual Improv* 20:192, 1994.
- 28 Bates DW, Boyle DL, Vaner Vliet MB, Schneider J, Leape LL: Relationship between medication errors and adverse drug events. *J Gen Intern Med* 10:199, 1995.
- 29 Kahn KL: Above all "do no harm" How shall we avoid errors in medicine? *JAMA* 274:75, 1995.
- 30 Anderson RE, Hill RB, Key CR: The sensitivity and specificity of clinical diagnostics during five decades: toward an understanding of necessary fallibility. *JAMA* 261:1610, 1989.
- 31 Goldman L, Sayson R, Robbins S, Conn LH, Bettman M, Weissberg M: The value of the autopsy in the three medical eras. *N Engl J Med* 308:1000, 1983.
- 32 Cameron HM, McGoogan E: A prospective study of 1152 hospital autopsies. I. Inaccuracies in death certification. *J Pathol* 133:273, 1981.
- 33 Bates DW, Spell N, Cullen D, Burdick E, Laird NM, Petersen LA, Small SD, Sweitzer B, Leape LL: The costs of adverse drug events in hospitalized patients. *JAMA* 277:307, 1997.
- 34 Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP: Adverse drug events in hospitalized patients—excess length of stay, extra costs, and attributable mortality. *JAMA* 277:301, 1997.
- 35 Leape LL: Examining errors in health care: developing a prevention, education, and research agenda. *Oncol Times* :48, 1996.

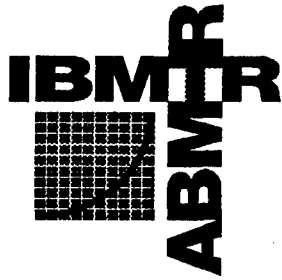


# IBMTR/ABMTR Statisticians' Manual

---

International Bone Marrow Transplant Registry  
Autologous Blood & Marrow Transplant Registry  
Medical College of Wisconsin  
8701 Watertown Plank Road • P.O. Box 26509  
Milwaukee, WI 53226 USA





# IBMTR/ABMTR Statisticians' Manual

## Table of Contents

I.	Study protocols for analyses using IBMTR/ABMTR data .....	2
II.	Study file preparation .....	5
III.	Intermediate and terminal events used in studies .....	12
IV.	Descriptive statistics .....	17
V.	Multivariate models for survival .....	21
VI.	Modeling 100-day mortality .....	30
VII.	Writing Committee memos .....	31

Appendix A IBMTR/ABMTR Study Proposal Form

Appendix B Sample IBMTR/ABMTR Study Protocol



## **I. STUDY PROTOCOLS FOR ANALYSES USING IBMTR/ABMTR DATA**

The Study Protocol is an invaluable tool for performing analyses of high scientific quality that address important clinical and biologic issues in a way that most efficiently uses the data and personnel resources of the IBMTR and ABMTR. The Study Protocol is also an essential communications tool that clarifies the study objectives of Working/Writing Committee participants and ensures that they will be met by the analyses conducted at the Statistical Center. Ideally, preparation of the Study Protocol will involve as many members of the relevant Committee as possible so that important aspects of the problem under study are addressed to the fullest extent possible. Preparation of the Study Protocol is an important opportunity for Statistical Center personnel to inform Working/Writing Committee participants about the capabilities and limitations of IBMTR/ABMTR data and resources. It also offers Writing/Working Committee participants to contribute their clinical and scientific expertise. A Study Protocol should be prepared as soon as a Study Proposal (see form in Appendix A) is approved by the relevant Working Committee. The following outline should be used, modified as necessary for the needs of particular projects. A sample Study Protocol is included in Appendix B.

### **A. OBJECTIVES**

The aims of the study should be stated as concisely and clearly as possible. A person reading the Objectives should have clear idea of the primary issue(s) being examined. Examples are: 1. to determine whether allogeneic transplants exert a graft-versus-tumor effect in multiple myeloma; 2. to determine the safety and efficacy of autotransplants for ovarian cancer; or, 3. to compare the efficacy of allogeneic and autologous transplants for acute myelogenous leukemia in first and second remission. Collecting and analyzing data are not objectives in themselves - the objective is the purpose for which the data will be used. Consequently, objectives such as "to collect and analyze data on autotransplants for multiple myeloma" should be avoided.

### **B. BACKGROUND**

This section, generally prepared by the Study Chair, should briefly summarize the rationale for the study, citing relevant previous work. A person reading the Background should have a clear idea of the importance of the intended study. This section gives the statistician performing the study a clearer idea of the clinical and biologic issues involved and identifies studies in the literature which examine similar issues that may provide insight for data analysis. The Background will often be prepared as part of the Study Proposal and may serve as the outline for the Introduction/Discussion of the final manuscript.

### C. STUDY POPULATION

The section should clearly define the selection criteria for patients to be included in the analysis. *It should be as specific as possible*, including requirements of age, performance status, disease and disease stage, years of transplant, prior treatment (e.g. persons with CML receiving only hydroxyurea and/or interferon pretransplant), donor type, specific transplant regimens (e.g. methotrexate and cyclosporine for GVHD prophylaxis) or any other restriction relevant to the study. *It is important that these restrictions be defined prospectively based on biologic and statistical principles and not after examination of outcomes.* If the study involves combining IBMTR/ABMTR data with data from another group, the selection criteria for patients in the other database should also be specified (e.g. persons < age 40 years achieving complete remission after induction therapy for AML and receiving high-dose cytarabine for consolidation).

### D. OUTCOMES

Outcomes to be studied should be defined clearly, including time-points, where relevant. Outcomes commonly analyzed are discussed in section III of this manual.

### E. VARIABLES TO BE ANALYZED

This section is important in that it requires study participants to determine which relevant variables are, in fact, available in the IBMTR/ABMTR database and the format in which the data are collected. All potential outcome and explanatory variables should be listed with suggested categories for analysis. The categories to be used should be discussed with the Study Chair and other Committee members to determine that they are based on sound biological principles and consistent with previous literature. Different studies may require different degrees of detail for specific variables (e.g. conditioning regimen may be considered simply as TBI versus no TBI or as TBI + Cy versus TBI + Cy + VP16 versus Busulfan + Cy versus other specific regimen depending on the objectives of the study). For studies involving combining IBMTR/ABMTR data with data from other groups, the availability of specific variables in both databases should be confirmed. An essential consideration in this regard is the timing of specific measurements. For example, the IBMTR/ABMTR collects data on performance score at the time of transplantation while a chemotherapy database may have available data on performance score at time of diagnosis or remission - since the measurements are at different time points, they cannot be considered equivalent variables. Specifying the list of variables in detail avoids confusion about comparability of data.

If the study requires collecting supplemental data for variables not routinely collected by IBMTR/ABMTR, these variables and plans for supplemental data collection should be specified in this section (see Section IID).

## **F. METHODS**

### **(1) General approach**

This section should describe in non-technical terms the approach to achieving each of the objectives of the study. Data limitations and implications of potential findings may be discussed. For example, to address the objective of determining whether there is a graft-versus-myeloma effect in allografts for multiple myeloma, the general approach might be to compare relapse rates after identical twin transplants and HLA-identical sibling allotransplants for myeloma, adjusting for other factors associated with relapse. A lower relapse rate after allografts would suggest that a graft-versus-myeloma effect exists. The level of detail in this section depends on the issues being addressed and the specifics of the study population.

### **(2) Statistical methods**

This section should include the specific methodology planned, with a discussion of its limitations if relevant. This should include estimations of the power of the analysis to achieve each of the objectives, given anticipated sample size. In contrast to prospective studies, where numbers of patients to be studied is determined by the power desired, IBMTR/ABMTR studies generally focus on a defined number of patients available in the database. The questions that can be answered, therefore, are determined by the numbers of patients available.

## **G. WRITING COMMITTEE PARTICIPANTS**

A Writing Committee must be formed for each study, generally derived from the Working Committee sponsoring the study. Centers contributing large numbers of patients to be included in the study should be contacted to determine whether they wish to have a representative on the Writing Committee, if they have no representative on the Working Committee. If the Study involves collaboration with another Group, the Group should determine the individuals to be included in the Writing Committee. Contact information should be listed for the Study Chair and Co-chairs and the Study Statistician.

## **H. TIME LINE**

A provisional time line for various landmarks in the study should be included. This is especially important when supplemental data must be collected (see section IID). Possible landmarks include: Preliminary analysis of patients to be studied (descriptive characteristics); preparation of supplemental data collection instrument; completion of supplemental data collection; preparation of study file; univariate analyses; multivariate analysis; first draft of manuscript.

## II. STUDY FILE PREPARATION

The aim in preparing a study file is to have a study population with selected (by study design) characteristics who are consecutively treated patients at participating centers with adequate follow-up and in large enough numbers to give the analysis sufficient statistical power for its goals. The IBMTR and ABMTR collect data on two levels: *Registration* data and *Research* data. All participating centers *register* consecutive transplants with basic data (age, sex, disease, disease stage and duration, graft type, donor type, conditioning regimen, graft treatment, GVHD prophylaxis and posttransplant disease status, survival, second cancers and primary cause of death). Many centers also submit detailed data collection forms (Report Forms) with comprehensive clinical and demographic data on a subset of these cases, determined by the Statistical Center and based on needs for current and anticipated studies. Data from Report Forms are entered in the *Research* database. *Registration* data allow analysis of trends in transplant use and outcome and identification of patients for specific studies. Study files, however, generally are generated from the *Research* database.

### A) DATA SELECTION

#### (1) Case Selection

Cases to be analyzed in a specific study will be determined through discussions between the statistician and the Study Chair. As stated in the guidelines for preparing Study Protocols, selection criteria should be defined prospectively based on biologic and statistical principles **not** after the examination of outcomes. The study population is usually limited by disease and type of transplant (either allogeneic or autologous). Other common restrictions include year of transplant, age at transplant, disease stage at transplant, and donor type and tissue type for allogeneic transplants. Restrictions should be applied to the database one at a time with the most important restrictions first and the number of available patients recorded after each restriction is added. Restrictions that result in a study population too small for sufficient statistical power may be liberalized if this would not compromise the scientific goals of the study.

A common problem in case selection is handling cases missing the information used to restrict the population. Whether or not these patients should be excluded should be discussed with the study chair. This results most frequently when the variable is one that has not been collected on all versions of the data collection forms (Report Forms). Discussion should focus on number of cases available for analysis, the number of patients missing the information and the potential biases that may be introduced by excluding these patients. It may be necessary to contact centers reporting these patients to request missing information. Supplemental questionnaires may be designed to capture this information.

## (2) Sequential Reporting

IBMTR/ABMTR policy states that all patients who begin their high-dose therapy (conditioning) must be registered with the IBMTR/ABMTR even if for some reason they do not receive their graft. A sequential numbering system (IUBMIDs) must be developed at each center, with each patient numbered consecutively at the time high-dose chemotherapy begins.

While the IBMTR/ABMTR conducts audits annually on randomly selected teams to verify sequential reporting, the statistician should also check for sequential reporting for each center with patients included in the study file. One method to check for sequential reporting is to sort all cases (regardless of disease) by IUBMID. A separate report should be generated for each center. The list of patient identifiers (IUBMID) should be consecutive with no large time intervals between transplant dates. It should be remembered that most but not all teams have separate numbering systems for autologous and allogeneic transplants. Any indication of non-consecutive reporting should be verified by the Communications Coordinator. Centers are required to *register* consecutive patients but are not required to *report* all cases; cases classified (by the Statistical Center) as exempt from reporting are indicated by the variable EXEMPT.

Centers with breaks in sequential reporting should be brought to the attention of the Scientific Director. The center will be contacted and a plan developed to help the team comply with the IBMTR/ABMTR policy of sequential reporting. All cases from centers with non-consecutive reporting should be deleted from the analysis, after discussion with the Scientific Director and Study Chair.

## (3) Variable selection

Before preparing the study file, the statistician should work closely with the Study Chair to prepare a list of all variables required for analyses which were included in the Study Protocol (see chapter I). Variables will include patient, disease and transplant characteristics and outcome variables (both time intervals and events). The list may be modified after input from the Writing Committee when the Study Protocol is circulated.

For patients with multiple transplants, pretransplant data from the first transplant are generally selected for analyses, while posttransplant data will include both first transplant outcomes and 'global' variables which reflect outcome from all transplants. **In general**, the engraftment, GVHD, infection and posttransplant disease status variables used are those which reflect events after the first transplant, while survival includes the patient's experience through all transplants. The date of second and subsequent transplants should be included in all study files.

## B) FOLLOW UP

While most IBMTR/ABMTR analyses use data captured on Report Forms and stored in the *Research* database, the survival, relapse/progression status and dates of relapse/progression and last contact in the research database may not be the most recent available because of delays in follow-up Report submission and entry. Update requests for previously registered cases are distributed approximately every six months and the updated information is added to the *Registration* database. Additionally, survival and disease status information from each follow-up Report Form is added to the *Registration* database as part of the log-in procedure, before the entire Report is keyed into the *Research* database. To use the most recent survival and relapse/progression information on each patient in analyses, last contact data from the *Registration* database must be merged into the *Research* database. The following SAS statements are used to merge two data sets, called *dreg* and *drep*, by TEAM and IUBMID:

```
PROC SORT DATA=DREG; BY TEAM IUBMID;
PROC SORT DATA=DREP; BY TEAM IUBMID;
DATA MERGED;
MERGE DREG DREP; BY TEAM IUBMID;
```

Note: The data sets must each be sorted by TEAM and IUBMID before merging.

While the variable names for survival status and survival interval are the same in the *Registration* and *Research* databases, the variables must be renamed in one of the data sets and values compared after merging. (Survivals should never be shorter in the *Registration* database.) A new SAS data set containing the updated survival information can then be created.

IBMTR/ABMTR rules require follow-up through death or 100 days (whichever occurs first) and yearly or at time of death thereafter. Follow-up on patients who die after transplant may be received more quickly than follow-up on patients still alive after transplant. This can lead to survival probabilities appearing worse than they actually are, especially for the more recent years. The purpose of the steps listed below is to ensure that, during the study period selected, patients both alive and dead after transplant have equivalent follow-up. The following steps help identify incomplete reporting:

1. Update patient status using *Registration* data through a chosen date (i.e. patient alive or dead on this day). A patient who dies after the chosen date is considered alive for the current analysis. In general this date should be one year before the study file is prepared to allow adequate time for follow-up to be reported and entered.
2. Create a variable for each patient called TIMEFU for the time between date of last contact and the chosen date. Have the Communications Coordinator request updates on surviving patients with TIMEFU > 12 months.

3. Identify teams, if any, with large proportions of patients with no recent follow-up. These should be contacted in a separate communication (FAX or phone) to determine whether follow-up can be provided in a timely manner for the patients in the study. If not, all patients from these center should be excluded from the study.

4. To identify teams with inconsistencies in the follow-up of dead and living patients the following SAS statements can be used. The median, range and five highest and lowest values and a frequency table for TIMEFU will be printed in the output by team for dead and alive patients:

```
PROC UNIVARIATE FREQ;
VAR TIMEFU;
BY TEAM DEAD;
```

For each team, compare values of variable TIMEFU for dead and alive patients. Since most transplant deaths occur early, TIMEFU should be longer for dead than alive patients. Centers that have, in general, shorter TIMEFUs for dead than living patients may be preferentially reporting deaths. These teams should be investigated further to determine whether this is true and brought to the attention of the Scientific Director. If adequate follow-up on survivors cannot be obtained, all patients in the center should be excluded from analysis.

## C) DATA REVIEW

### (1) Missing Values

All variables in the study file should be reviewed for missing values before analyses begin. Patients with missing values for key variables may need to be excluded. Missing values result from three causes:

1. Data not requested: data not collected on an older version of a Report Form
2. Data unknown: Center indicates data not known e.g. HSV serology not tested.
3. Data not reported: Item not completed on Report Form.

One way to view the scope of missing data problems, is to create a column titled 'N evaluable' on tables for the Writing Committee. The statistician and Study Chair can review the initial tables and make a plan to address the problem, if necessary. If values for a particular variable are missing for a large percentage of the study population and the variable is not a key one, the variable may be dropped. Alternatively, a related variable which provides similar information may be substituted. In cases where the missing values are critical, the center may be contacted if the missing data falls into categories 1 or 3 above.

## (2) Outlier Assessment

Before analyses can begin, data for all patients must be reviewed to determine that all data points appear reasonable. Each dependent and independent variable included in the study file must be checked. Values should fall within expected ranges and all negative values flagged. One way to look for outliers is to use PROC UNIVARIATE in SAS. The following statement will give, along with other information, the median, range, 5% and 95% quantiles, and a stem and leaf plot for DEPVAR1:

```
PROC UNIVARIATE FREQ PLOT;  
VAR DEPVAR1;
```

Values above the 95% quantile and below the 5% quantile should be discussed with the Study Chair to determine if the values are appropriate. In some cases, cross tabulations among related variables should be done. The Study Chair can act as a resource in these matters. Report Forms of patients with outliers should be reviewed. In some cases the information may have been entered incorrectly, or the data manager may have made a note in the margin of the Report with an explanation of the value. There may also be attached letters and comments at the end of a Form with further details. When reviewing the Form, also look at the back of the last page to see if the team has been contacted regarding this matter. The team may have already responded to a previous request by the IBMTR/ABMTR regarding the variable. The Communications Coordinator may have recent letters regarding outliers that have not yet been processed and attached to the Report Forms. Finally, it may be necessary to contact the center that completed the Report Form to verify the value in question (see section II.D).

## (3) Variables with 'Other' categories

Data collection forms change as technology changes and new drugs and procedures are developed. Some studies may include patients with data collected on older versions of the Report Form. When a drug or procedure is rare, the response to a question may be put into an 'other' category with a space provided to write in the specific information. As the drug comes into frequent use, a new category is created on a new version of the Report Form. At times data in these "other" categories will be needed for analyses. Currently, these data are entered as text field and are retrievable from the database. In the past, only the "other" or a few prespecified categories of "other" were entered. If it is necessary to know what the "other" was, the statistician must work with the Manager of Information Systems to assign personnel to extract and enter this information from the Report Forms.



## D) INTERACTION WITH TEAMS

It is sometimes necessary to communicate with Individual centers in preparing a study file. Reasons include:

1. Missing data
2. Data discrepancies/outliers
3. Need for supplemental data not collected on current Report Forms

For discrepancies and missing data, the Communications Coordinator usually contacts the individual center regarding these matters via letter or fax. The following information should be included with each request to facilitate response by the center: registry, Registry ID number, Team number, IUBMID, disease, birth date, and transplant date. For missing data, provide the specific Report Form number, page and item number. For discrepancies and outliers, provide the specific Report Form number, page, item number and the specific question you want answered. If several teams involving many patients must be contacted regarding the same variable, please create worksheets for each center, suitable for faxing, listing the patient information cited above, and space for the team to write in the response. The sheets should be titled with the specific project name and full center name at the top of the page. If a center is responding about multiple patients, the number of patients for each team should be given at the end of each team worksheet. A draft of a letter to the team, to be enclosed with the worksheet, should also be given to the Communications Coordinator. The brief letter should state the project name and purpose of the request, what data are required and the date by which the data are required.

New or more specific data, not collected on the Report Form, is sometimes required for all patients in the study. For a single item, the method described above for obtaining responses for the same variable from multiple teams should be used. Worksheets should be created for every team and a letter drafted, to be included with each worksheet.

Some studies require a supplemental data collection form to be prepared to collect information on new topics involving multiple questions, and dates. The statistician should work closely with the Study Chair and with Manager of Information Systems in designing the new supplemental form. After an initial draft is completed, the draft should be distributed to the rest of the Working Committee for comments and piloted by several data managers to ensure that the responses are as expected. Once the final form is available, it should be given to the Communications Coordinator along with worksheets for every team and a draft of a letter to be included with each worksheet as described above.

## **E) DATABASE CORRECTIONS**

Whenever a team responds with missing data or resolves a discrepancy, the Form must be corrected with red ink, your initials and date noted, and the letter or fax from the team attached to the form. The Report Form is then forwarded to the Systems Coordinator with a note specifying the data base change. (Some changes need physician review before the change is incorporated in the database; this is the responsibility of the Systems Coordinator.)

It may be necessary to also make these changes directly to the study file ('hard code' the changes) if analyses are proceeding quickly. There will be a lag between the time the Systems Coordinator receives the changes and the time an updated database retrieval with the appropriate changes is made.

### III. INTERMEDIATE AND TERMINAL EVENTS USED IN STUDIES

#### A) GENERAL OUTCOMES

##### (1) Engraftment

*Neutrophil Recovery* -- defined for separate targets of either  $\geq 500$  or  $\geq 1000$  neutrophils/mm<sup>3</sup> as the time to achieve the specific indicator (NEUT5 or NEUT10). The interval variables are INTXNT5 and INTXNT10, respectively, which are measured in days. The interval for a patient who has not achieved the specific indicator is equal to SURVDAYS. This event is summarized by the cumulative distribution function (1-Survival curve).

*Platelet Recovery* -- defined for separate targets of either  $\geq 20,000$ ,  $\geq 50,000$  or  $\geq 100,000$  platelets/mm<sup>3</sup> as the time to achieve the specific indicator (PLAT20, PLAT50 or PLAT100). This event is evaluable at 7 days from the last platelet transfusion. The interval variables are INTXP20, INTXP50, INTXP100, respectively, which are measured in days. The interval for a patient who has not achieved the specific indicator is equal to SURVDAYS. This event is summarized by the cumulative distribution function (1-Survival curve).

*Graft failure* -- Failure to achieve neutrophils  $\geq 500$ /mm<sup>3</sup> or achievement of  $\geq 500$  neutrophils/mm<sup>3</sup> followed by a decrease to  $< 500$ /mm<sup>3</sup>. The indicator variable is REJECT and the interval variable is INTXFAIL, which is measured in months. The interval for a patient who never achieves neutrophils  $\geq 500$ /mm<sup>3</sup> is 0.03. The interval for a patient who achieves  $\geq 500$ /mm<sup>3</sup> and then has a decrease is the first day the neutrophils are  $< 500$ /mm<sup>3</sup>. The interval for a patient who does not have graft failure (REJECT=0) is equal to INTXSURV. This event is summarized by the cumulative distribution function (1-Survival curve).

##### (2) Graft-versus-host disease (GVHD)

*Acute GVHD* -- development of Grade I-IV acute GVHD. The time of first attainment of acute GVHD is the event time even if the maximum grade occurs later. Patients are at risk for this event at 21 days after transplant, if they have evidence of engraftment. In most analyses patients with a grade of II-IV are considered to have acute GVHD and patients with a grade of 0-I are not considered to have acute GVHD. The indicator variable for any Grade II-IV GVHD is AGVHIX1. A variable which indicates both the presence and severity of acute GVHD is AGVH1. The interval variable is DATXAGV1, measured in days. In some studies, particularly those involving donors other than HLA-identical siblings, the incidence of grade III-IV AGVHD is of interest. This indicator variable is AGVHIX34. The interval variable is DATXAG34, measured in days. The interval for a patient who has not achieved the specific acute GVHD indicator is equal to SURVDAYS. This event is summarized by the cumulative distribution function (1-Survival curve).

*Chronic GVHD* -- development of any chronic GVHD. The time of first attainment of chronic GVHD is the event time. Patients are at risk for this event at 90 days after transplant. The indicator variable for any chronic GVHD is CGVHIX1. The interval variable is INTXCGV1, measured in months. The interval for a patient who has no chronic GVHD is equal to INTXSURV. This event is summarized by the cumulative distribution function (1-Survival curve).

### **(3) 100 Day Mortality**

This event is death prior to 100 days posttransplant. Patients alive at last observation with less than 100 days of follow-up are not considered at risk for this event. The relevant data for this event is a binary variable, MORT100, with the value 1 if they die prior to 100 days and 0 if they are alive at day 100. This event is summarized by the estimated probability of surviving 100 days.

### **(4) Survival**

The variable which indicates which individuals die is SURVHI. The codes 1 and 3 correspond to censored observations. The code 2 corresponds to a death. The time to death (or last contact for survivors) is represented in the variable INTXSURV, measured in months. Patients are at risk for this event at the time of transplant. The event is summarized by a survival curve.

## **B. LEUKEMIA-SPECIFIC OUTCOMES**

### **(1) Treatment-related Mortality (also called Transplant-related Mortality or Non-relapse Mortality)**

This event is defined as death in continuous remission. Patients who relapse or have persistent leukemia are considered censored for this event. The time to the event is coded in the variable INTXRHI, measured in months. For a censored patient without relapse or persistent leukemia, the interval interval is equal to INTXSURV. The variable TXMORT is the event indicator with a code of 1 reflecting death without disease and a code of 0 reflecting a censored observation. Patients are at risk for this event at the time of transplant. This event is summarized by the cumulative distribution function (1-Survival curve).

## **(2) Relapse**

This event is defined as a clinical relapse of leukemia. Patients who die without disease are considered censored for this event. The time to the event is coded in the variable INTXRHI, measured in months. For a patient who has not relapsed the interval is equal to INTXSURV. For patients who receive a transplant while not in remission and do not achieve remission the time to the event is set at INTXRHI=0.03 months. The variable REALAPS is the event indicator with a code of 1 reflecting relapse and a code of 0 reflecting a censored observation. Patients are at risk for this event at transplant. This event is summarized by the cumulative distribution function (1-Survival curve).

Some patients, particularly those with chronic myelogenous leukemia, may have recurrence or persistence of a chromosome or molecular marker of their disease without clinical relapse. In most but not all studies, these patients are treated as being in remission until clinical evidence of leukemia develops. A discussion of the definition of relapse with the Study Chair should precede analysis of this variable.

## **(3) Leukemia -Free Survival (sometimes called Disease Free Survival)**

This event corresponds to treatment failure. It is defined as death or relapse. The time to this event is the minimum of the death and relapse time and is coded in the variable INTXRHI, measured in months. For a patient who is alive in remission the interval is equal to INTXSURV. The variable LFS is the event indicator with a code of 1 reflecting death or relapse and a code of 0 reflecting a censored observation. Note that one should check that  $LFS=TXMORT+REALAPS$ . Patients are at risk for this event at the time of transplant. The event is summarized by a survival curve.

## **C. LYMPHOMA AND SOLID TUMOR SPECIFIC OUTCOMES**

### **(1) Treatment Related Mortality**

In general the definition is the same as for leukemia, i.e. death in continuous remission. However, lymphoma and solid tumors, even if cured, may take some time to resolve after transplant. Additionally, tests done to evaluate the status of these diseases may not be done for some time after transplant. Consequently a patient may die before the status of the lymphoma or solid tumor is determined. Any death occurring in the first 28 days after transplantation for a lymphoma or solid tumor is considered to be treatment related. Deaths occurring in the next 72 days are assumed to be treatment-related if the disease status is reported as unknown or not evaluable. The latter cases should be reviewed by the Study Chair. The indicator variable is TXMORTL with a value of 0 for censored cases and a value of 1 for patients reflecting treatment-related mortality. The interval variable is INTXREL, which is the time to relapse or death in remission, measured in months. For patients who are censored alive, INTXREL is equal to INTXSURV.

## **(2) Progression**

This event is defined as an increase in the size of sites of known disease or development of new sites of disease after transplant. It may follow a period of "stable" disease where the lymphoma or solid tumor has < 50% reduction in known sites of disease but not new sites of disease and no increase of disease at any site. It may follow a partial remission where the tumor had a 50-99% reduction in size with no new sites of disease. It may follow a complete remission. Any recurrence of tumor or increase in size of tumor after a complete or partial remission is considered progression, even if the extent of tumor is less than pretransplant. Patients who die without progression (may have stable disease, partial or complete remission) are considered censored for this event. The time to the event is coded in the variable INTXPROG, measured in months. For censored patients the variable INTXPROG is equal to INTXSURV. The variable PROGRESS is the indicator of progression with a value of 1 reflecting progression and a value of 0 denoting a censored observation. Patients are at risk of this event 28 days after transplant. This event is summarized by the cumulative distribution function (1-survival).

## **(3) Progression- Free Survival**

This event is defined as death or progression. The time to this event is the minimum of the death and the progression times. The time to the event is coded in the variable INTXPROG, measured in months. For patients who have not progressed, INTXPROG is equal to INTXSURV. The variable PFS is the event indicator with a value of 1 reflecting death in the first 28 days posttransplant or death or progression after day 28 posttransplant. A code of 0 denotes a censored observation. Patients are at risk for this event at the time of transplant. This event is summarized by a survival curve.

## **(4) Relapse (Or Recurrence)**

This event is defined as clinical recurrence of disease after a posttransplant remission. *For patients transplanted in remission or for patients who achieve a complete remission after transplant*, recurrence is the same as progression. The interval is coded in the variable INTXREL, measured in months. The variable RECUR is the indicator of recurrence with a code of 1 reflecting relapse and a code of 0 reflecting a censored observation. Patients transplanted in remission or who achieve remission after transplant are at risk after 28 days posttransplant for this event. This event is summarized by the cumulative distribution function (1-Survival curve).

## **(5) Disease-Free Survival**

The event is defined as death or recurrent disease. The time to this event is the minimum of the death and relapse times, where patients who never have a complete remission posttransplant are considered to experience the event at day 1. The time is coded in the variable INTXREL, measured in months. The variable DFS is the event indicator with a code of 1 reflecting the event has occurred and a code of 0 reflecting a censored observation. The event is summarized by a survival curve.

**TABLE OF VARIABLE NAMES**

<b><u>Variable</u></b>	<b><u>Indicator (values)</u></b>	<b><u>Interval From Transplant (units)</u></b>
<b><u>Engraftment</u></b>		
500 neutrophils/mm <sup>3</sup> *	NEUT5 (0,1)	INTXNT5 (days)
1000 neutrophils/mm <sup>3</sup> *	NEUT10 (0,1)	INTXNT10 (days)
20,000 platelets/mm <sup>3</sup> *	PLAT20 (0,1)	INTXP20 (days)
50,000 platelets/mm <sup>3</sup> *	PLAT50 (0,1)	INTXP50 (days)
100,000 platelets/mm <sup>3</sup> *	PLAT100 (0,1)	INTXP100 (days)
Graft Failure	REJECT (0,1)	INTXFAIL (months)
<b><u>GVHD</u></b>		
Acute GVHD grade 0-4	AGVH1 (0,1,2,3,4)	DATXAGV1 (days) or INTXAGV1 (months)
grade 0,1 vs 2,3,4	AGVHIX1 (0,1)	DATXAGV1 (days) or INTXAGV1 (months)
grade 0,1,2 vs 3,4*	AGVHIX34 (0,1)	DATXAG34 (days) or INTXAG34 (months)
Chronic GVHD grade 0,1,2,4	CGVH1 (0,1,2,4)	DATXCGV1 (days) or INTXCGV1 (months)
grade 0 vs 1,2,4	CGVHIX1 (0,1)	DATXCGV1 (days) or INTXCGV1 (months)
<b><u>100 Day Mortality</u></b>		
100 day mortality*	MORT100 (0,1)	
<b><u>Survival</u></b>		
Vital Status	SURVHI (1,2,3)	INTXSURV (months)
<b><u>Leukemia-Specific Outcomes</u></b>		
Treatment-related mortality	TXMORT (0,1)	INTXRHI (months)
Relapse	REALAPS (0,1)	INTXRHI (months)
Leukemia-free mortality	LFS (0,1)	INTXRHI (months)
<b><u>Lymphoma and Solid Tumor Specific Outcomes</u></b>		
Treatment-related mortality*	TXMORTL (0,1)	INTXREL (months)
Progression*	PROGRESS (0,1)	INTXPROG ( months)
Relapse/Recurrence*	RECUR (0,1)	INTXREL (months)
Disease-free survival*	DFS (0,1)	INTXREL (months)

\* Variable is NOT currently coded in retrieval; must be computed in study file

## IV. DESCRIPTIVE STATISTICS

Descriptive statistics are used to summarize the characteristics of a data set. They are used to check for outliers, to test for differences in the study population when a hypothesis testing model is to be built and to help in discretizing continuous covariates for use in future analyses.

### A) DISCRETE COVARIATES

For the discrete covariates, we calculate the number and percentage of patients for each category. In a hypotheses testing study the chi-square test is used to check whether the covariate has same distribution for all levels of the main effect.

Summary statistics and tests are performed using the SAS procedure FREQ. For example, the following SAS procedure will yield the number and percentage of males and females for each treatment group, and *p-value* of the chi-square test:

```
PROC FREQ; TABLES SEX*GROUP / CHISQ;
```

When the sample size is small relative to the size of a contingency table, chi-square test may not be a valid test. In this case SAS will print a warning message that the chi square test is not valid. In such a case, Fisher's exact test is a more appropriate test. We then change "chisq" option to the option "exact" in the SAS code which will give us the *p-value* of Fisher's exact test.

### B) CONTINUOUS COVARIATES

For continuous covariates we report, in writing committee memos or manuscripts, medians and ranges for the variable. For discussion at statistical staff meetings or with the clinical investigator, we use the SAS procedure PROC UNIVARIATE to compute summary statistics that allow us to check for outliers. The coding for this procedure for a covariate age is

```
PROC UNIVARIATE PLOT FREQ; VAR AGE;
```

This command will produce summary statistics (mean, median, range, standard deviation, etc.), a stem-and-leaf plot or a histogram, and the estimated frequencies for each value of the variable. To identify outliers one could add the statement ID PATIENTNO; , for example, where PATIENTNO is some identifier of the patient. This will associate the value of PATIENTNO with the values UNIVARIATE prints for the five largest and smallest observations. Using a BY variable, one can have SAS produce a UNIVARIATE analysis for each level of the factor of primary interest in a hypothesis testing study.

When the goal of the study is to compare outcomes between treatment groups, the Kruskal-Wallis test is used to check if the distribution of a continuous factor is the same over the groups. The SAS procedure used is PROC NPAR1WAY which is coded as follows:

```
PROC NPAR1WAY WILCOXON; CLASS GROUP; VAR AGE;
```

### C) FOLLOW-UP TIME

To compare the survival probabilities, we need to study the follow-up time. We use the product-limit estimator proposed by Kaplan-Meier to estimate the probability of the follow-up time, and log-rank test to test if the cohorts have same probability of follow-up times. To do so, let TIME be the time of event or end of follow-up, and STATUS be the indicator of censorship; that is STATUS=1 if patient is still alive; 0 otherwise. Note that here we are coding deaths as censored observations and usual censored observations as events since we are trying to estimate the distribution of the on study times if patients had not died.



The SAS procedure LIFETEST will estimate the probability distribution of the follow-up time, the median follow-up time, the range of follow-up times (largest and smallest on study times) and *p-value* of the log-rank test which is used to check for differences between groups:

```
PROC LIFETEST; TIME TIME*STATUS(0); STRATA GROUP;
```

## D) SURVIVAL

The survival curves are useful for preliminary examination of the data, for computing the common interested quantities such as median survival time or the probability of survival at some point in time, and for evaluating the fit of regression models. The standard tests for comparing survival curves across the different treatment groups are important for analyzing the data. In survival analyses the time to event data could be censored and/or truncated. Here we only discuss the methods involving right censored time to event data. For other type censored or truncated data see Klein and Moeschberger (1997).

### (1) Summary Curves

The standard estimator of the survival curve is the product-limit estimator which was proposed by Kaplan-Meier (1958), and is often called the Kaplan-Meier estimator or the actuarial estimate. The variance of the product-limit estimator is estimated by Greenwood's formula. The SAS's PROC LIFETEST procedure provides this estimates of survival functions and it's standard error. Let TIME be the event time and STATUS be indicator of the noncensorship, that is, STATUS=1 if event occurred and 0 otherwise. The SAS codes are

```
PROC LIFETEST;
TIME TIME*STATUS(0);
```

This command will produce the summary survival curve. To make plots of the survival curves an output data set can be produced which contains the survival estimates and their standard errors. An example of the coding is as follows:

```
PROC LIFETEST DATA=TEMP NOPRINT
OUTSURV=PLOTME;
TIME INTXRHI*NLFS(0);
STRATA DISPX;
```

This coding produces the data set TEMP which contains the following variables:

```
DISPX -- The stratification variable
INTXRHI --The time variable
_CENSOR_ -- The indicator of censoring (1-censored, 0-dead)
SURVIVAL --The estimate of the survival function at time INTXRHI in strata
DISPX
SDF_LCL SDF_UCL -- 95% Naive confidence interval for the survival function
_STRTUM_ -- Strata number
```

Note that for a censored observation the values for the confidence interval are missing.

To plot the survival curves the following code could be used. In this case there are 5 levels to the variable DISPX. We will create variables S1, ..., S5 which have the estimates for the respective strata. (In the data statement the variables R1, ..., R5 are the estimates of 1-SURVIVAL used when drawing graphs for relapse curves). To Indicate a censored observation we will put the symbol "I" at each censored observation. The values of the survival function at the

censored observation are coded in CS1, ..., CS5 (CR1, ..., CR5 for relapse). The data set revised is used in plotting.

```

DATA REVISED; SET PLOTME;
IF _STRTUM_=1 THEN DO;
  S1=SURVIVAL;
  R1=1-SURVIVAL;
  IF _CENSOR_= 0 THEN CS1=.;
  ELSE DO; CS1=S1; CR1=R1; END;
END;
ELSE IF _STRTUM_=2 THEN DO;
  S2=SURVIVAL;
  R2=1-SURVIVAL;
  IF _CENSOR_= 0 THEN CS2=.;
  ELSE DO; CS2=S2; CR2=R2; END;
END;
ELSE IF _STRTUM_=3 THEN DO;
  S3=SURVIVAL;
  R3=1-SURVIVAL;
  IF _CENSOR_= 0 THEN CS3=.;
  ELSE DO; CS3=S3; CR3=R3; END;
END;
ELSE IF _STRTUM_=4 THEN DO;
  S4=SURVIVAL;
  R4=1-SURVIVAL;
  IF _CENSOR_= 0 THEN CS4=.;
  ELSE DO; CS4=S4; CR4=R4; END;
END;
ELSE IF _STRTUM_=5 THEN DO;
  S5=SURVIVAL;
  R5=1-SURVIVAL;
  IF _CENSOR_= 0 THEN CS5=.;
  ELSE DO; CS5=S5; CR5=R5; END;
END;

```

PROC GPLOT is used to draw the graph. We are plotting 10 curves so 10 SYMBOL statements are needed. For the first 5 a step function is drawn. These are the curves S1, ..., S5. For the next 5, no curve is drawn. Only the symbol | is plotted.

```

PROC GPLOT DATA=REVISED;
SYMBOL1 REPEAT=5 COLOR=BLACK I=STEPLJ V=NONE W=1 L=1;
SYMBOL2 R=5 COLOR=BLACK I=NONE F=SWISS V='|';
PLOT (S1 S2 S3 S4 S5 CS1 CS2 CS3 CS4 CS5)*INTXRHI/OVERLAY;
RUN;

```

## (2) Comparisons of Survival Curves

If two different treatments are given to two groups separately, one of the most important questions would be "Did two treatments make a difference in the probability of survival?". To answer this question, we need to test the null hypothesis that the survival functions are same across the two treatment groups, that is  $H_0: S_1(t) = S_2(t)$ , for all  $t$ , where  $S_1(t)$  and  $S_2(t)$  are the survival functions for treatment group 1 and 2 separately. We use a log-rank test for testing this null hypothesis (see Klein and Moeschberger Section 7.3). The SAS codes for the log-rank test are

```
PROC LIFETEST;
TIME TIME*STATUS(0);
STRATA GROUP;
```

Note that the "TEST" statement in PROC LIFETEST is not used here.

The above test is a comparison of the entire survival curves. Occasionally we wish to compare two curves at a fixed point in time,  $T_0$ . To perform this test the following statistic is used

$$Z = \frac{S_1(T_0) - S_2(T_0)}{\sqrt{V[S_1(T_0)] + V[S_2(T_0)]}}$$

where  $V[S_k(T_0)]$  is the estimated variance of the Kaplan-Meier Estimator for group  $k$ ,  $k=1,2$ . This test is typically done by hand on a calculator using the output of PROC LIFETEST.

### (3) Confidence Intervals for Survival function

As noted above the output data set from PROC LIFETEST contains a 95% confidence interval for the survival function. Recent statistical literature suggests that these intervals are suspect for small to moderate samples. A better way of constructing intervals is to use the log transformed intervals (Klein and Moeschberger Section 4.3). The formula for these intervals is as follows

$$(S(t)^{1/\theta}, S(t)^\theta) \text{ where } \theta = \exp\left\{\frac{Z_{1-\alpha/2} \sigma(t)}{\ln[S(t)]}\right\}, \text{ and } \sigma^2(t) = V[S(t)]/S(t)^2.$$

Using the output data set from LIFETEST a 95% confidence interval can be computed as follows:

```
DATA NEW; SET OLD;
SE=(SDF_UCL- SDF_LCL)/(2*1.96*SURVIVAL);
THETA=EXP(1.96*SE/LOG(SURVIVAL));
LOWER=SURVIVAL**(1/THETA);
UPPER=SURVIVAL**THETA;
```

Note that the confidence intervals constructed in this manner are pointwise intervals.

### E) 100 Day mortality

When analyzing bone marrow transplant data it is sometimes important to study 100 day mortality. In the research database, virtually all patients either died within 100 days or had follow-up time longer than 100 days since 100 days of follow-up is required for the initial report form. In the registration database, there are some cases with follow-up time less than 100 days. However, the percentage of such cases is very small (less than 1%). For those patients with follow-up times less than 100 days, whether they will die within 100 days is unknown. We exclude these cases when analyzing the 100 day mortality rate. We use a chi-square test to test whether the 100 day mortality rates are same across the treatment groups. Define the variable  $Z=1$  if patients died within 100 days and 0 otherwise. The SAS codes are

```
PROC FREQ; TABLES Z*GROUP / CHISQ;
```

## V MULTIVARIATE MODELS FOR SURVIVAL

In this section we discuss statistical procedures for modeling multivariate survival. Multivariate survival modeling is used in two related situations: The first is the situation where we wish to compare two or more groups after making adjustments for other factors which may influence outcome. The second is where we wish to determine which risk factors may be related to a given outcome. We shall term these hypothesis testing and exploratory model building analyses, respectively.

### A. Definitions

#### Factors

The analysis to be performed is a regression analysis where the endpoint is the time to some event (See Section III for a definition of the event times). The time to event is called the dependent variable. Explanatory information is contained in a set of *factors*. A factor is a set of explanatory covariates that describes a particular attribute of the patient being transplanted. Associated with a factor is a degree of freedom. The *degree of freedom* is the number of independent variables which make up the factor.

When the phenomena under consideration is categorical with  $k$  categories, then the factor consists of  $k-1$  binary covariates with each indicating a given level of the covariate (one level is the baseline so only  $k-1$  levels are needed). It should be noted that the coding within a factor is not unique, since any one of the  $k$  levels can be used as the baseline. However, when making an inference about a factor any of the equivalent codings will give rise to the same conclusion.

As an example consider the coding of a factor which represents the sex of the donor and recipient of an Allo transplant. This factor will have three degrees of freedom and require the definition of three binary covariates. One coding, which has the male donor and male recipient (M->M) as the baseline is:

$$\begin{aligned} Z_1 &= \begin{cases} 1 & \text{if F-> F} \\ 0 & \text{otherwise} \end{cases} \\ Z_2 &= \begin{cases} 1 & \text{if F-> M} \\ 0 & \text{otherwise} \end{cases} \\ Z_3 &= \begin{cases} 1 & \text{if M-> F} \\ 0 & \text{otherwise} \end{cases} \end{aligned}$$

An alternate coding (with the same baseline is)

$$\begin{aligned} Z_1 &= \begin{cases} 1 & \text{if Female donor} \\ 0 & \text{otherwise} \end{cases} \\ Z_2 &= \begin{cases} 1 & \text{if Female recipient} \\ 0 & \text{otherwise} \end{cases} \\ Z_3 &= \begin{cases} 1 & \text{if Female Donor and Recipient} \\ 0 & \text{otherwise} \end{cases} \end{aligned}$$

Other examples of factors are as follows:

Factor	Coding	Degrees of Freedom
Age as a continuous factor	$Z = \text{Age}$	1
Age Categorized into 0-10 <sup>1</sup> , 10-20, >20	$Z_1 = \begin{cases} 1 & \text{if } 10 < \text{Age} \leq 20 \\ 0 & \text{otherwise} \end{cases}$ $Z_2 = \begin{cases} 1 & \text{if } \text{Age} > 20 \\ 0 & \text{otherwise} \end{cases}$	2
Year of Transplant <sup>2</sup> (Patients transplanted in 87-92)	$Z_1 = \begin{cases} 1 & \text{if } 88 \\ 0 & \text{otherwise} \end{cases}$ $Z_2 = \begin{cases} 1 & \text{if } 89 \\ 0 & \text{otherwise} \end{cases}$ $Z_3 = \begin{cases} 1 & \text{if } 90 \\ 0 & \text{otherwise} \end{cases}$ $Z_4 = \begin{cases} 1 & \text{if } 91 \\ 0 & \text{otherwise} \end{cases}$ $Z_5 = \begin{cases} 1 & \text{if } 92 \\ 0 & \text{otherwise} \end{cases}$	5

1) 0-10 baseline

2) 87 Baseline

Factors can be either *fixed time* or *time dependent* factors. A fixed time factor is one whose value is known at the time of transplant (or at the "zero" time of the study). Examples of fixed time factors are year of transplant, preparative regimen, age, sex, GVHD prophylaxis, etc. Fixed time covariates are dealt with in Chapter 8 of Klein and Moeschberger

Time dependent factors are those whose values are not known at the time of transplant. These may be measurements taken at some planned point after transplant, (e.g. Karnofsky score at 6 months post transplant), the occurrence of intermediate events (e.g., occurrence of acute GVHD, platelet recovery time, etc.), events which happen at some time after transplant (e.g. second transplant), or artificially created (e.g., factors used to check model assumptions or factors to adjust for non proportional hazards (See V.C below)).

### Censoring and Truncation

*Right censoring* occurs when at the last observation of the subject the event under study has not yet occurred. This may be because either the patient is still alive and disease free at their last observation time, because the patient was lost to follow-up, or because some other event not under study occurred. Censored data is partial information about the timing of the event of interest in that all we know is that for this patient the event has yet to occur at the last time we saw the patient. The following table summarizes censoring for some common events we study.

Event of Interest	Patient Status at last follow-up which leads to censoring	
	Death	Alive
Relapse or Progression		Alive and Disease free Dead without Disease
Treatment related mortality		Alive and Disease Free
Acute GVHD		Dead without acute GVHD Alive without acute GVHD
Chronic GVHD		Dead without chronic GVHD Alive without chronic GVHD

*Left Truncation* occurs when some intermediate event must occur before the patient becomes at risk to experience the event in which we are interested. That is when the event time,  $X$ , is measured from some landmark but only subjects who experience some intermediate event at time,  $V$ , are to be included in the study. This is the case, for example if we wish to draw inference about  $X$ , the time from transplant to death or relapse, for those patients whose platelets have recovered to a self sustaining level. If  $V$  is the time until platelets recover for the patient, then only patients who experience this intermediate event are entered into the study. Life lengths in this study will be left truncated. The times  $V$  are sometimes called *delayed entry times*.

Left truncation also occurs when we are comparing patients given a transplant to those given chemotherapy. Since we only observe patients who were transplanted in our data base, if the "zero" point is the time of diagnosis, then our patients are not a risk to die until they are transplanted and as such they are left truncated at the time of transplant. Section 9.4 of Klein and Moeschberger discuss left truncation.

### Cox Regression Model and Relative Risks

The basic model for analysis is the proportional hazards model or the Cox regression model. For this model the hazard rate for an individual with set of covariates  $(Z_1(t), \dots, Z_p(t))$  is

$$h[t | Z_1(t), \dots, Z_p(t)] = h_0(t) \exp[\beta_1 Z_1(t) + \dots + \beta_p Z_p(t)].$$

Here the  $\beta$ 's are called *risk coefficients* and  $h_0(t)$  is the arbitrary *baseline hazard rate*. Estimation of the risk coefficients for this model is based on a *partial likelihood function*. While there are several formulations for this partial likelihood we shall use the default partial likelihood available in SAS®, namely *Breslow's* partial likelihood. (See Klein and Moeschberger Section 8.3).

Estimates of the  $\beta$ 's, denoted by  $b_1, \dots, b_p$ , and the covariance matrix of the estimates are available in the SAS® procedure PHREG.

When all the factors are fixed then the *relative risk* of the event for a patient with a set of covariates,  $Z_1, \dots, Z_p$  as compared to a patient with covariates  $Z_1^*, \dots, Z_p^*$  is the ratio of their respected hazard rates, which in this model is given by

$$\exp[\beta_1 (Z_1 - Z_1^*) + \dots + \beta_p (Z_p - Z_p^*)]. \quad (1)$$

When  $Z_k$  are binary covariates (i.e. 0 1 valued) the quantity  $\exp[\beta_k]$  is often called the relative risk of the covariate  $Z_k$ . Here this quantity is the ratio of the hazard rate of someone with a value of 1 for this covariate as compared to someone with a value of zero for this covariate, when all other covariates are the same for the two individuals. When  $Z_k$  is one of the covariates that make up a factor then this is the relative risk of an individual with category  $Z_k$  compared to a baseline individual, again all other factors held the same. Relative risk of an individual with category  $k$  as compared to an individual with category  $j$  of a given factor is given by  $\exp[\beta_k - \beta_j]$ , which is a special case of (1).

100x(1- $\alpha$ ) confidence intervals for the relative risk are given by the following formula:

$$\begin{aligned} \text{Estimate} &= \exp[b_k] \\ \text{Confidence Interval} &= (\exp\{b_k - z_{1-\alpha/2} \text{SE}[b_k]\}, \exp\{b_k + z_{1-\alpha/2} \text{SE}[b_k]\}) \end{aligned}$$

$$\text{Estimate} = \exp[\beta_1 (Z_1 - Z_1^*) + \dots + \beta_p (Z_p - Z_p^*)]$$

Confidence Interval =

$$(\exp\{b_1 (Z_1 - Z_1^*) + \dots + b_p (Z_p - Z_p^*) - z_{1-\alpha/2} S\}, \exp\{b_1 (Z_1 - Z_1^*) + \dots + b_p (Z_p - Z_p^*) + z_{1-\alpha/2} S\}),$$

where

$$S^2 = \sum_{j=1}^p \text{Var}[b_j] (Z_j - Z_j^*)^2 + \sum_{i \neq j} \text{Cov}[b_j, b_i] (Z_j - Z_j^*) (Z_i - Z_i^*)$$

and  $Z_{1-\alpha/2}$  is the  $(1-\alpha/2)$  percentile of a standard normal.

## B. Creating Factors For Dependent Variables

### 1. Categorical Data

If the variable has  $k$  categories then  $k-1$  binary covariates are created. Each covariate is the indicator of whether a patient is in a particular category. One category is the baseline and when a patient is in this category all of the  $k-1$  covariates are zero.

Each category must contain at least 5% of the sample and at least 5% of the events to be considered as a separate category. If this criterion is not met then the category must be collapsed with another biologically compatible category or cases with this category should be excluded from the study.

### 2. Missing values

When the number of missing values is small or the number of events with missing data is small then these cases are excluded from the study. By a small number of cases we mean less than 5% of the data or less than 20, whichever number is smaller. By a small number of events we mean less than 5% of the events or 5 events, whichever is smaller.

When the number of missing values is large then missing is considered as a separate factor and the number of categories is increased by 1.

These determinations should be made before any attempt at modeling the factors related to the event time is performed and before any diagnostic checks are made.

### 3. Discretizing a continuous covariate

Categorical covariates are easier to interpret and should be used in most cases. To determine the cut points to use the following procedure is used.

Step 1. Use biologically relevant cut points. These cut points are based on the physician investigators knowledge of the biology of the disease and transplant regime under study. They may be based on the transplant literature, consensus of the Writing or Working committee, or based on accepted practice in previous IBMTR/ABMTR studies. These cut points should be listed and discussed in the study protocol. Some categories for common covariates for all disease are listed in the following table:

Factor	Categories
Karnofsky Score Pre Transplant	<90, ≥90
Patient Age	By Decade (0-9, 10-19, ..., 40-50, >50)
Donor Age	By Decade (0-9, 10-19, ..., 40-50, >50)
Year of Transplant	80-85, 86-90, >90
WBC count at Diagnosis	< vrs ≥ 75 x10 <sup>9</sup> /L

Some disease specific factors specific to studies of leukemia are as follows:

Time to achieve first remission	< vrs ≥ 8 weeks
Duration of first remission	< vrs ≥ 8 weeks
Interval between transplant and most recent remission	< vrs > 1 year
WBC at Diagnosis	AML: < vrs ≥ 75 x10 <sup>9</sup> /L ALL (adults): < vrs ≥ 30 x10 <sup>9</sup> /L ALL (Children): < vrs ≥ 100 x10 <sup>9</sup> /L CML : < vrs ≥ 20 x10 <sup>9</sup> /L

Step 2. When cut points can not be agreed to in step one then a statistical method is used to find the cut point. A set of possible cut points is made. In theory the cut point to discretize a continuous covariate can at any value in the data set that corresponds to an event, the set of cut points will be restricted to "nice" values, typically integers or some multiple of the integers (e.g. for ages 5, 10, 15, 20, etc. years). Separate proportional hazards models are fit which includes only the single factor for each plausible discretation of the covariate. The partial log likelihood is recorded for each of these models (or the -2xlog likelihood value). The categorization which gives the largest of these partial likelihoods is then used in subsequent analyses. Note that in this technique the number of categories must be predetermined and each of the likelihoods is for a factor with the same degrees of freedom.

NOTE: The proposed categories for all continuous covariates must be circulated to the Writing Committee for review before any multivariate analysis is performed.

### 3. Creating Time Dependent Covariates

There are two types of time dependent covariates, internal and external covariates. Internal covariates are intrinsic to the transplant process (e.g. acute GVHD) and external covariates are artificially created covariates typically arising by the need to either check the proportionality assumption or to adjust fixed covariates for non-proportional hazards. The creation of external covariates is discussed in Section V.C.

An internal covariate for an intermediate event is coded as follows:

$$Z(t) = \begin{cases} 1 & \text{if time to intermediate event} \leq t \\ 0 & \text{otherwise} \end{cases}$$

In PROC PHREG we could code acute GVHD as follows:



```

PROC PHREG;
MODEL TSUR*DEAD(0)=AGVH;
IF TAGVH <=TSUR AND IAGVH=1 THEN AGVH=1; ELSE AGVH=0;

```

Here TSUR is the time to the event; DEAD the event indicator with 0 indicating a censored observation; TAGVH the time to acute GVHD and IAGVH the indicator of acute GVHD with 1 denoting that acute GVHD has occurred.

*Caveat emporia:* When a time dependent covariate for an intermediate event is used only patients at risk for the event should be in the data set. For example to study acute GVHD only patients who have survived at least 21 days are included in the study. See Section III for these inclusion criterion.

## C. Checking Model Assumptions

### 1. Testing for proportional hazards

To check the assumption of proportional hazards an external time dependent covariate approach is used. Here a time dependent covariate is created for each of the covariates which make up a given factor. The covariate is of the form  $Z(t) = Z \ln(t)$ . A model is fit with both the original fixed time covariates and the created time dependent covariates. If the factor has  $k$  degrees of freedom then a Wald test, with  $k$  degrees of freedom, is performed to test that the hypotheses all the risk coefficients associated with the time dependent covariates are equal to zero. If this hypothesis is rejected than the factor has non proportional hazards. A 5% significance level is used for this test.

The testing for proportional hazards is performed separately for each factor. When the goal of the analysis is to test a particular hypothesis then the main factor of interest is included in each model.

The SAS<sup>®</sup> code to perform this analyses for a 3 degree of freedom factor with covariates Z1, Z2, Z3, a time to event TSUR and an event indicator DEAD (with code 0 for censored observations) is as follows:

```

PROC PHREG;
MODEL TSUR*DEAD(0)=Z1 Z2 Z3 ZP1 ZP2 ZP3;
PROP: TEST ZP1=ZP2=ZP3=0;
ZP1=Z1*LOG(TSUR);
ZP2=Z2*LOG(TSUR);
ZP3=Z3*LOG(TSUR);

```

## B ADJUSTMENTS FOR NON PROPORTIONAL HAZARDS

When the proportional hazards assumption is rejected than an adjustment to the model is needed. The adjustment depends on the number of non proportional hazards found, and whether estimates or tests of the effect of the factor with non proportional hazards is of interest.

If there are few factors, the factors are not of primary interest in the study and these factors have few categories then the analyses should be based on a stratified model. Here a single variable is created which includes a distinct value (the actual values of the variable are irrelevant) for each level of the factor. The model is then stratified on these new variables. In the above example the following SAS<sup>®</sup> code would be used to test a hypotheses about a new covariate, MAIN, stratifying on the factor Z1, Z2, Z3.

```

DATA NEW; SET OLD;
STRAT=0;
IF Z1=1 THEN ST=1;
IF Z2=2 THEN ST=2;
IF Z3=3 THEN ST=3;
PROC PHREG;
MODEL TSUR*DEAD(0)=MAIN;
STRATA ST;

```

A rule of thumb for determining if stratification is to be used is that each stratum should contain at least 20 observations and at least 5 events.

When stratification is not warranted then an artificial time dependent covariate is created to handle the non proportional hazards. That is we create two time dependent covariates for a given non-proportional hazards covariate. These are the early ( $t \leq \tau$ ) and late ( $t > \tau$ ) effects of covariate represented by the covariates

$$Z_E(t) = \begin{cases} Z & \text{if } t \leq \tau \\ 0 & \text{otherwise} \end{cases} \quad Z_L(t) = \begin{cases} Z & \text{if } t > \tau \\ 0 & \text{otherwise} \end{cases}$$

To find  $\tau$  the approach for finding the best cut point for a continuous covariate is used (See Section V.B.3.). In theory the only values one needs to check are the observed event times but in practice one should attempt to pick a set of biologically plausible values  $\tau$  and check the likelihood at these points. Once  $\tau$  is found then the proportional hazards assumption must be checked for each of the newly created time dependent covariates. If the assumption is found not to be valid then the above process is repeated.

## D. Stepwise Model Building

### 1 Initial Search

Stepwise model building is done either in hypothesis testing or exploratory analysis problems. The difference between the two is in the hypothesis testing situation the main effect to be tested is included in all models. The procedure is only used after the factors have been checked for proportional hazards and all problems with missing values have been resolved by either cleaning the data set or by creation of a missing category. The data set for this procedure must be the same for each of the models to be run for the procedure to be valid. The automated procedures in SAS<sup>®</sup> can only be used when all factors are single degree of freedom factors.

If there are  $M$  factors (other than the main effect) to be considered then the model building is as follows:

Step 1: Fit  $M$  models with each model containing only a single factor. Find the Wald  $p$ -value associated with the test of no effect of this factor on outcome. The factor with the smallest  $p$ -value ( $< 0.05$ ) is put into the model. Note if none of the factors are significant at the 5% level then the final model has no factors in it (except for the main effect in the hypothesis testing framework).

Step  $J$ ,  $J=2, \dots, M$ :

- A. Fit  $M-(J-1)$  models with the  $J-1$  factors left in the model from step  $J-1$  along with one of the  $M-J+1$  factors not in the model at the previous step included in the model. Find the Wald  $p$ -value for each new factor.
- B. If none of the new factors are significant at the 5% level (i.e. all have a  $p$ -value  $> 0.05$ ) then stop and used the model from step  $J-1$ .

C. If one of the factors has a p-value less than 0.05 then add it to the model and go to step J+1.

The model from this procedure is the working model. If all factors (except the possible main effect) are significant then it is the stage one model. If there is some factor, added at an earlier step, which is no longer significant then further tests should be performed on the model to remove non significant factors. In most cases this means that two of the factors are highly associated and the covariate which is simplest to interpret should be included in the final model. Finding the final model in this case will involve comparing models with and without the factor. Note models can be compared on the basis of the Akaike Information Criterion,  $AIC = -2 \log L + 2p$ , where  $p$  is the number of regression parameters in the model and  $L$  is the partial log likelihood.

## 2. Collapsing Categories

Once a first stage model is found it is reasonable to examine, in this model, the potential of collapsing categories for the individual factors. This should be done in collaboration with the physician investigator on the project so that biologically implausible categories are not created. If there are  $k$  categories there are  $k(k-1)/2$  tests to be performed. The tests are comparisons of each category with each other. For example if there are four categories, coded by three binary covariates  $Z_1$ ,  $Z_2$ , and  $Z_3$ , then the  $4 \times 3/2 = 6$  tests are as follows:

$H_0 \beta_1 = 1$  (category 1 = baseline)

$H_0 \beta_2 = 1$  (category 2 = baseline)

$H_0 \beta_3 = 1$  (category 3 = baseline)

$H_0 \beta_1 = \beta_2$  (category 1 = category 2)

$H_0 \beta_1 = \beta_3$  (category 1 = category 3)

$H_0 \beta_2 = \beta_3$  (category 2 = category 3).

Based on these tests the decision to recategorize the factor can be made and a phase two model with revised factors can be constructed. Of course the factors need to be retested in this revised model.

## 3. Testing for interactions

Interactions are tested in the phase two model. Which interactions to check should be a collaborative decision between the physician investigator and the statistician. In general it is advisable to check for interactions between a main effect and each of the factors being used to adjust for differences in the treatment arms.

To check for an interaction of a factor with  $M$  levels and a factor with  $P$  levels requires the creation of  $M \times P - 1$  binary covariates. To test for interaction we create  $(M-1) \times (P-1)$  new covariates by multiplying each of the  $(M-1)$  binary covariates of factor 1 by one of the  $(P-1)$  covariates of factor 2. A model is fit with the main effects of factors 1 and 2 ( $M+P-2$  covariates) and the  $(M-1) \times (P-1)$  new covariates (and any other factors in the phase two model). A Wald test, with  $(M-1) \times (P-1)$  is performed to test the hypothesis that the interaction covariates are all zero. If this test has a p-value greater than 0.05 then an interaction is not present.

If an interaction is found between two factors then the two factors are pooled into a single factor with  $(M \times P)$  categories ( $M \times P - 1$  binary covariates) found by picking one category from factor 1 and one from factor 2. Using the technique in Section V.D.2 the dimensionality of this factor is reduced to achieve a new model.

## E Testing for center effects

To test for possible center effects a random effects score test developed by Commenge and Andersen (1995) is used (See Klein and Moeschberger Section 13.2). The test is performed on the final model for the study and tests the hypothesis that there is no center effect against the hypothesis of a random center effect. A FORTRAN program is available to perform the test. Input to the program is the estimates of the risk coefficients from the final model, the estimated covariance matrix of the risk coefficients and the raw data.

If the score test rejects the hypothesis of no center effect then an adjustment for this effect is made using a Gamma frailty model (See Klein and Moeschberger Section 13.2). A SAS macro for this procedure is available.

## F PROC PHREG

The SAS procedure PHREG is used to perform most of the analyses discussed in this Section. It can be used with a slight modification for either right censored data or for right censored and left truncated data. The general form of the procedure for right censored data is

```
PROC PHREG options;
MODEL time*censoring(codes) = list of covariate/ options;
STRATA list /option;
Label : TEST hypothesis; (Can be repeated)
Program Statements.;
```

Here the code in italics is optional while the code in Caps is required. In this case time is the name of the variable containing the on study times, censoring is the name of the variable containing the censoring codes and values in (code) is a list of the codes for censored observation.

For left censored or delayed entry data an alternate form of the model statement is used. Here we say

```
MODEL (time1,time2)*censoring(codes) =list of covariate/ options;
```

In this case time1 is the time the subject first becomes at risk and time2 is the time at which the person was last seen. Individuals are in the risk set only for times between time1 and time2.

Before discussing the options for the procedure consider the following two examples of the model statement. For the first suppose that only transplant patients are being analyzed, that the event is overall survival with an on study time of intxsurv and an event indicator of survhi with values of 1 and 3 corresponding to censored observations. Then the model statement is coded as

```
MODEL intxsurv*survhi(1,3) = list/options;
```

If we wished to compare transplant to chemotherapy patients, say, then the second form of the model would be used. Suppose the time on study is measured from diagnosis and the variable TSUR holds the time values and the death indicator is DEAD with a value 0 corresponding to a censored observation. BMT patients are left truncated in this model and only become at risk at the time of transplant, while chemotherapy patients are at risk at time 0. We create a time variable ETIME, with value 0 for a chemotherapy patient and a value equal to the waiting time from diagnosis to transplant for a BMT patient. The model statement is now

```
MODEL (ETIME, TSUR)*DEAD(0) = list of covariate/ options;
```

Options of primary interest in the PHREG procedure are as follows.

In the PROC statement :

SIMPLE -- Gives the summary statistics for each fixed covariate.

COVOUT OUTEST=data set --Outputs a SAS data set with the parameter estimates and the covariance matrix. This can be inputted into PROC IML to find, for example, relative risks not routinely computed in PHREG.

In the MODEL statement

COVB -0 Prints the covariance matrix of the estimates

RISKLIMITS-- Prints estimates and 95% confidence intervals for the relative risk of each covariate compared to baseline.

ITPRINT--Prints the iteration history. This is important to look at to determine if the numerical routine to estimate the risk coefficients has in fact converged. NOTE SAS will not routinely tell you that there is a problem with convergence.

In the STRATA statement

MISSING -- Tells SAS to have missing as one of the strata. If this is not there SAS will toss out anyone with a missing value for any of the strata.

## VI. Modeling 100 Day Mortality

Special techniques are needed to model 100 day mortality (or mortality at any fixed point in time). The techniques in section V are not appropriate since they model the entire survival curve, not the value at a fixed point in time. The approach used to develop a multivariate model parallels that discussed in Section V using a logistic regression model rather than a proportional hazards model.

To model 100 day mortality the data set consists of all individuals who die in the first 100 days and all patients who survive with at least 100 days of follow-up. Any patient with less than 100 days of follow-up who did not die is removed from the data set.

The only covariates that can be modeled are those known at the time of transplant. No time dependent covariates are allowed. Factors are created as discussed in Section V and missing values are handled as discussed there. A single dependent variable is created with a value of 1 if the patient dies in the first 100 days and a value of 0 if they survive 100 days.

The statistical model for the data is the logistic model, namely,

$$\ln \left\{ \frac{P[100 \text{ day survival} \mid Z_1, \dots, Z_p]}{1 - P[100 \text{ day survival} \mid Z_1, \dots, Z_p]} \right\} = \beta_1 Z_1 + \dots + \beta_p Z_p.$$

In place of the relative risk, the odds ratio is used for 100 day mortality. Here  $\exp[\beta_1]$ , for example, is the ratio of the odds for an individual with covariate  $Z_1 = 1$  as compared to the odds for an individual with  $Z_1 = 0$  (and all other covariates the same). More complicated odds ratios can be computed using the formulas in Section V with the relative risk replaced by odds ratio.

Model building for 100 day mortality is identical to that for the Cox model. The exception is that PROC LOGISTIC is used in place of PROC PHREG. The format for the procedure is:

```
PROC LOGISTIC options;
MODEL Y=list/options;
Label: TEST hypothesis;
```

Here Y is the indicator of survival at 100 days. Options are identical to those in PROC PHREG.

## VII. WRITING COMMITTEE MEMOS

The primary mission of the IBMTR and ABMTR is to bring together data and expertise from many transplant centers to facilitate scientific studies of important issues in hematopoietic stem cell transplantation. IBMTR/ABMTR studies benefit not only from the large numbers of patients available for analysis but, just as importantly, from the diverse talents of participants in the Working/Writing Committees which supervise each study. To derive maximum benefit from this expertise requires good communication between the Statistical Center and the Committees and among Committee members. Face-to-face meetings are infrequent, since members are geographically widely dispersed. The Writing Committee Memo is the primary vehicle for this communication. Writing Committee memos should provide concise information about the status of studies at each stage of progress, allowing Writing Committee members to provide substantive input on all aspects of the study including design, patient population, explanatory and outcome variables, and interpretation of univariate and multivariate analyses. The following is a list of landmarks in a study's course which generally warrant preparation and distribution of a Writing Committee memo. It should not be considered all-inclusive. Writing Committee memos should be prepared whenever substantive deviations from the original study plan are felt to be necessary and/or whenever the Committee's formal input would be beneficial.

### (1) Study proposal

The original study proposal submitted for consideration approved should be circulated to the relevant Working Committee(s) once the study is approved, soliciting individuals interested in participating in the Writing Committee. The cover letter for this memo should briefly restate the primary objectives of the study, the intended study population and the initial sample size calculations made when the proposal was considered. The principle investigator should be identified with contact information (address, phone, fax, e-mail). Centers contributing data for large numbers of patients meeting the provisional patient eligibility criteria should be determined. If these centers do not have a representative on the relevant Working Committee(s) for the study, the center director should also receive this memo offering the opportunity to participate on the Writing Committee. This memo should also request suggestions for study design. Example: "The Statistical Center will shortly prepare a protocol (analysis plan) for \_\_\_\_\_ in collaboration with the (principle investigator). If you have suggestions related to the study design, including patients and outcomes to be studied and variables to be considered, please send these in writing to the (principle investigator) with a copy to the Statistical Center." The memo should include a fax response sheet asking the respondent to indicate whether or not he/she wishes to be part of the Writing Committee and having space for comments.

### (2) Study Protocol (See section I)

The Study Protocol should be prepared and reviewed by the principle investigator and then distributed to the Writing Committee, asking for comments. If the comments result in substantive revisions to the protocol, a revised draft should also be circulated.

### **(3) Description of the study population**

The patient eligibility criteria should be clearly defined and patient-, disease-, and treatment-related variables described. Overall outcomes may be included but no univariate or multivariate analyses. Categories of variables for these analyses should be defined.

### **(4) Univariate analyses/Multivariate analyses**

Results should be presented clearly in Table and Figure format with results summarized in the cover letter. Any surprising findings should be highlighted in the cover letter.

### **(6) Revised analyses**

Additional analyses may be performed or other changes to the study done in response to comments from Writing Committee members. These should be presented in table format, with a cover memo addressing each of the comments/criticisms received. It is important that Committee members are notified in writing that their suggestions were taken seriously (as they are) and appropriate action taken.

### **(7) Manuscript drafts**

There will be at least two drafts circulated (often more), the first draft and the draft to be submitted for publication. The latter should include Authorship and Assignment of Copyright forms for signature, if required by the journal to which the paper will be submitted.

### **(8) Confidentiality**

Unpublished data in Writing Committee memos are confidential. Each Writing Committee memo should include the following statement:

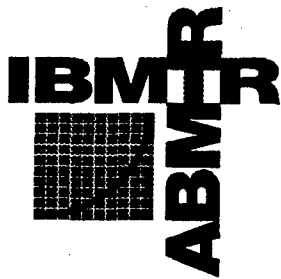
“The enclosed data are confidential. If used publicly, the following statement must be included: ‘The data presented here were obtained from the IBMTR/ABMTR Statistical Center. The analysis has not been reviewed or approved by the Advisory Committee of the IBMTR or ABMTR. The data may not be published without prior approval of the Advisory Committees.’ If the data are used in an oral presentation, please send us the name, place and dates of the meeting where the data are presented, and the title of your presentation.”

**(9) Authorship**

Membership on a Writing Committee is not sufficient for authorship on a manuscript. Each Writing Committee memo should include the following statement:

“You should note that IBMTR/ABMTR rules require that any member of a Writing Committee who does not make a substantive contribution to the design, analysis, interpretation or manuscript withdraw as a co-author or, alternatively, the lead author may remove names of non-contributors.”





# IBMTR/ABMTR Statisticians' Manual

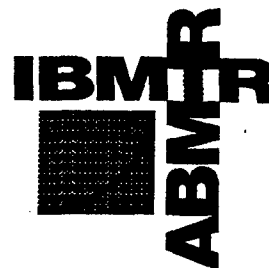
## Appendix A IBMTR/ABMTR Study Proposal Form

---

International Bone Marrow Transplant Registry  
Autologous Blood & Marrow Transplant Registry  
Medical College of Wisconsin  
8701 Watertown Plank Road • P.O. Box 26509  
Milwaukee, WI 53226 USA



**Statistical Center**  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee, WI, 53226, USA  
Telephone: 414-456-8325  
Fax: 414-266-8471



## STUDY PROPOSAL GUIDELINES

The rules of the IBMTR/ABMTR state that anyone may propose a study. The person proposing the study must complete a Study Proposal Outline. This is reviewed by the Statistical Center and relevant Working Committee Chair(s). Studies deemed feasible and consistent with the Registries' scientific goals are forwarded to the Working Committee for further input and assignment of a priority score. Studies are initiated at the discretion of the Working Committee Chair, Scientific Director and the Advisory Committee Chair based on priority scores, competing projects and available resources. A Writing Committee is formed to supervise the study. Interested members of the Working Committee and others are permitted to serve on the Writing Committee. To assure co-authorship of the manuscript, members of the Writing Committee must make timely and substantive contributions to study design, data analysis, interpretation of results or preparation of the typescript for publication. Members of the Writing Committee who do not fulfill this requirement are expected to withdraw as a co-author or, alternatively, their names will be deleted by the lead author.

Lead authorship (the person with primary responsibility for the study) is usually the person first proposing a study. The only exception to this policy is, for example, if the person proposing a study has only a trivial proportion of the cases to be studied, while a member of the Working Committee with a large proportion of the patients also requests primary responsibility. When multiple requests for primary responsibility for a single study are received, the person with the largest number of patients in the study is awarded primary responsibility.

The person awarded primary responsibility is required to prepare a first draft of the typescript within 60 days of first receipt of data from the Statistical Center. Failure to do so can result in forfeiture of lead authorship.

**Statistical Center**  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee, WI 53226, USA  
Telephone: 414-456-8325  
Fax: 414-266-8471



[Name of Study]

## STUDY PROPOSAL OUTLINE

Please prepare a brief description (no more than three pages) of the proposed study as you envision it. Use the outline below and send your description to the Statistical Center as soon as possible.

- I. Study Title
- II. Specific Aims
- III. Scientific Justification  
(1-2 paragraphs on the key issues and their importance)
- IV. Patient Eligibility Criteria
- V. Design of Study (Scientific Plan)  
This section should describe how the specific aims will be addressed using information from the IBMTR/ABMTR database. Carefully review IBMTR/ABMTR data collection forms to determine data availability. Include a list of variables you believe will be informative and the outcome variables you wish to analyze. Specify whether additional data would have to be collected and how this would be done.



# **IBMTR/ABMTR Statisticians' Manual**

## **Appendix B      Sample IBMTR/ABMTR Study Protocol**

---

International Bone Marrow Transplant Registry  
Autologous Blood & Marrow Transplant Registry  
Medical College of Wisconsin  
8701 Watertown Plank Road • P.O. Box 26509  
Milwaukee, WI 53226 USA





**Statistical Center**

8701 Watertown Plank Road  
P.O. Box 26509  
Milwaukee, Wisconsin 53226 U.S.A.  
Telephone: 414-456-8325  
Fax: 414-266-8471



**UNRELATED DONOR VERSUS AUTOLOGOUS BONE MARROW TRANSPLANTS  
FOR ACUTE MYELOGENOUS LEUKEMIA**

*(NOVEMBER 1996)*

**STUDY CONTACTS**

Mary M. Horowitz, MD, MS  
Scientific Director, IBMTR/ABMTR  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee, WI 53266  
Tele: 414-456-8325  
Fax: 414-266-8471

Marlies E.H.M. Van Hoef, MD  
Visiting Assistant Professor, IBMTR/ABMTR  
Medical College of Wisconsin  
8701 Watertown Plank Road  
Milwaukee, WI 53266  
Tele: 414-456-8787  
Fax: 414-266-8471

Hillard M. Lazarus, MD  
University Hospitals of Cleveland  
Department of Medicine  
11100 Euclid Avenue  
Cleveland, OH 44108  
Tele: 216-8443629  
Fax: 216-844-5979/7406

Craig Kollman, PhD  
National Marrow Donor Program  
3433 Broadway Street NE, Suite 400  
Minneapolis, MN 55413  
Tele: 612-627-5820  
Fax: 612-627-5899

**CO-INVESTIGATORS**

James Armitage, MD  
Robert Peter Gale, MD, PhD  
Rob Geller, MD  
Armand Keating, MD  
Paul Martin, MD  
Carole Miller, MD  
Jacob Rowe, MD  
Thomas Spitzer, MD  
Martin Tallman, MD  
Daniel Weisdorf, MD

**Table of Contents**

**Page**

1.0 Objectives ..... 3

2.0 Background ..... 3

    2.1 Autologous transplantation ..... 3

    2.2 Unrelated donor transplantation ..... 3

3.0 Preliminary studies ..... 4

4.0 Analysis plan ..... 5

    4.1 Eligibility criteria ..... 5

    4.2 Definition of endpoints ..... 5

    4.3 Potential confounding variables ..... 5

    4.4 Data retrieval ..... 7

    4.5 Statistical methods ..... 8

    4.6 Sample size calculations ..... 9

5.0 References ..... 10

Table 1 ..... 13

Table 2 ..... 14

Table 3 ..... 15

Table 4 ..... 16

Table 5 ..... 16

## **1.0 OBJECTIVES**

To compare outcome of unrelated donor and autologous bone marrow transplants for acute myelogenous leukemia (AML) in first and second remission. Outcomes to be studied include:

- 1.1 Hematopoietic recovery;
- 1.2 Treatment-related mortality;
- 1.3 Leukemia recurrence;
- 1.4 Leukemia-free survival;
- 1.5 Overall survival.

## **2.0 BACKGROUND**

Intensive induction and consolidation chemotherapy has improved the outcome of patients with AML. About 60% of adults and 80% of children achieve complete remission. However, leukemia recurs in 50-70% (1-11). Post-consolidation myeloablative treatment and bone marrow transplantation from an HLA-identical sibling is associated with lower recurrence rates and 50-60% five-year disease-free survival rates for patients transplanted in first remission (12-14). Autologous or unrelated donor transplants are of interest as alternative treatment options, since only 30% of patients have an HLA-identical sibling.

### **2.1 AUTOLOGOUS TRANSPLANTATION**

Treatment-related mortality after autotransplants is about 15% compared to 30% after HLA-identical sibling transplants. Three-year probabilities of survival after autotransplants for AML are 35-60% for patients treated in first remission and 25-35% for patients in second remission (15-22). Relapse rates are higher after autologous transplants compared to HLA-identical sibling transplants. This may be a result of leukemic contamination of the graft and/or lack of graft-versus-leukemia effects. Some data suggest less relapse and better outcome with total body irradiation (TBI) containing regimens (21) and ex vivo purging with mafosfamide (15, 23), 4-hydroxycyclophosphamide (24-26) or monoclonal antibodies (27). Regardless of transplant regimen, relapse (30-50% incidence for patients transplanted in first remission and 40-60% for those transplanted in second remission) is the major cause of treatment failure (18, 20, 22).

### **2.2 UNRELATED DONOR TRANSPLANTATION**

Until recently, use of unrelated donors for transplants was severely limited by availability. Availability increased dramatically over the past five years through establishment of large panels of HLA-typed volunteer donors, such as that maintained by the National Marrow Donor Program (NMDP). Approximately 70% of patients searching the NMDP file find an HLA-A, B and DR antigen matched donor on preliminary searches though fewer actually proceed to

transplant. It takes 2-6 months before a suitable donor is identified, evaluated and scheduled for donation. Many patients will relapse in this interval. The few studies that report unrelated donor transplants show lower leukemia-free survival than after HLA-identical sibling transplants. Poorer outcome is attributable to higher treatment-related mortality from graft-versus-host disease (GVHD). The risk of relapse is low, probably due to GVHD-associated graft-versus-leukemia effects (28, 29). In one study from UCLA, matched unrelated donor transplants for high risk AML had two-year leukemia-free survival rates of  $23 \pm 12\%$ , one-year relapse rates of  $24 \pm 16\%$  and 57% grade II-IV GVHD (30). The Canadian Bone Marrow Transplant group reported 40% two-year event-free survival after matched unrelated donor transplants for various malignancies (7/35 were AML); most transplants are done in relapse or second or subsequent remission (31). The NMDP recently reported results of 79 AML patients receiving unrelated donor transplants (32). Twenty-five patients, transplanted in first and second remission, had two-year disease-free survival of 40%. Forty percent leukemia-free survival at two years was reported in the low-risk group and 20% in the high-risk group (32). The probability of grade II-IV acute GVHD was 64% and of chronic GVHD 55% (33). This result was consistent with an NMDP report of 462 patients with various malignancies receiving unrelated donor transplants (33). T-cell depletion of donor marrow reduces the incidence of GVHD (25-50%) after unrelated donor transplants (34-37) but does not convincingly increase survival. The Seattle group compared outcome for unrelated donor and autologous transplants in advanced acute leukemia ( $n=120$ ) (38). There was not a significant difference ( $p=0.45$ ) in five-year leukemia-free survival. However, only six of 23 unrelated and 11 of 41 autologous transplant recipients with AML were transplanted in second remission and none in first remission.

### 3.0 PRELIMINARY STUDIES

The Autologous Blood and Marrow Transplant Registry of North America (ABMTR) has collected data on 469 recipients of autotransplants for AML in first or second remission, registered between January 1, 1989 and December 31, 1994. Characteristics of these patients are shown in Table 1.

The NMDP facilitated 163 unrelated donor transplants for AML in first or second remission in the United States during the same period. Characteristics are shown in Table 2.

The International Bone Marrow Transplant Registry (IBMTR) has collected data for 55 unrelated donor transplants for AML in first and second remission, transplanted during the same period in non-USA centers. Characteristics are shown in Table 3.



## **4.0 ANALYSIS PLAN**

### **4.1 ELIGIBILITY CRITERIA**

The analysis will include persons receiving autologous or unrelated donor bone marrow transplants for AML in first and second remission between January 1989 and December 1994, with age  $\leq 50$  years, reported to the ABMTR, IBMTR or NMDP.

### **4.2 DEFINITION OF ENDPOINTS**

The following endpoints will be studied:

- 4.2.1 Hematopoietic recovery: Time to neutrophils (ANC)  $> 0.5 \times 10^9/L$  for three consecutive days will be the primary measure for comparisons of hematopoietic recovery.
- 4.2.2 Leukemia recurrence: Time to first leukemia recurrence will be compared. Patients will be censored at death in continuous complete remission, second transplant or, for patients surviving in continuous complete remission, at last contact.
- 4.2.3 Leukemia-free survival: Leukemia-free survival is defined as survival in continuous complete remission. Leukemia relapse and death in remission are considered events. Patients surviving in continuous complete remission will be censored at last contact.
- 4.2.4 Survival: Events are deaths from any cause. Surviving patients are censored at last contact, regardless of intervening treatment.

### **4.3 POTENTIAL CONFOUNDING VARIABLES**

Many factors may affect transplant outcome. Since this is a non-randomized study, careful attention will be paid to potential confounding factors. These are outlined below with suggested categories for analysis.

- 4.3.1 Patient-related factors
- Age: continuous
  - Gender: male vs female
  - Karnofsky performance score:  $<$  vs  $\geq 90\%$
- 4.3.2 Disease related factors
- Remission status: first remission (CR1) vs second remission (CR2)
  - Cytogenetic abnormalities: t(9;22), -7, -7q, -5, -5q, 11q ( $\pm$ others) vs others vs none vs not tested/available
  - FAB classification: FAB M1, 2 vs M3 vs M4 vs M5-7 vs unclassified

- WBC count at diagnosis:  $< vs \geq 75 \times 10^9/L$
- Prior treatment: Use of high-dose cytarabine ( $\geq 1g/m^2/d$ ) during induction/consolidation chemotherapy: yes vs no
- Time to achieve first remission:  $< vs \geq 8$  weeks
- Duration of first remission:  $< vs \geq 1$  year

#### 4.3.3 Transplant-related factors (allo and auto)

- Year of transplant: continuous variable
- Interval between transplant and most recent remission: continuous variable
- Conditioning regimen: TBI-based vs other possible categories
- Growth factors post-transplant: none vs G-CSF/GM-CSF ( started within 72 hours posttransplant)

#### 4.3.4 Transplant-related factors (autologous)

- Marrow purging: yes vs no

#### 4.3.5 Transplant-related factors (allogeneic only)

- GVHD prophylaxis: CsA vs MTX vs CsA+MTX vs T-cell depletion
- Gender-match: male-female vs female-male vs gender-match
- Donor age: continuous
- CMV status donor/recipient: -/- vs -/+ vs +/+ vs +/-
- Donor recipient HLA-match: definition to be determined

#### 4.3.6 Time varying effects

Experience has shown that some of the factors listed in 4.3.1 - 4.3.5 have differential effects on outcome in different time periods. In particular, the primary factor of type of transplant most likely will have different effects in the early and late periods after transplant. This problem is addressed by considering models that allow for distinct relative risks in different time periods.

## 4.4 DATA RETRIEVAL

The IBMTR/ABMTR statistical center and NMDP will each prepare a data file for patients meeting the eligibility criteria in section 4.1 and including the following variables:

### 4.4.1 Patient-related variables

- Patient ID number
- Date of birth
- Gender
- Karnofsky performance score pretransplant
- CMV status pretransplant
- Recipient HLA-type (for patients who received an unrelated donor graft)

### 4.4.2 Disease-related variables

- Date of diagnosis
- Cytogenetics
- FAB classification
- WBC count at diagnosis
- High-dose cytarabine treatment
- Number of induction courses to CR1
- Number of consolidation courses in CR1
- Date of CR1
- Date of first relapse (for CR2 patients)
- Date of CR2 (for CR2 patients)
- Remission state at transplant

### 4.4.3 Transplant-related variables (allo and auto)

- Date of transplant
- Conditioning regimen
- Center ID number

### 4.4.4 Transplant-related variables (autologous)

- Bone marrow purging

### 4.4.5 Transplant-related variables (allogeneic)

- GVHD prophylaxis
- T-cell depletion
- Donor date of birth
- Donor gender
- Donor CMV status
- Donor HLA-type

#### 4.4.6 Follow-up parameters

- Date of achievement of ANC  $>0.5 \times 10^9/L$  as defined in section 4.1.1
- Date of onset acute and chronic GVHD (unrelated only)
- Highest grade of acute and chronic GVHD (unrelated only)
- Date of first posttransplant leukemia recurrence
- Date of death
- Cause of death
- Date of second transplant, if applicable
- Date of last contact

### 4.5 STATISTICAL METHODS

Patient-, disease- and transplant-related factors will be compared between the two transplant types, using Chi-square test for categorical and Mann-Whitney test for continuous variables.

The data will be analyzed by using a proportional hazards model (39). For this analysis separate models will be fit, using relevant risk factors (section 4.3), to both the autologous and unrelated donor groups. These models will identify variables that require adjustment in each patient group to assure that the comparisons made in later stages are not confounded by other factors. For both of these models the proportional hazards assumption for all variables will be examined using a time-varying covariate and by graphical methods. Factors found to have non-proportional hazards will be adjusted for in subsequent analysis by using a stratified proportional hazards model or by using a set of time-dependent covariates.

Once a set of factors associated with outcome is determined for each of the transplant types, models which directly compare the two types of transplants will be built. A step in this process is to determine if the effect of a given factor is the same for both types of transplants. This will be examined by fitting a proportional hazards model, stratified on transplant type, and examining the interaction term between the factor of interest and the type of transplant. If this interaction term is significant then the final model will have an interaction term between the factor and type of transplant and separate inferences about the effect of transplant type will be made for each level of the confounding factor. The final model constructed by this technique will include all the factors found plus a term for transplant type. The proportional hazards assumption will again be examined, and should it be found that the hazards are non-proportional for the effects of interest, the best fitting model with time-varying risk coefficients will be found. Here the best cut-off point between early and late effects is found by finding the model that yields the largest partial likelihood.

Multivariate regression using partial logistic regression will also be used to compare outcome of autologous and unrelated donor transplants, controlling for

the risk factors identified above (40). Unlike traditional logistic regression, this technique allows for censored data much like a Kaplan-Meier curve or Cox proportional hazards model. The partial logistic model can be very restrictive, imposing conditions analogous to the Cox model, or it can be very flexible, approaching the non-parametric Kaplan-Meier curve as the number of parameters modelled increases. The number of parameters needed will be determined by the fit to the data. A parametric bootstrap will be used to compute confidence intervals and perform tests of significance (41, 42).

#### 4.6 SAMPLE SIZE CALCULATIONS

Table 1 describes 469 patients receiving autotransplants for AML in first and second remission transplanted between January 1989 through December 1994 for whom comprehensive data are available. Three hundred thirty six patients were transplanted in CR1 and 133 in CR2. Table 2 describes the 163 unrelated donor transplants reported to the NMDP in the same period. Sixty one transplants were for AML in CR1 and 102 for AML in CR2. Table 3 describes the 55 non-USA unrelated donor transplants reported to the IBMTR in the same period. Twenty four transplants were for AML in CR1 and 31 for AML in CR2.

Tables 4 and 5 show the power to detect specified differences in leukemia-free survival with autologous versus unrelated donor transplants, assuming inclusion of all unrelated donor transplants reported to either NMDP or IBMTR (Tables 2 and 3). The displayed data are based on the assumption that 50% of autotransplant recipients for AML in CR1 and 30% of those with AML in CR2 are alive and disease-free three years post-transplant (non-published data from ABMTR). It must be noted that the probability of detecting a difference between treatment groups with given power depends on the amount of censoring and variation in risk factors between the groups. This may induce potential discrepancies that interfere with the power calculations.

## 5.0 REFERENCES

1. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute leukemia. *N Eng J Med* 1994;331:896-903.
2. Champlin RE, Gale RP. Acute myelogenous leukemia: Recent advances in therapy. *Blood* 1987;69:1551-1562.
3. Miescher PA, Jaffe ER, Gale RP (eds). Keystone Symposia Workshop: Curing Leukemia. *Semin Hematology* 1991;28(suppl 4).
4. Weinstein HJ, Mayer RJ, Rosenthal DS, et al. Chemotherapy for acute myelogenous leukemia in children and adults: VAPA update. *Blood* 1983;62:315-319.
5. Creutzig U, Ritter J, Riehm H, et al. The childhood AML studies BFM-78 and -83: Treatment results and risk factor analysis. In: *Acute leukemias: Prognostic factors and treatment strategies* (ed. by T. Buchner, G Schellong, W Hiddemann, et al) pp. 71-75, Springer, Berlin, 1987.
6. Amadori S, Ceci A, Comelli A, et al. Treatment of acute myelogenous leukemia in children. Results of Italian cooperative study AIEOP/LAM 8204. *J Clin Oncol* 1987;5:1356-1363.
7. Mandelli F, Petti MC, Spiriti MA, et al. Acute non-lymphoid leukemia treatment: an update. *Haematologica* 1988;73:1-6.
8. Dillman RO, Davis RB, Green MR, et al. A comparative study of two different doses of cytarabine for acute myeloid leukemia: a phase III trial of cancer and leukemia group B. *Blood* 1991;78:2520-2526.
9. Wiernik PH, Banks PLC, Case Jr DC, et al. Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. *Blood* 1992;79:313-319.
10. Schiller GJ, Nimer SD, Territo MC, et al. Bone marrow transplantation versus high-dose cytarabine-based consolidation chemotherapy for the treatment results in childhood acute myelogenous leukemia: A report of the German Cooperative Study AML-BFM-78. *Blood* 1985;65:298-304.
11. Phillips GL, Reece DE, Shepherd JD, et al. High-dose cytarabine and daunorubicin induction and post-remission chemotherapy for the treatment of acute myelogenous leukemia in adults. *Blood* 1991;77:1429-1435.
12. International Bone marrow Transplant registry. Transplant or chemotherapy in acute myelogenous leukemia. *Lancet* 1989;1:1119-1122.
13. Clift RA, Buckner CD, Thomas ED, et al. The treatment of acute non-lymphoblastic leukemia by allogeneic marrow transplantation. *Bone marrow Transplant* 1987;2:243-258.
14. European Group for Bone Marrow transplantation: Working party on Leukemia. Allogeneic bone marrow transplantation of leukemia in Europe. *Lancet* 1988;1:1379-1382.
15. Gorin NC, Aegerter P, Auvert B, et al. Autologous bone marrow transplantation for acute myelocytic leukemia in first remission: a European survey of the role of marrow purging. *Blood* 1990;75:1606-1614.
16. Lowenberg B, Verdonck LJ, Dekker AW, et al. Autologous bone marrow transplantation in first remission: results of a Dutch prospective study. *J Clin Oncol* 1990;8:287-294.
17. McMillan AK, Goldstone AH, Linch DC, et al. High-dose chemotherapy and autologous bone marrow transplantation in acute leukemia. *Blood* 1990;76:480-488.

18. Carella AM, Gaozza E, Santini G, et al. Autologous unpurged bone marrow transplantation for acute non-lymphoblastic leukemia in first complete remission. *Bone Marrow Transplant* 1988;3:537-541.
19. Spinolo JA, Dicke KA, Horowitz, et al. Double intensification with amsacrine/high-dose cytarabine and high-dose chemotherapy with autologous bone marrow transplantation produces durable remission in acute myelogenous leukemia. *Bone marrow transplant* 1990;5:111-118.
20. Korbling M, Hunstein W, Fliedner TM, et al. Disease-free survival after autologous bone marrow transplantation in patients with acute myelogenous leukemia. *Blood* 1989;74:1898-1904.
21. Labopin M, Gorin NC. Autologous marrow transplantation in 2502 patients with acute leukemia in Europe: a retrospective study. *Leukemia* 1992;6(suppl 4):95-99.
22. Ravindranath Y, Yeager AM, Chang MN, et al. Autologous bone marrow transplantation versus intensive consolidation chemotherapy for acute leukemia in childhood.
23. Korbling M, Fliedner TM, Holle R, et al. Autologous blood stem cell (ABSCT) versus purged bone marrow transplantation (pABMT) in standard risk AML: influence of source and cell composition of the autograft on hemopoietic reconstitution and disease-free survival. *Bone marrow transplant* 1991;7(5):343-349.
24. Rowley SD, Jones RJ, Piantadosi S, et al. Efficacy of ex vivo purging for autologous bone marrow transplantation for acute myeloid leukemia using monoclonal antibody-purged bone marrow. *Blood* 1990;75:1199-1206.
25. Linker CA, Ries CA, Damon LE, et al. Autologous bone marrow transplantation for acute myeloid leukemia using busulphan plus etoposide as a preparative regimen. *Blood*; 1993;81(2):311-318.
26. Dusenbery KE, Daniels KA, McClure JS, et al. Randomized comparison of cyclophosphamide-total body irradiation versus busulphan-cyclophosphamide conditioning in autologous bone marrow transplantation for acute myeloid leukemia. *Int J Radiol Oncol* 1995;31(1):119-128.
27. Ericson SG, Colby E, Welch L, et al. Engraftment of leukocyte subsets following autologous bone marrow transplantation in acute myeloid leukemia using anti-myeloid (CD14 and CD15) monoclonal antibody-purged bone marrow. *Bone Marrow Transplant* 1992;9(2):129-137.
28. Beatty PG. Results of allogeneic bone marrow transplantation with unrelated or mismatched donors. *Semin in Oncol* 1992;19(3 suppl 7):13-19.
29. Beatty PG. Results of allogeneic bone marrow transplantation with unrelated or mismatched donors. *Semin in Oncol* 1992;19(3 suppl 7):13-19.
30. Schiller G, Feig SA, Territo M, et al. Treatment of advanced leukemia with allogeneic bone marrow transplantation from matched unrelated donors. *Br J Haematol* 1994;88(1):72-78.
31. Phillips GHL, Burnett MJ, Brain MC, et al. Allogeneic bone marrow transplantation using unrelated donors: a pilot study of the Canadian bone marrow transplant group. *Bone Marrow Transplant* 1991;8(6):477-487.
32. Perkins HA, Kollman C, Howe CW. Unrelated-donor marrow transplants: the experience of the national Marrow Donor Program. *Clin Transplants* 1994;295-301.

33. Kernan NA, Bartsch G, Ash RC, et al. Analysis of 462 transplantations from unrelated donors facilitated by the National Donor Marrow Program. *N Eng J Med* 1993; 328(9):593-602.
34. Cullis JO, Szydlo RM, Cross NCP, et al. Matched unrelated donor bone marrow transplantation for chronic leukemia in chronic phase: comparison of ex vivo and in vivo T-cell depletion. *Bone Marrow Transplant* 1993; 11 (Suppl 1):107.
35. Mackinnon S, Hows JM, Goldman JM, et al. Bone marrow transplantation for chronic myeloid leukemia: The use of histocompatibility unrelated volunteer donors. *Exp Hematol* 1990;18:421.
36. Drobyski WR, Ash RC, Casper JT, et al. Effect of T-cell depletion as GVHD prophylaxis on engraftment, relapse and disease-free survival in unrelated marrow transplantation for chronic myelogenous leukemia. *Blood* 1994;83:1980.
37. Ash RC, Casper JT, Chitambar CR, et al. Successful allogeneic transplantation of T-cell depleted bone marrow from closely HLA-matched unrelated donors. *N Eng J Med* 1990;322:485.
38. Busca A, Anasetti C, Anderson G, et al. Unrelated donor or autologous transplantation for treatment of acute leukemia. *Blood* 1994;83:3077-3084.
39. Andersen PK, Bogan O, Gill RD, et al. *Statistical Models Based on Counting Processes*. Springer Verlag, New York 1992.
40. Efrom B. Bootstrap Confidence Intervals for a Class of parametric problems. *Biometrika* 1985;72:45-58.
41. CiCiccio TJ, Romano JP, et al. A review of Bootstrap Confidence Intervals. *J of Royal Statist Soc* 1988;50(3):338-354.
42. Cox RD. Regression analysis and life tables. *J of Royal Statist Soc* 1972;B 34:187-220.



Table 1. Characteristics of patients with AML in CR1 and CR2, who received autologous bone marrow transplantation and for whom comprehensive data are available.

Variable	CR1 (%) <sup>a</sup> median (range) <sup>b</sup>	CR2 (%) <sup>a</sup> median (range) <sup>b</sup>
Number of patients	336	133
Year of transplant		
1989	45 (13)	25 (19)
1990	50 (15)	28 (21)
1991	81 (24)	22 (17)
1992	73 (22)	29 (22)
1993	80 (24)	26 (20)
1994	7 ( 2)	3 ( 2)
Age in years	25 (1-65)	32 (1-63)
Male sex	164 (49)	73 (55)
Karnofsky performance score $\geq$ 90%	282 (84)	97 (73)
WBC at diagnosis ( $\times 10^9/l$ )	8 (1-690)	7 (1-479)
FAB		
M1	50 (15)	26 (20)
M2	92 (27)	42 (32)
M3	35 (10)	13 ( 10)
M4	66 (20)	36 (27)
M5	49 (15)	7 ( 5)
M6	---	---
M7	6 ( 2)	2 ( 2)
Unclassified	22 ( 7)	7 ( 5)
Granulocytic sarcoma	16 ( 5)	16 ( 5)
Conditioning regimen		
BU + CY $\pm$ other	236 (70)	93 (70)
TBI + CY $\pm$ other	21 ( 6)	19 (14)
TBI + other	31 ( 9)	9 ( 7)
BU $\pm$ other	13 ( 4)	3 ( 2)
CY + VP16 + nitrosurea	20 ( 6)	3 ( 2)
Graft purged	198 (60)	92 (70)
Missing <sup>c</sup>	5 (1)	2 (2)

<sup>a</sup> for categorical variables, <sup>b</sup> for continuous variables, <sup>c</sup> data are only missing for purging  
Abbreviations: WBC=white blood count; FAB=French-American-British; BU=busulfan;  
CY=cyclophosphamide; TBI=total body irradiation

Table 2. Characteristics of unrelated donor transplants for AML in CR1 and CR2 from the NMDP.

Variable	CR1 (%) <sup>a</sup> median (range) <sup>b</sup>	CR2 (%) <sup>a</sup> median (range) <sup>b</sup>
Number of patients	61	102
Year of transplant		
1989	3 (5)	4 (4)
1990	7 (11)	10 (10)
1991	7 (11)	24 (23)
1992	12 (20)	15 (15)
1993	15 (25)	16 (16)
1994	17 (28)	33 (32)
Age in years	25 (0-48)	26 (0-55)
Male sex	43 (71)	62 (61)
Karnofsky Performance score $\geq 90\%$	52 (85)	77 (75)
Conditioning regimen		
Bu + CY	12 (20)	16 (16)
TBI + CY	-	-
TBI + CY + other	32 (53)	58 (57)
TBI + other	3 (5)	7 (7)
TBI + Cy + Arac	9 (15)	12 (12)
TBI + Cy + VP16	5 (8)	9 (9)
GVHD prophylaxis		
CsA	1 (2)	3 (3)
CsA + other, no MTX	2 (3)	9 (9)
CsA + MTX	27 (44)	52 (51)
T-cell depletion	-	-
T-cell depletion + other	25 (41)	28 (27)
Other	6 (10)	10 (10)
Donor male sex	31 (51)	65 (64)
Donor age	35 (20-52)	37 (21-55)

<sup>a</sup> for categorical variables, <sup>b</sup> for continuous variables.

Abbreviations: BU=busulfan; CY=cyclophosphamide; TBI=total body irradiation; CsA=cyclosporin; MTX=methotrexate

Table 3. Characteristics of unrelated donor transplants for AML in CR1 and CR2 reported to the IBMTR.

Variable	CR1 (%) <sup>a</sup> median (range) <sup>b</sup>	CR2 (%) <sup>a</sup> median (range) <sup>b</sup>
Number of patients	24	31
Year of transplant		
1989	2 ( 8)	3 (10)
1990	3 (13)	3 (10)
1991	2 ( 8)	7 (23)
1992	5 (21)	8 (26)
1993	6 (25)	3 (10)
1994	6 (25)	7 (23)
Age in years	20 (1.3-50)	25 (3.6-46)
Male sex	14 (58.3)	16 (51.6)
Karnofsky Performance score $\geq 90\%$	17 (70.8)	25 (80.6)
WBC at diagnosis ( $\times 10^9/L$ )	9.6 (1.3-210)	6.3 (0.7-199)
missing	1 ( 4)	2 ( 6)
FAB		
M1	5 (21)	5 (16)
M2	3 (13)	8 (26)
M3	-	10 (32)
M4	7 (29)	4 (13)
M5	5 (21)	3 (10)
M6	4 (17)	-
unclassified	-	1 ( 3)
Conditioning regimen		
Bu + CY	4 (17)	2 ( 6)
TBI + CY	9 (38)	10 (32)
TBI + CY + other	6 (25)	9 (29)
TBI + other	-	1 ( 3)
TBI + Cy + Arac	-	2 ( 6)
TBI + Cy + VP16	4 (17)	5 (16)
Other	1 ( 4)	2 ( 6)
GVHD prophylaxis		
CsA	1	3 (10)
CsA + other, no MTX	1	2 ( 6)
CsA + MTX	17	18 (26)
T-cell depletion	1	1 ( 3)
T-cell depletion + other	4	7 (23)
Donor male sex	35.9 (0.4-50)	35 (21-56)
Donor age	14 (58.3)	20 (64.5)

<sup>a</sup> for categorical variables, <sup>b</sup> for continuous variables. Abbreviations: BU=busulfan; CY=cyclophosphamide; TBI=total body irradiation; CsA=cyclosporin; MTX=methotrexate

Table 4. Power to detect a difference in leukemia-free based on 50% 3-year leukemia-free survival in 336 evaluable autologous transplants ( $H_0$ ) and 85 evaluable unrelated donor transplants ( $H_1$ ) for AML in first remission.

$H_1$	Difference in LFS (%)	Power	$H_1$	Difference in LFS (%)	Power
55	5	0.1290	45	5	0.1290
60	10	0.3845	40	10	0.3845
65	15	0.7127	35	15	0.7127
70	20	0.9258	30	20	0.9258
75	25	0.9912	25	25	0.9912
80	30	0.9996	20	30	0.9996

---

$H_1$  = assumed LFS in unrelated donor transplants

Table 5. Power to detect a difference in leukemia-free based on 30% 3-year leukemia-free survival in 133 evaluable autologous transplants ( $H_0$ ) and 133 evaluable unrelated donor transplants ( $H_1$ ) for AML in second remission.

$H_1$	Difference in LFS (%)	Power	$H_1$	Difference in LFS (%)	Power
35	5	0.1377	25	5	0.1474
40	10	0.4015	20	10	0.4714
45	15	0.7171	15	15	0.8418
50	20	0.9177	10	20	0.9874
55	25	0.9863	5	25	0.9999
60	30	0.9988			

---

$H_1$  = assumed LFS in unrelated donor transplants



# ABMTR Newsletter

Published by the IBMTR/ABMTR Statistical Center • Medical College of Wisconsin  
8701 Watertown Plank Road • P.O. Box 26509 • Milwaukee, WI 53226 U.S.A.  
Telephone: (414) 456-8325 • Fax: (414) 456-6530

December 1998

Volume 5, Number 1

## REGISTER NOW...

### 1999 Tandem BMT Meetings at Keystone Resort, Colorado

by D'Etta Waldoch, CMP, IBMTR/ABMTR Associate Director-International Programs

#### Table of Contents:

Message from the  
ABMTR Executive  
Committee Chair ..... 2

Message from the  
Scientific Director ..... 3

IBMTR/ABMTR  
Summary Slides ..... 4

Foundation & Corpo-  
rate Support of the  
IBMTR/ABMTR ..... 11

IBMTR/ABMTR  
Corporate Membership  
Program ..... 11

Statistical Center  
Personnel ..... 12

ABMTR Advisory  
Committee Listing ..... 12

If the tandem meetings of IBMTR/ABMTR and ASBMT (American Society for Blood and Marrow Transplantation) were successful in 1995 (and they were!), the 1999 Meetings should prove phenomenal. Back to back at Keystone Resort, participants of the 1999 IBMTR/ABMTR Participants' Meeting (February 28-March 3) and the 1999 Annual Meeting of the ASBMT (March 3-6) can once again optimize travel funds by attending two meetings in a single week. Program chairs for the Tandem Meetings (Dr. Daniel Weisdorf, University of Minnesota, Minneapolis, for the IBMTR/ABMTR and Dr. Richard Jones, Johns Hopkins University, Baltimore for the ASBMT) have planned a coordinated scientific program addressing key topics in the basic and clinical science of blood and marrow transplantation. About 1,000 attendees are expected.

The IBMTR/ABMTR Keynote Speaker is Robert E. Wittes, M.D., Director of the Division of Cancer Treatment, Diagnosis and Centers, at the National Institutes of Health. Dr. Wittes will discuss *Problems and Opportunities Facing Biomedical/Clinical Research in the Next Decade* on Monday, March 1.

An important addition to this year's agenda is an Advanced Statistics Workshop for Clinicians, conducted by Dr. John Klein, Statistical Director of the IBMTR/ABMTR, and Prof. Niels Keiding, University of Copenhagen.

All IBMTR/ABMTR Working Committees will meet to plan the next year's activities. Meetings are open to all interested in taking an *active* role in ongoing studies. All Working Committee members should plan to attend.

Physicians and scientists working in the field of blood and marrow transplantation have the opportunity to submit abstracts for presentation at either the IBMTR/ABMTR Poster Session or the ASBMT Poster Sessions. Late afternoon Poster Sessions will be combined with hosted receptions, featuring Keystone's award-winning light buffet-style cuisine and beverages.

Data management professionals will present their abstracts at a poster session on Monday, March 1 from 4:00-5:30 pm. Two of these abstracts will be selected for oral presentation during the Data Management Poster Session.

Data Management Workshops will be conducted on two tracks. While both will discuss current IBMTR/ABMTR Registration and Reporting procedures, Track I will review fundamental concepts for first-time attendees. Track II, designed for those who have attended previous Workshops, will emphasize special topics and roundtable discussions.

StemSoft Software Inc. will offer several training sessions during the Tandem BMT Meetings. Fees for participating in each session are \$400. Sessions are limited to 40 participants each, and are subject to cancellation if less than half full. Contact Joan Sheehan at StemCell Software Inc. in Vancouver, BC (Canada) at ☎ 800-667-0322 or ☎ 604-877-0713, or stemsoft@stemcell.com.

Oncology Nursing Society (ONS) Workshops, supported by an unrestricted educational grant from Bristol-Myers Oncology, will be held mid-week, on Tuesday and Wednesday, March 2-3. Coordinated by Susan O'Connell, MSN, RN, OCN of the

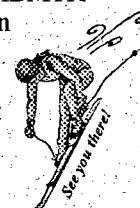
ONS BMSCT Special Interest Group, topics will include pharmacology of new agents used for blood and marrow transplant, quality of life, innovative approaches to symptom and homecare management of transplant patients, outpatient BMT, gene therapy, nursing research and ethical issues in transplantation.

For general questions about meeting format or registration, please contact: D'Etta Waldoch, CMP, Associate Director-International Programs, IBMTR/ABMTR, Medical College of Wisconsin at HRC Suite 2500, 8701 Watertown Plank Road, Milwaukee, WI 53226 USA; ☎ 414-456-8377; fax: 414-827-4997; email: detta@compuserve.com

**SPECIAL ISSUE**  
**Report on State-of-the-Art in**  
**Blood and Marrow Transplantation with**  
**Guide to IBMTR/ABMTR Summary Slides**  
**(see pages 4-10)**

The ABMTR Newsletter is funded by unrestricted educational grants from Pfizer Inc.

Ortho Biotech Inc.  
and  
Cell Therapeutics, Inc.



## Message from the Executive Committee Chair



Armand Keating, MD  
Chair, Executive  
Committee

## New Chair Sees Evolving and Dynamic Role for ABMTR Research Programs

The Autologous Blood and Marrow Transplant Registry continues to flourish as the following statistics aver. Since 1989, 254 participating centers in the United States, Canada, Mexico and South America registered a total of 42,496 patients with the Statistical Center. (Registration includes providing basic pre- and posttransplant clinical data.) In 1997, ABMTR centers registered 6,914 new patients. The distribution of autotransplants performed between 1992 and 1997 and registered with the ABMTR is shown in the table below. *Comprehensive* data are available on 11,921 (28%) autotransplants for specific diseases.

Twelve IBMTR/ABMTR Working Committees with 378 physicians voluntarily design, analyze and publish studies using this extensive database. In 1998, the ABMTR added a new subcommittee—Autoimmune Disease—chaired by Dr. Richard Burt, in response to rapidly increasing interest in the role of autotransplants in this area. A total of 90 IBMTR/ABMTR studies are at varying stages of completion; 40% involve autotransplants. Indeed, the process to initiate new studies has been so successful that a prioritization exercise was undertaken in 1998 to focus on the most compelling investigations.

This happy state of affairs reflects the outstanding contributions, guidance and wisdom provided by my predecessor, Jim Armitage. I am deeply honored to take over from Jim and not at all surprised that little in the way of a change in direction appears necessary at present. This does not mean that the ABMTR is static. This is far from the case. In fact, there is ample evidence that it is maturing and evolving rapidly and, in my view, appropriately. A good example is the increased interaction with the IBMTR through com-

binated scientific Working Committees. Additionally, closer collaborations underway with the American Society for Blood and Marrow Transplantation (ASBMT), the National Marrow Donor Program (NMDP) and the European Group for Blood and Marrow Transplantation (EBMT) are likely to be academically fruitful. The jointly planned Tandem Meetings of the IBMTR/ABMTR and ASBMT to be held in March 1999 is a case in point. It is becoming evident that all parties can derive benefit from such cooperation without any loss of identity and also fulfill their specific objectives to a greater extent than if they were to go it alone.

A further evolutionary change is the increased professionalism of fund-raising that has been thrust upon the ABMTR and IBMTR. While peer-reviewed grants from national agencies are the mainstay of our budget, particularly a major grant from the U.S. National Institutes of Health, they are insufficient for our needs and other sources of funds are urgently required. Susan Ladwig, the Associate Director of Development at the Statistical Center, has done an outstanding job in this regard and is coordinating a variety of new approaches to enhance fund-raising. Funds must cover not only the vital scientific activities of the Center, but also its well established and important educational role in assisting the profession and the public. Here, too, the tools are evolving—a new website is being launched this year that will provide easier access to information and solicit financial support.

It is clear that the ABMTR is a dynamic and evolving organization and, in this context as well, I have every confidence that its many active members will be willing to help meet the challenges that will undoubtedly face us in the next year and beyond.



ABMTR Executive Committee Chair, Dr. Armand Keating, MD, is Professor and Chief, Medical Services, Ontario Cancer Institute/Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada

Distribution and frequencies of autotransplants performed between 1992 and 1997, and registered\* with the ABMTR

Disease	1992 & 93	1994 & 95	1996 & 97**
Breast cancer	2779 (33)	4503 (40)	5695 (43)
Non-Hodgkin lymphoma	2446 (29)	2807 (25)	3082 (23)
Hodgkin lymphoma	965 (12)	1036 (9)	1106 (8)
Acute myelogenous leukemia	730 (8)	727 (6)	521 (4)
Multiple myeloma	357 (4)	742 (7)	1405 (10)
Acute lymphoblastic leukemia	172 (2)	168 (2)	124 (1)
Neuroblastoma	194 (2)	238 (2)	221 (2)
Testicular cancer	133 (2)	98 (1)	164 (1)
Ovarian cancer	131 (2)	273 (2)	322 (2)
Brain tumor	109 (1)	91 (1)	109 (1)
Chronic myelogenous leukemia	61 (1)	88 (1)	98 (1)
Other malignancy	340 (4)	436 (4)	579 (4)
<b>Total</b>	<b>8417</b>	<b>11207</b>	<b>13426</b>

\*Registration data includes basic pre- and posttransplant clinical information; comprehensive clinical data are collected on a subset of registered cases.

\*\* Data incomplete

## Expanded Information and Report Forms Now Available on the New IBMTR/ABMTR Web Site

This issue of the *ABMTR Newsletter* presents our 1998 Summary Slides on State-of-the-Art in Blood and Marrow Transplantation and serves as an interpretation guide for their use. The slides will be sent to all IBMTR/ABMTR Participating Teams and to IBMTR/ABMTR Corporate Members early next year. This year's Summary Slides were supported by generous educational grants from **Ortho Biotech Inc., Cell Therapeutics, Inc., and Pfizer Inc.** Based on feedback regarding previous editions, we anticipate these slides will be valuable educational and presentation tools.

**1998 IBMTR/ABMTR SUMMARY  
SLIDES ON CURRENT STATUS OF  
BLOOD & MARROW  
TRANSPLANTATION  
AVAILABLE SOON**

Two sets of 29 slides summarizing current use of allogeneic and autologous transplants will be sent to all participating teams of the IBMTR/ABMTR free of charge. The slides were supported by generous educational grants from Pfizer Inc., Ortho Biotech Inc. and Cell Therapeutics, Inc. IBMTR/ABMTR teams may purchase additional sets for \$50.00. If your budget does not permit this purchase, limited educational grants are available through the Statistical Center. Slide sets are available to other organizations and individuals for \$100.

If you have questions about the new slides, please contact  
Melodee Nugent, MA,  
IBMTR/ABMTR Information Specialist  
☎ (414) 456-8323 or  
by fax at (414) 456-6530.

We are also pleased to announce that the IBMTR/ABMTR web site will have its premier showing at the 1998 ASH Meetings in Miami, Florida. The web site was supported through a generous educational grant from Searle. The new site will feature the 1998 Summary Slides, current and past issues of the *IBMTR* and *ABMTR Newsletters*, Report Forms which can be printed directly from the site, information on

the upcoming 1999 Tandem BMT Meetings, and listings of IBMTR/ABMTR Executive, Advisory and Working Committee members, Statistical Center personnel, publications, and participating centers. Future phases will add exciting new features and functionalities including Working Committee discussion rooms, on-line completion of IBMTR/ABMTR Registration forms, and additional information services features including disease-specific reports and statistical information.

Please visit  
our website at  
[www.ibmtr.org](http://www.ibmtr.org)

supported by an  
unrestricted educational  
grant from Searle

### In Memoriam

With great sadness, I would like to inform you of the death of Mrs. Barbara (Babs) H. Bortin, a valued member of the Statistical Center of the International Bone Marrow Transplant Registry who passed away on August 15, 1998, after a hard-fought battle against ovarian cancer. Mrs. Bortin was the wife of the late Mortimer M. Bortin, MD, founding Scientific Director of the International Bone Marrow Transplant Registry (IBMTR). Mrs. Bortin aided Dr. Bortin in his efforts in establishing and nurturing the IBMTR/ABMTR through its early years. She subsequently joined the IBMTR's data management staff in 1985 after retiring from a career with the Milwaukee Public Schools. She was a devoted supporter of the IBMTR and continued her work with the Statistical Center through much of her illness. Her expertise, kindness and friendship will be greatly missed. Anyone wishing to send the family condolences may do so by addressing them to the IBMTR/ABMTR Statistical Center, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA so they can be forwarded to her family. The family requests that donations in Mrs. Bortin's name be made to the Mortimer M. Bortin Memorial fund, which Mrs. Bortin helped establish.



Mary M. Horowitz,  
MD, MS is  
Scientific Director  
of the IBMTR/ABMTR  
and Professor of  
Medicine at the Medical  
College of Wisconsin

## Message from the Scientific Director

Mary M. Horowitz,  
MD, MS  
Scientific Director

# NEW SUMMARY SLIDES SHOW CURRENT TRENDS IN BMT

By J. Douglas Rizzo, MD, IBMTR/ABMTR Assistant Scientific Director

Since 1972 the International Bone Marrow Transplant Registry (IBMTR) has collected outcome data from blood and marrow transplant centers worldwide. More than 375 centers now participate. The IBMTR database includes information for about 40% of allogeneic bone marrow transplants done between 1970 and 1997. In 1991, the Autologous Blood & Marrow Transplant Registry (ABMTR) began collecting outcome data on autotransplants from centers in North and South America. More than 250 autotransplant centers now participate. The ABMTR database includes information for about 50% of autotransplants done in North and South America between 1989 and 1997.

Using these data, the Statistical Center peri-

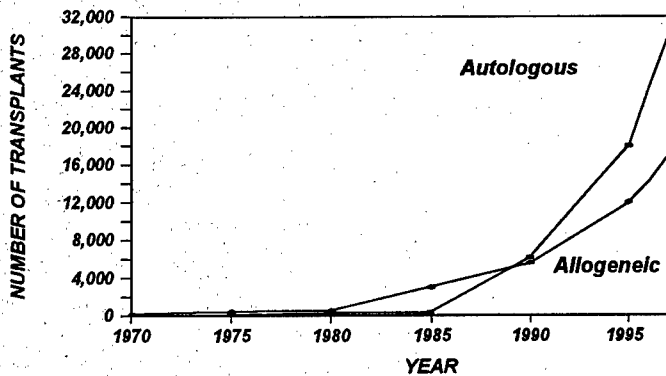
odically prepares and distributes slides summarizing current use and outcome of allogeneic and autologous hematopoietic stem cell transplants (SCT). This year's Summary Slides, made possible by generous educational grants from Pfizer Inc., Ortho Biotech Inc. and Cell Therapeutics, Inc., are described below.

**Slide 1:** Use of blood and marrow transplants continues to increase dramatically. We estimate 17,000 allogeneic and 30,000 autologous transplants were done in 1997.

**Slides 2 & 3:** Currently, 375 centers participate in the IBMTR worldwide, and 254 centers participate in the ABMTR. Numbers of participating centers continue to increase.

**Slide 4:** Most autotransplants use hematopoietic progenitor cells collected from blood. Fewer than 10% are done with bone marrow alone. Although over 70% of allografts still use bone marrow cells, use of allogeneic cells collected from peripheral blood increased significantly in the last few years to about 20% of the total. Though use is increasing, there are still relatively few transplants using umbilical cord blood cells.

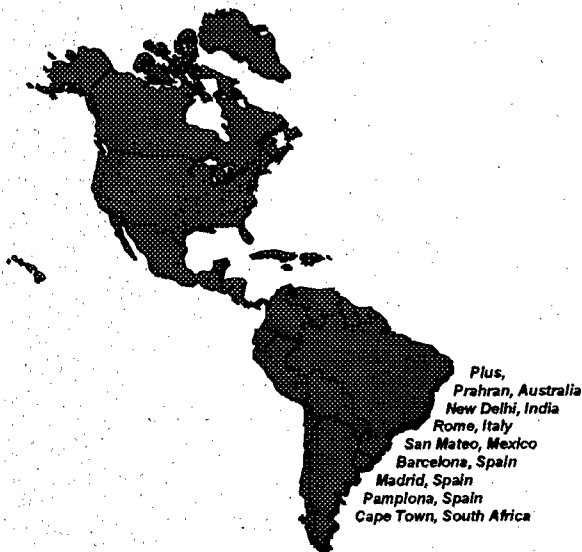
**Slides 5 & 6:** For both allogeneic and autologous transplants, the proportion of patients over the age of 40 years at the time of transplant continues to increase. This may reflect advances in supportive care with resultant decreases in transplant-related toxicity and the application of transplant to dis-



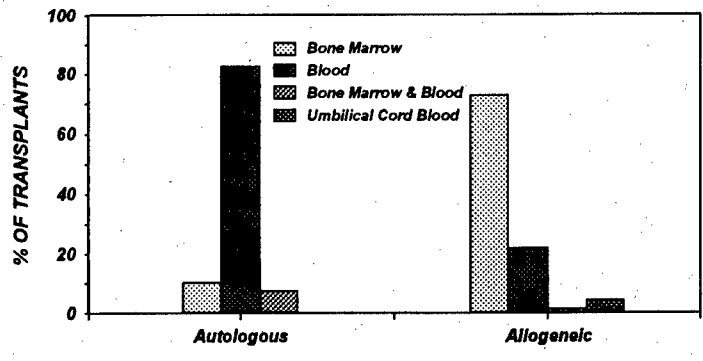
Slide 1. Annual Number of Blood and Marrow Transplants Worldwide, 1970-1997



Slide 2. Location of Centers Participating in the IBMTR, 1998



Slide 3. Location of Centers Participating in the ABMTR, 1998



Slide 4. Stem Cell Sources, 1997



eases affecting older patients (e.g. multiple myeloma).

**Slide 7:** This slide illustrates indications for allogeneic and autologous stem cell transplants in North America. The most common indications for allogeneic and autologous transplants differ. For acute and chronic leukemias, myelodysplasia (MDS), and non-malignant diseases (aplastic anemia, immune deficiencies, inherited metabolic disorders), allogeneic transplant is the predominant approach. Autotransplants are used most commonly for breast, ovarian and other solid malignancies, Hodgkin and non-Hodgkin lymphomas and multiple myeloma. Breast cancer remains the most common indication for SCT in North America, accounting for nearly

one third of all transplants. Non-Hodgkin lymphoma is the second most common indication, followed by acute myelogenous leukemia (AML) and multiple myeloma.

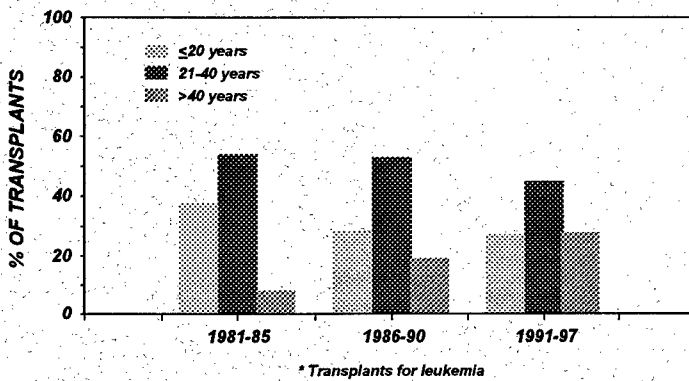
**Slide 8:** Most allogeneic transplants are from HLA-identical sibling donors. However, only about 30% of transplant candidates have such a donor. Increasing availability of HLA-typed volunteer donors through large national and international registries has led to increasing use of unrelated donors for bone marrow transplants. Transplants from unrelated donors now account for about 25% of allogeneic transplants.

**Slide 9:** Leukemia remains the most common indication for allogeneic stem cell trans-

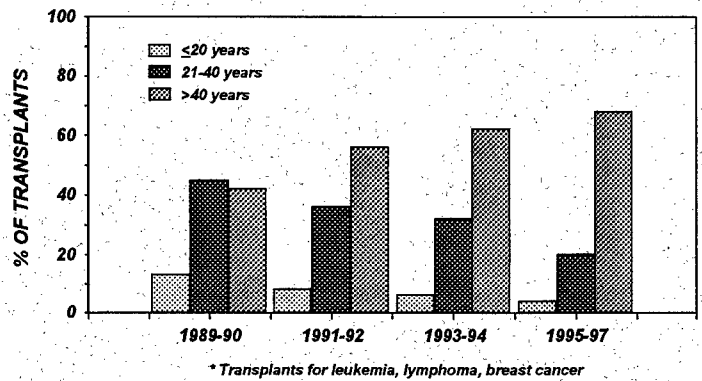
plantation worldwide. CML and AML each account for nearly one third of the allogeneic transplants performed throughout the world. Lymphoma, MDS/myeloproliferative syndromes, aplastic anemia and other non-malignant diseases each comprise approximately 10% of allogeneic transplants.

**Slides 10 & 11:** 100-day mortality is often used as a gauge of procedure-related toxicity. Allogeneic transplants are associated with relatively high risks of graft-versus-host disease (GVHD), infections and liver toxicity, resulting in high early mortality. Among HLA-identical sibling transplants done in 1996-97 and reported to the IBMTR, 100-day

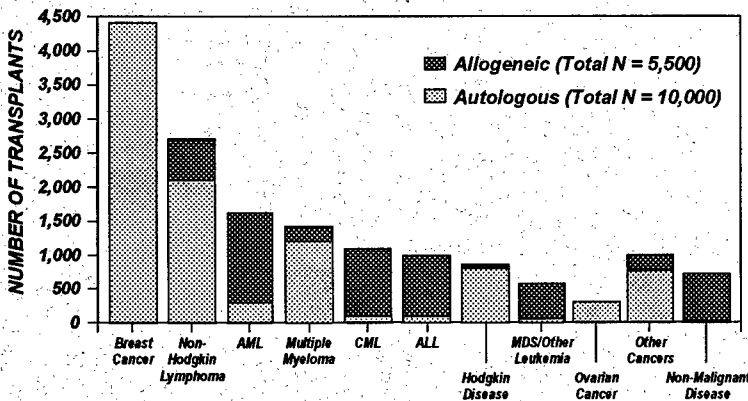
(continued on next page)



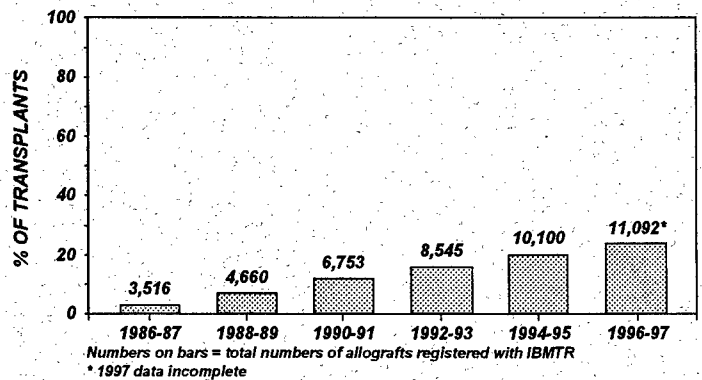
Slide 5. Trends in Allogeneic BMT Recipient Age\*, 1981-1997



Slide 6. Trends in Autologous Transplants Recipient Age\*, 1989-1997



Slide 7. Indications for Blood and Marrow Transplantation in North America, 1997



Slide 8. Percent of Allogeneic Transplants from Unrelated Donors

(continued from previous page)

mortality rates range from about 10% for persons with acute leukemia in first remission to almost 40% for those with advanced leukemia. 100-day mortality rates in aplastic anemia and immune diseases range between 10% and 15%. Recurrence or progression of primary disease is responsible for nearly 40% of all deaths following HLA-identical sibling transplants, with GVHD and infection each responsible for 20% of deaths.

**Slides 12 & 13:** Early mortality is generally lower following auto- than allotransplants. Among patients receiving autotransplants in 1996-97, those treated for stage II/III breast cancer had 100-day mortality rates of <5%, while patients treated for acute leukemia not in remission had >20% early mortality. Pri-

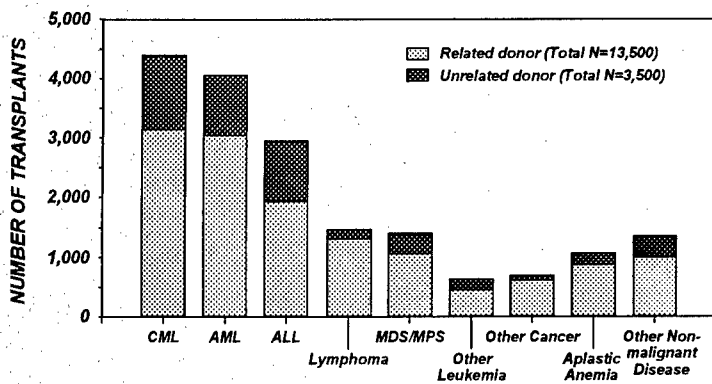
mary disease recurrence accounts for the great majority of deaths in autotransplant recipients.

**Slide 14:** CML is the most frequent indication for allogeneic bone marrow transplantation worldwide. Among 3,703 recipients of HLA-identical sibling transplants done between 1990 and 1996, reported to the IBMTR, 3-year probabilities of survival were  $67 \pm 2\%$  for 2,308 transplants performed within 1 year of diagnosis and  $59 \pm 3\%$  for 1,395 patients transplanted more than one year after diagnosis.

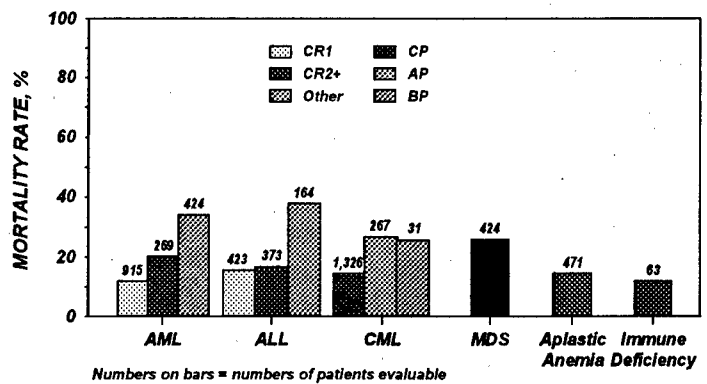
Only about 30% of persons with CML have an HLA-identical sibling donor. Unrelated donor transplants can cure CML but are associated with higher risks of GVHD and

transplant-related mortality. Additionally, unrelated donor transplants are often delayed because of the time required to identify a donor and reluctance to risk the higher transplant-related mortality. Delaying transplantation may adversely affect outcome. For patients receiving unrelated donor transplants, the 3-year probabilities of survival were  $51 \pm 7\%$  for 278 patients transplanted within the first year of diagnosis, and  $40 \pm 4\%$  for 773 patients transplanted beyond the first year.

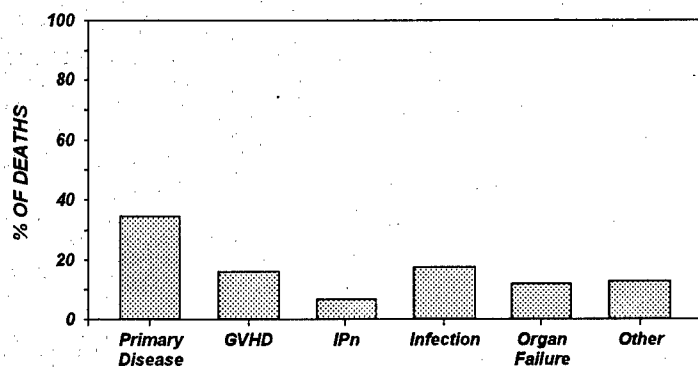
**Slide 15:** Results of HLA-identical sibling transplants for AML correlate with remission state. Among 3,581 recipients of HLA-identical sibling transplants for AML performed between 1990 and 1996, reported to the



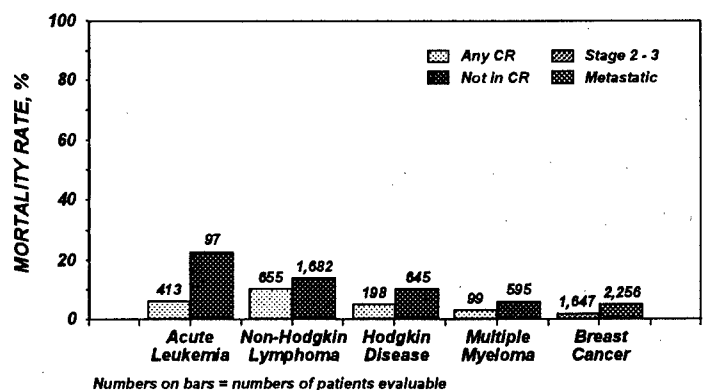
**Slide 9. Indications for Allogeneic Blood and Marrow Transplantation Worldwide, 1997**



**Slide 10. 100-day Mortality after HLA-identical Sibling Transplants, 1996-1997**



**Slide 11. Causes of Death after HLA-identical Sibling Transplants, 1990-1997**



**Slide 12. 100-day Mortality after Autotransplants, 1996-1997**

IBMTR, 3-year probabilities of survival were  $63\pm 2\%$  for 2,917 transplants in first remission, and  $44\pm 4\%$  for 664 patients in second or subsequent remission. Survival was generally worse in patients receiving transplants from unrelated donors. Recipients of unrelated donor transplants in first remission had a 3-year probability of survival of  $50\pm 8\%$ , while those in second remission or greater had a 3-year probability of survival of  $36\pm 8\%$ .

**Slide 16:** Among patients receiving autologous transplants for AML between 1990 and 1996, reported to the ABMTR, the 3-year probabilities of survival were  $57\pm 3\%$  for 1,030 patients in first remission at time of transplant,  $40\pm 5\%$  for 453 in second remission,

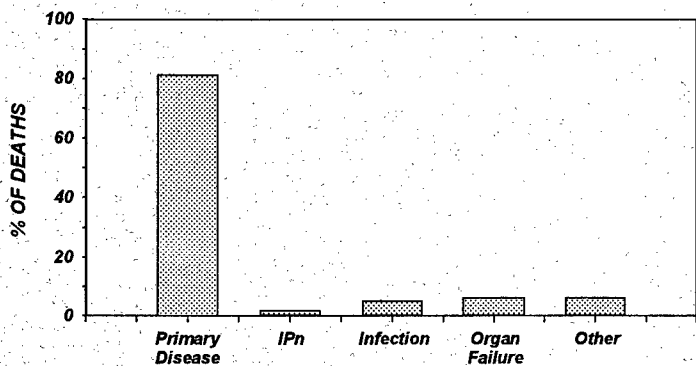
and  $22\pm 7\%$  for 201 patients not in remission at time of transplant.

**Slide 17:** Most patients with ALL are cured with conventional chemotherapy. Consequently, bone marrow transplants are generally reserved for patients failing conventional therapy, i.e., in relapse or second or subsequent remission, or patients in first remission with prognostic factors predicting a high risk of failure with conventional therapy. The most frequent indications for transplants in first remission are older age, high leukocyte count at diagnosis, Ph<sup>1</sup> and other chromosome abnormalities and difficulty obtaining a first remission. Among 2,611 recipients of HLA-identical sibling transplants between 1990 and 1996, reported to the IBMTR, 3-year

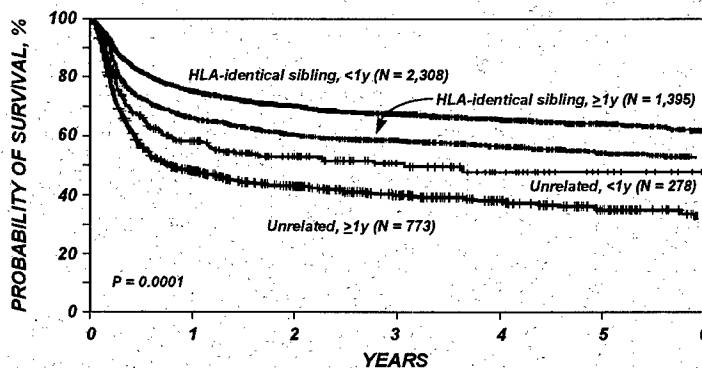
probabilities of survival were  $56\pm 3\%$  for 1,314 transplants done in first remission and  $44\pm 3\%$  for 1,297 in second or subsequent remission.

Although associated with higher transplant-related mortality, unrelated donor transplants may be considered for patients with ALL unlikely to be cured with chemotherapy. Among patients transplanted in second remission, there is little difference in overall survival between HLA-identical sibling and unrelated donor transplants, since higher GVHD rates are offset by lower relapse rates after unrelated donor transplants. Among 186 recipients of unrelated donor transplants

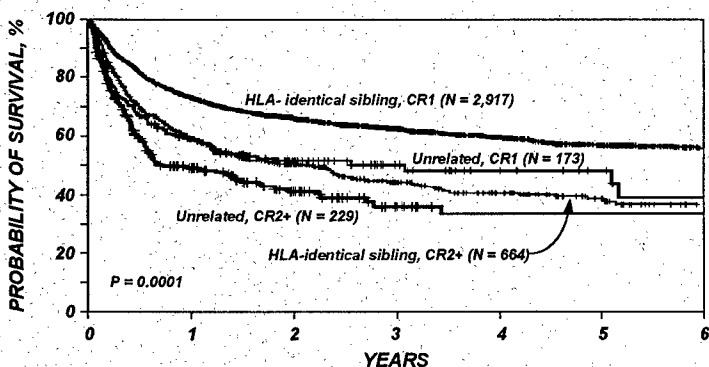
(continued on next page)



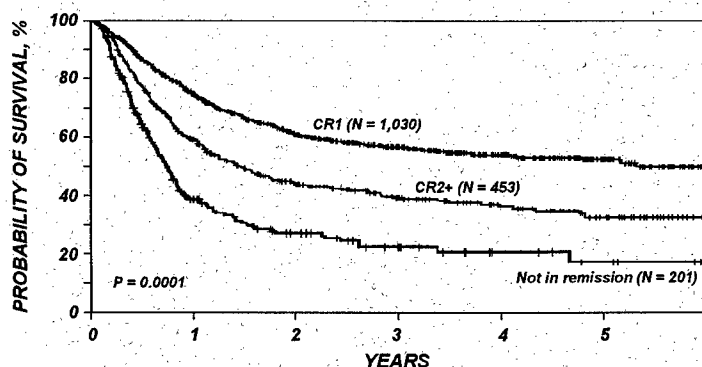
Slide 13. Causes of Death after Autotransplants, 1990-1997



Slide 14. Probability of Survival after BMT for CML in Chronic Phase by Donor Type and Disease Duration, 1990-1996



Slide 15. Probability of Survival after Allogeneic BMT for Acute Myelogenous Leukemia by Donor Type and Remission Status, 1990-1996



Slide 16. Probability of Survival after Autotransplants for Acute Myelogenous Leukemia, 1990-1996

(continued from previous page)

for ALL in first remission reported to the IBMTR, 3-year probability of survival was  $46 \pm 8\%$ ; among 517 receiving unrelated donor transplants in second or subsequent remission, it was  $36 \pm 7\%$ .

**Slide 18:** Among 399 recipients of autotransplants for ALL between 1990 and 1996, reported to the ABMTR, 3-year probabilities of survival were  $47 \pm 10\%$  for 139 transplants done in first remission,  $35 \pm 7\%$  for 227 done in second or subsequent remission, and  $14 \pm 14\%$  for 33 done in relapse.

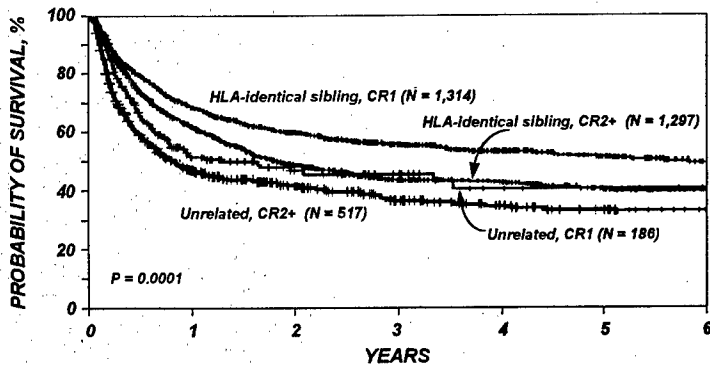
**Slide 19:** Allogeneic bone marrow transplantation can cure some patients with myelodysplastic syndromes. For 238 patients receiving HLA-identical sibling trans-

plant between 1990 and 1996 for refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) at time of transplant, survival probability at 3 years was  $53 \pm 7\%$ . For 633 patients with refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), or chronic myelomonocytic leukemia (CMML), 3 year probability of survival was  $37 \pm 4\%$ .

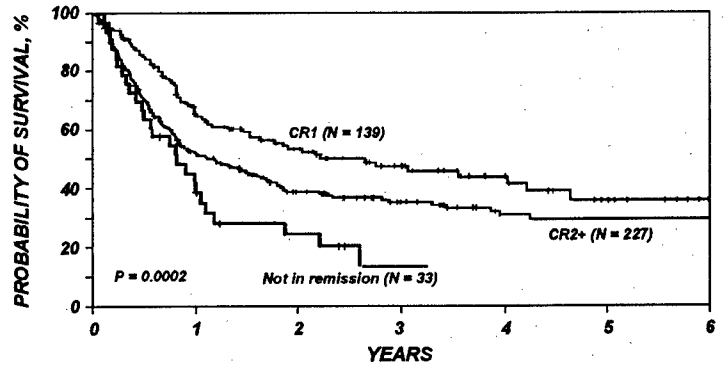
**Slide 20:** Allogeneic transplantation is the treatment of choice for young patients with aplastic anemia who have an HLA-identical sibling. 3-year probabilities of survival after 1,608 HLA-identical sibling transplants between 1990 and 1996, reported to the IBMTR, were  $76 \pm 3\%$  for 825 patients <20 years of

age and  $66 \pm 4\%$  for 783 patients older than 20 years. Results were not as good in 266 recipients of unrelated donor transplants:  $49 \pm 8\%$  in 183 patients <20 years and  $33 \pm 10\%$  in 83 older patients.

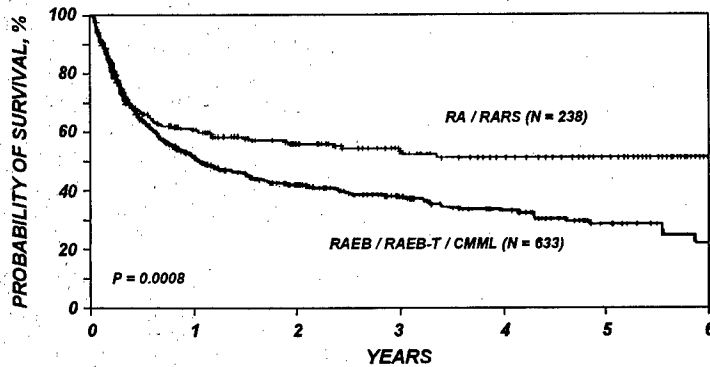
**Slide 21:** Most patients with Hodgkin disease are cured with conventional chemotherapy. However, for the 20-30% failing conventional therapy, autotransplants are effective salvage therapy. Among 2,331 autotransplants between 1990 and 1996, reported to the ABMTR, 3-year probabilities of survival were  $51 \pm 6\%$  for 428 patients never in remission,  $84 \pm 9\%$  for 88 patients transplanted in first remission,  $58 \pm 3\%$  for 549 transplants in first relapse and  $78 \pm 4\%$  for 1,266 patients transplanted in second or



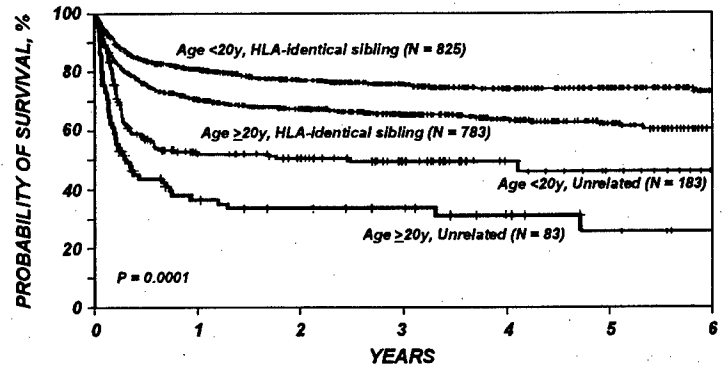
**Slide 17. Probability of Survival after Allogeneic BMT for Acute Lymphoblastic Leukemia by Donor Type and Remission Status, 1990-1996**



**Slide 18. Probability of Survival after Autotransplants for Acute Lymphoblastic Leukemia, 1990-1996**



**Slide 19. Probability of Survival after HLA-identical Sibling Transplants for Myelodysplastic Syndromes, 1990-1996**



**Slide 20. Probability of Survival after Allogeneic BMT for Severe Aplastic Anemia by Age and Donor Type, 1990-1996**

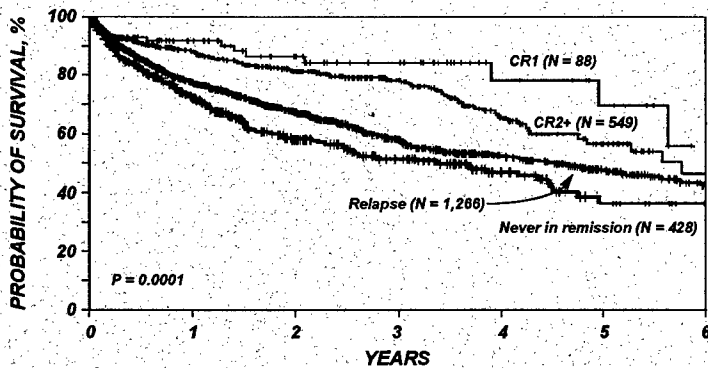
subsequent remission. Relapse is less frequent but treatment-related mortality is higher with HLA-identical sibling transplants, with 3-year probability of survival of approximately 50% in 216 patients, regardless of stage.

**Slides 22 & 23:** Autotransplants are also commonly used for non-Hodgkin lymphoma (NHL). Among 878 patients receiving autotransplants for low-grade NHL, 3-year probabilities of survival were  $78 \pm 11\%$  for 104 patients in first remission,  $65 \pm 5\%$  for 442 in first relapse,  $75 \pm 11\%$  for 105 in second remission and  $60 \pm 8\%$  for 227 never achieving remission with standard chemotherapy.

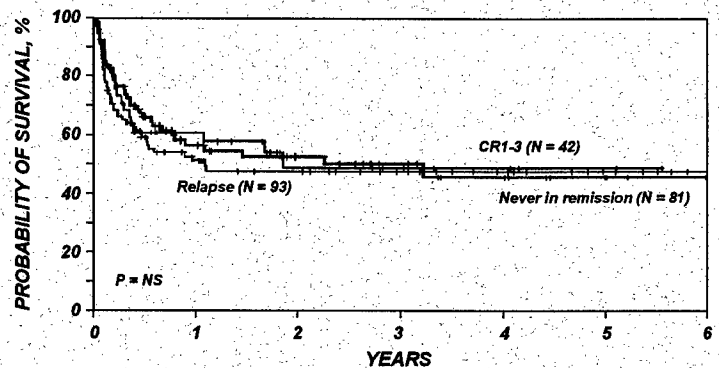
**Slides 24 & 25:** Among 2,814 patients receiving autotransplants for intermediate grade or immunoblastic NHL, 3-year probabilities of survival were  $70 \pm 6\%$  for 289 patients in first remission,  $40 \pm 3\%$  for 1,298 in first relapse,  $52 \pm 5\%$  for 502 in second remission and  $42 \pm 4\%$  for 725 never achieving remission with conventional chemotherapy. Most failures after autotransplants for NHL are due to relapse. 3-year survival rates after HLA-identical sibling transplants for these lymphomas were  $39 \pm 15\%$  for 46 patients in first or second remission,  $30 \pm 10\%$  for those not achieving remission ( $n=107$ ), and  $26 \pm 10\%$  for 116 patients transplanted in relapse.

**Slides 26 & 27:** Stem cell transplantation is increasingly used for multiple myeloma, a disease considered incurable with conventional therapy. 3-year survival after HLA-identical sibling transplants reported to the IBMTR between 1990 and 1996 was  $37 \pm 3\%$  regardless of duration of myeloma at the time of transplant. For 836 patients receiving autologous transplant within 18 months of diagnosis of myeloma, 3-year survival was  $53 \pm 5\%$ . It was  $40 \pm 7\%$  for 290 patients receiving autotransplants longer than 18 months after diagnosis.

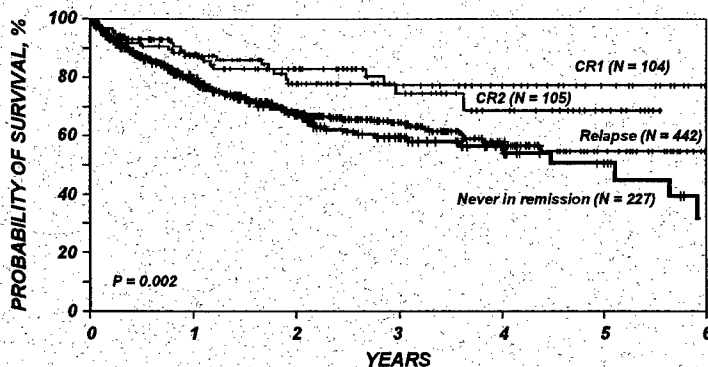
(continued on next page)



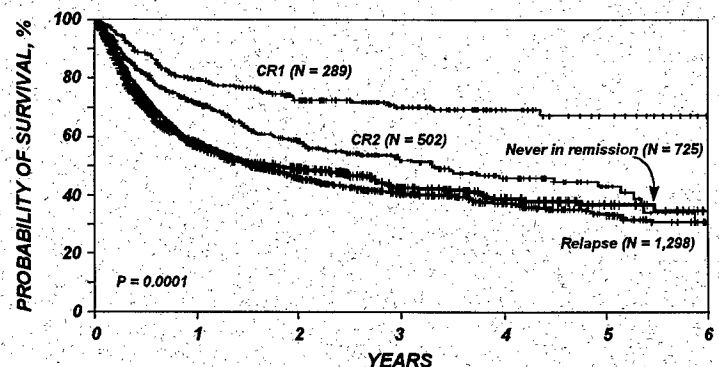
Slide 21. Probability of Survival after Autotransplants for Hodgkin Disease, 1990-1996



Slide 22. Probability of Survival after HLA-identical Sibling BMT for Low Grade Non-Hodgkin Lymphoma, 1990-1996



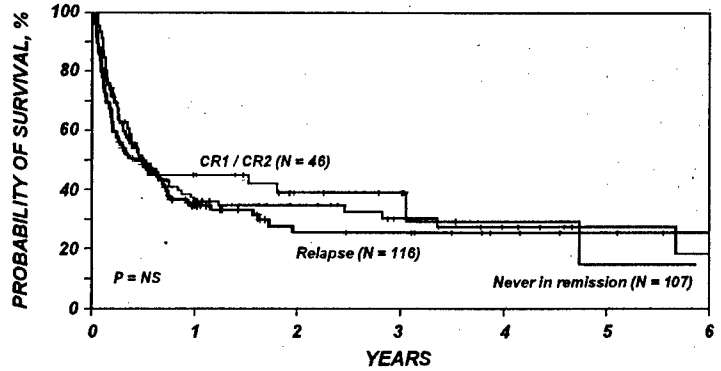
Slide 23. Probability of Survival after Autotransplants for Low Grade Non-Hodgkin Lymphoma, 1990-1996



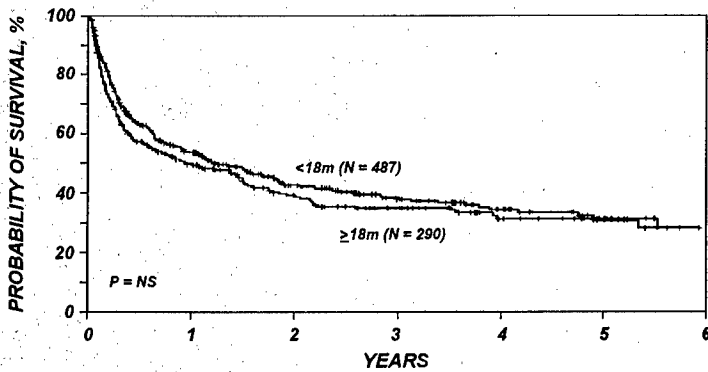
Slide 24. Probability of Survival after Autotransplants for Intermediate Grade or Immunoblastic NHL, 1990-1996

(continued from previous page)

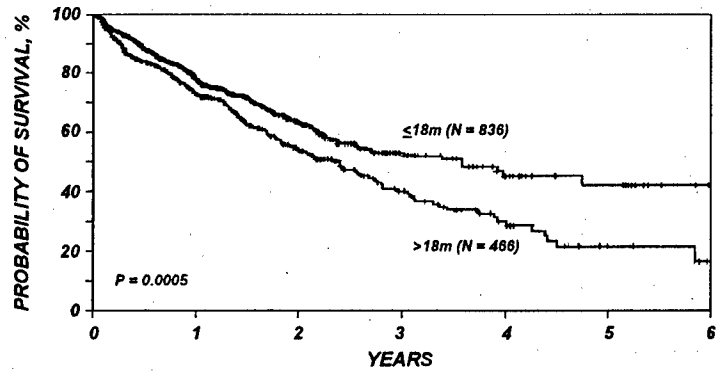
**Slides 28 & 29:** Breast cancer is the most frequent indication for autotransplant in North America. Among 9,162 women receiving autotransplants for breast cancer between 1990 and 1996 and reported to the ABMTR, 3-year probabilities of survival were  $75 \pm 3\%$  in 1,536 women with Stage 2 disease,  $68 \pm 4\%$  in 1,366 women with Stage 3 disease,  $55 \pm 6\%$  in 570 women with inflammatory breast cancer and  $33 \pm 2\%$  in 5,690 women with metastatic breast cancer. Outcome in metastatic breast cancer was significantly better for women who achieve a complete remission with conventional therapy prior to transplant. Among the 4,657 women transplanted for metastatic disease in whom pretransplant response to chemotherapy was known, 3-year probability of survival was  $48 \pm 3\%$  in 1,401 with a complete response,  $30 \pm 2\%$  in 2,330 with a partial response and  $19 \pm 3\%$  in 926 women with resistant disease.



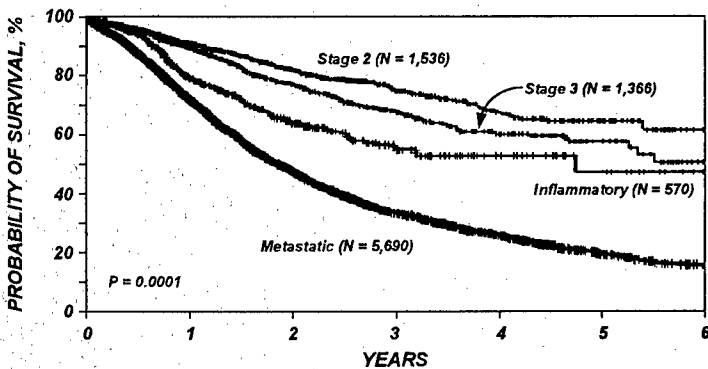
**Slide 25. Probability of Survival after HLA-identical Sibling BMT for Intermediate Grade or Immunoblastic NHL, 1990-1996**



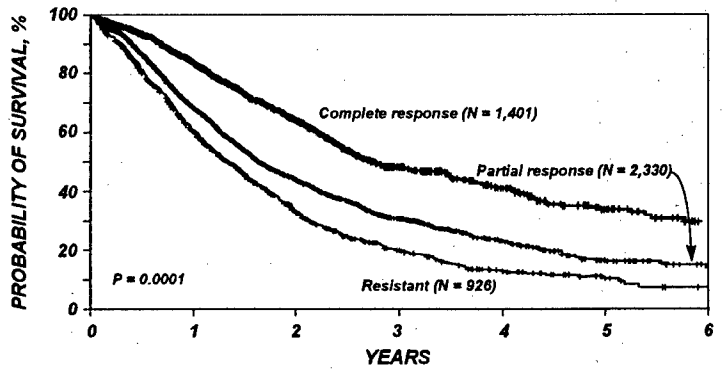
**Slide 26. Probability of Survival after HLA-identical Sibling BMT for Multiple Myeloma by Disease Duration, 1990-1996**



**Slide 27. Probability of Survival after Autotransplants for Multiple Myeloma by Disease Duration, 1990-1996**



**Slide 28. Probability of Survival after Autotransplants for Breast Cancer, 1990-1996**



**Slide 29. Probability of Survival after Autotransplants for Metastatic Breast Cancer by Pretransplant Chemosensitivity, 1990-1996**

## FOUNDATION AND CORPORATE SUPPORT OF THE IBMTR / ABMTR

All of us at the IBMTR/ABMTR Statistical Center thank the many contributors who have joined our international collaboration for research in blood and marrow transplantation. Private support for the Registries continues to be vitally important since federal grants cover only 50 percent of the Statistical Center's budget. We gratefully acknowledge the support of the Medical College of Wisconsin; the National Cancer Institute; the National Institute of Allergy and Infectious Disease; the National Heart, Lung and Blood Institute; the Department of Defense; and the generosity of the following foundations and corporations:

### Non-Federal Support Listing for the IBMTR / ABMTR (Grant Awards Since 1997)

- |  |  |   |
|--|--|---|
| <i>Astrom Biosciences</i>              | * <i>Fujisawa Healthcare, Inc.</i>           | <i>Novartis Pharmaceuticals, Inc.</i>     |
| * <i>Alpha Therapeutic Corporation</i> | <i>Genentech, Inc.</i>                       | * <i>Orphan Medical, Inc.</i>             |
| * <i>American Oncology Resources</i>   | <i>Glaxo Wellcome, Inc.</i>                  | * <i>Ortho Biotech Inc.</i>               |
| * <i>Amgen, Inc.</i>                   | <i>Hoechst Marion Roussel, Inc</i>           | <i>Osiris Therapeutics</i>                |
| <i>Anonymous</i>                       | * <i>Human Genome Sciences</i>               | <i>John Oster Family Foundation</i>       |
| <i>Astra Arcus AB</i>                  | <i>ICN Pharmaceuticals, Inc.</i>             | <i>Jane &amp; Lloyd Pettit Foundation</i> |
| * <i>Astra USA</i>                     | <i>Immunex Corporation</i>                   | <i>Alirio Pfiffer Bone Marrow</i>         |
| * <i>Baxter Fenwal</i>                 | <i>IMPATH/BIS</i>                            | <i>Transplantation Support</i>            |
| * <i>Bayer Corporation</i>             | * <i>IntraBiotics Pharmaceuticals, Inc.</i>  | <i>Association (Brazil)</i>               |
| * <i>Berlex Laboratories</i>           | * <i>Kaiser Permanente</i>                   | * <i>Pfizer Inc.</i>                      |
| <i>Biochem Pharma</i>                  | <i>The Kettering Family Foundation</i>       | * <i>Pharmacia and Upjohn</i>             |
| * <i>BioWhittaker, Inc.</i>            | * <i>Kirin Brewery Company (Japan)</i>       | * <i>Principal Life Insurance Company</i> |
| * <i>Blue Cross and Blue Shield</i>    | <i>Robert J. Kleberg, Jr. &amp; Helen C.</i> | <i>Quantum Health Resources</i>           |
| <i>Association</i>                     | <i>Kleberg Foundation</i>                    | <i>RGK Foundation</i>                     |
| <i>The Lynde and Harry Bradley</i>     | <i>Herbert H. Kohl Charities</i>             | <i>Rhone Poulenc Rorer</i>                |
| <i>Foundation</i>                      | <i>Laboratory Corporation of America</i>     | * <i>Roche Laboratories</i>               |
| * <i>Bristol-Myers Squibb Company</i>  | * <i>The Liposome Company</i>                | <i>Rockwell Automation/Allen-</i>         |
| * <i>CellPro, Inc.</i>                 | <i>Nada and Herbert P. Mahler</i>            | <i>Bradley Co.</i>                        |
| * <i>Cell Therapeutics, Inc.</i>       | <i>Charities</i>                             | <i>RPR Gencell</i>                        |
| * <i>CeloxLabs</i>                     | <i>Mayer Ventures</i>                        | * <i>SangStat Medical Corporation</i>     |
| * <i>Centeon</i>                       | * <i>MDS Nordion</i>                         | <i>Schering AG (Germany)</i>              |
| <i>Center for Advanced Studies in</i>  | <i>Med Immune, Inc.</i>                      | * <i>Schering-Plough Oncology</i>         |
| <i>Leukemia</i>                        | <i>MGI Pharma, Inc.</i>                      | * <i>Searle</i>                           |
| <i>Cerus Corporation</i>               | * <i>Milliman &amp; Robertson, Inc.</i>      | * <i>SEQUUS Pharmaceuticals</i>           |
| * <i>Chimeric Therapies, Inc.</i>      | <i>Milstein Family Foundation</i>            | * <i>Smith Kline Beecham</i>              |
| * <i>Chiron Therapeutics</i>           | <i>Miltenyi Biotech</i>                      | <i>Pharmaceutical</i>                     |
| <i>Circle Medical Products</i>         | <i>The Milwaukee Foundation/</i>             | <i>Stackner Family Foundation</i>         |
| * <i>COBE BCT Inc.</i>                 | <i>Elsa Schoeneich Medical</i>               | <i>Joan and Jack Stein Foundation</i>     |
| * <i>Coram Healthcare</i>              | <i>Research Fund</i>                         | <i>StemCell Technologies Inc</i>          |
| <i>Coulter Corporation</i>             | <i>NCGS and Associates, Inc.</i>             | <i>SubSpecialty Software</i>              |
| <i>Charles E. Culpeper Foundation</i>  | * <i>Nexell Therapeutics, Inc.</i>           | * <i>SyStemix, Inc., A Novartis</i>       |
| <i>Eleanor Naylor Dana Charitable</i>  | * <i>NeXstar Pharmaceuticals, Inc.</i>       | <i>Company</i>                            |
| <i>Trust</i>                           | <i>Samuel Roberts Noble Foundation</i>       | * <i>Therakos</i>                         |
| <i>Deborah J. Dearholt Memorial</i>    | <i>Northwestern Mutual Life Insurance</i>    | <i>TS Scientific and Planer Products</i>  |
| <i>Fund</i>                            | <i>Company Foundation</i>                    | * <i>United Resource Networks</i>         |
| <i>The Eppley Foundation for</i>       |  | <i>Velos Medical Informatics</i>          |
| <i>Research</i>                        |  | * <i>Wyeth-Ayerst Laboratories</i>        |
| * <i>Empire Blue Cross Blue Shield</i> | * <i>Corporate Member</i>                    | <i>Xcyte Therapies</i>                    |

### IBMTR / ABMTR CORPORATE MEMBERSHIP PROGRAM

Several corporations have joined the IBMTR/ABMTR Corporate Membership Program (see above). The annual membership program provides member organizations with informational materials on blood and bone marrow transplantation developed by the IBMTR/ABMTR Information Resource Service.

The program includes subscriptions to the *Statistical Center Report on Survival Statistics for Blood and Marrow Transplants*, *IBMTR and ABMTR Newsletters*, the worldwide *IBMTR/ABMTR Directory of Blood and Marrow Transplant Teams*, and the *IBMTR/ABMTR Summary Slides on State-of-the-Art in Blood and Marrow Transplantation* as well as invitations to our meetings and educational forums and access to the IBMTR/ABMTR databases for simple analyses. These resources are useful for marketing managers, medical directors, research directors, product managers, case managers or transplant coordinators.

For additional information on the Corporate Membership Program, please contact Susan Ladwig, Associate Director of Development ☎ (414) 456-8363, Fax: (414) 456-6530.

By  
**Susan Ladwig, MA**  
Associate Director  
of Development,  
Statistical Center

### A Special Thank You to our 1999 Tandem BMT Meeting Supporters

AMGEN, INC.  
BAXTER FENWAL DIVISION/  
NEXELL THERAPEUTICS, INC.  
BERLEX LABORATORIES  
BIOWHITTAKER  
BRISTOL-MYERS SQUIBB  
ONCOLOGY  
CARDEN JENNINGS PUBLISHING  
CELL THERAPEUTICS, INC.  
CELLPRO, INC.  
CERUS CORPORATION  
CHIRON THERAPEUTICS  
COBE BCT  
FUJISAWA HEALTHCARE, INC.  
HOECHST MARION ROUSSEL  
IMPATH/BIS  
IMMUNEX CORPORATION  
LABORATORY CORPORATION OF  
AMERICA  
THE LIPOSOME COMPANY, INC.  
MEDIIMMUNE, INC.  
MILTENYI BIOTECH  
NEXTSTAR PHARMACEUTICALS  
ORPHAN MEDICAL, INC.  
OSIRIS THERAPEUTICS, INC.  
PFIZER INC.  
PHARMACIA & UPJOHN, INC.  
RHONE-POULENC RORER  
ROCHE LABORATORIES INC.  
SANGSTAT MEDICAL  
CORPORATION  
SCHERING-PLOUGH ONCOLOGY  
SEARLE  
SEQUUS PHARMACEUTICALS,  
INC.  
STEMCELL TECHNOLOGIES INC  
SUBSPECIALTY SOFTWARE  
SYSTEMIX, INC., A NOVARTIS  
COMPANY  
THERAKOS  
VELOS MEDICAL INFORMATICS  
WYETH-AYERST LABORATORIES  
XCYTE THERAPIES, INC.

**STATISTICAL  
CENTER  
PERSONNEL**



*The ABMTR Newsletter is funded by unrestricted educational grants from Pfizer Inc.*

*Ortho Biotech Inc. and Cell Therapeutics, Inc.*

**MARY M. HOROWITZ, MD, MS**  
Scientific Director  
**J. DOUGLAS RIZZO, MD**  
Assistant Scientific Director

**JOHN P. KLEIN, PhD**  
Statistical Director  
**MEI-JIE ZHANG, PhD**  
Assistant Professor/Biostatistician  
**KATHLEEN A. SOBOCINSKI, MS**  
Associate Statistical Director  
**MELODEE L. NUGENT, MA**  
Information Specialist

**FAUSTO R. LOBERIZA, JR., MD, MS**  
Biostatistician  
**WALESKA S. PÉREZ, MPH**  
Biostatistician  
**JUDY VEUM STONE, MS**  
Biostatistician  
**JING TAO-WU**  
Research Assistant

**BARBARA A. McGARY, BS**  
Manager of Information Systems

**BARBARA B. LIU, MS**  
Database Programs Manager

**RUMEN N. GEORGIEV**  
Programmer

**SHARON K. NELL**  
Communications Coordinator

**JANE E. REBRO**  
Assistant Communications Coordinator

**DIANE J. KNUTSON, BS**  
Systems Coordinator

**HEMANT A. PATANI, MD**  
Research Assistant

**CLAUDIA A. ABEL**  
Data Coordinator

**ANGELA S. KUMMEROW**  
Data Coordinator

**HONGYU TIAN**  
Data Coordinator

**PATRICIA A. VESPALEC**  
Data Coordinator

**YING HU**  
Data Entry Assistant

**JAIME KNUTSON**  
Data Entry Assistant

**MITA A. PATANI**  
Data Entry Assistant

**ANN G. PERELES**  
Data Entry Assistant

**LILY QIAN**  
Data Entry Assistant

**JANELLE M. STANO**  
Data Entry Assistant

**D'ETIA WALDOCH, CMP**  
Associate Director, International Programs

**KATHLEEN KOVATOVIC, PharmD**  
Audit Coordinator

**LINDA M. SCHNEIDER**  
Desktop Publishing Specialist

**SUSAN U. LADWIG, MA**  
Associate Director of Development

**LISA J. LEHRMANN**  
Program Coordinator

**KIM R. JACKSON**  
Administrative Assistant

**SANDRA L. SOBOTKA**  
Administrative Assistant

**JEAN M. EDER**  
Staff Assistant

**ABMTR Advisory Committee**

**Armand Keating, MD**  
(Chair)  
University of Toronto  
Toronto, Ontario, CANADA

**Karen Antman, MD**  
Columbia University  
New York, NY USA

**James O Armitage, MD**  
University of Nebraska  
Medical Center  
Omaha, NE USA

**Charles S August, MD**  
Miami Children's Hospital  
Miami, FL USA

**Karl G Blume, MD**  
Stanford University  
Medical Center  
Stanford, CA USA

**Bruce Camitta, MD**  
Medical College  
of Wisconsin  
Milwaukee, WI USA

**Richard E Champlin, MD**  
MD Anderson  
Cancer Center  
Houston, TX USA

**Paul A Chervenick, MD**  
H. Lee Moffitt  
Cancer Center  
Tampa, FL USA

**Peter F Coccia, MD**  
University of Nebraska  
Medical Center  
Omaha, NE USA

**Karel A Dicke, MD, PhD**  
Arlington Cancer Center  
Arlington, TX USA

**Gerald J Eifenbein, MD**  
H. Lee Moffitt  
Cancer Center  
Tampa, FL USA

**Joseph W Fay, MD**  
Baylor University  
Medical Center  
Dallas, TX USA

**Robert Peter Gale, MD, PhD**  
Salick Health Care, Inc.  
Los Angeles, CA USA

**John Graham-Pole, MD**  
University of Florida  
Gainesville, FL USA

**Subhash C Gulati, MD**  
New York Hospital/Cornell  
Medical Center  
New York, NY USA

**Geoffrey P Herzig, MD**  
Roswell Park  
Cancer Institute  
Buffalo, NY USA

**Roger H Herzig, MD**  
University of Louisville  
Louisville, KY USA

**Mary M Horowitz, MD, MS**  
Medical College  
of Wisconsin  
Milwaukee, WI USA

**David D Hurd, MD**  
Wake Forest University  
Cancer Center  
Winston-Salem, NC USA

**Sundar Jagannath, MD**  
St. Vincent's Comprehensive  
Cancer Center  
New York, NY USA

**Herbert Kaizer, MD**  
Rush Presbyterian  
St. Luke's Medical Center  
Chicago, IL USA

**John P Klein, PhD**  
Medical College  
of Wisconsin  
Milwaukee, WI USA

**Hillard M Lazarus, MD**  
Case Western Reserve  
University  
Cleveland, OH USA

**Carole B Miller, MD**  
Johns Hopkins  
Oncology Center  
Baltimore, MD USA

**Lee M Nadler, MD**  
Dana-Farber  
Cancer Institute  
Boston, MA USA

**Gordon L Phillips, MD**  
Markey Cancer Center  
Lexington, KY USA

**Norma KC Ramsay, MD**  
University of Minnesota  
Minneapolis, MN USA

**James A Russell, MD**  
Alberta Children's Hospital  
Calgary, Alberta CANADA

**Robert C Seeger, MD**  
Children's Hospital  
of Los Angeles  
Los Angeles, CA USA

**Elizabeth J Shpall, MD**  
University of Colorado  
Health Sciences Center  
Denver, CO USA

**Gary L Spitzer, MD**  
Gerogetown University  
Medical Center  
Washington DC USA

**Patrick J Stiff, MD**  
Loyola University  
Maywood, IL USA

**William P Vaughan, MD**  
University of Alabama  
at Birmingham  
Birmingham, AL USA

**Julie M Vose, MD**  
University of Nebraska  
Medical Center  
Omaha, NE USA

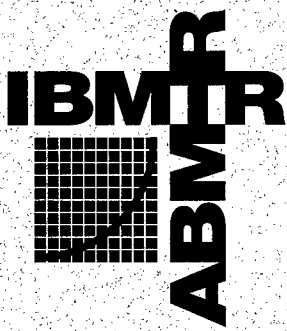
**Roy S Weiner, MD**  
Tulane University  
School of Medicine  
New Orleans, LA USA

**Daniel J Weisdorf, MD**  
University of Minnesota  
Minneapolis, MN USA

**Stephanie F Williams, MD**  
University of Chicago  
Medical Center  
Chicago, IL USA

**Steven N Wolff, MD**  
Vanderbilt University  
Medical Center  
Nashville, TN USA





# ABMTR Newsletter

Published by the IBMTR/ABMTR Statistical Center • Medical College of Wisconsin  
8701 Watertown Plank Road • P.O. Box 26509 • Milwaukee, WI 53226 U.S.A.  
Telephone: (414) 456-8325 • Fax: (414) 456-6530

December 1997

Volume 4, Number 1

## COMMUNITY RESPIRATORY VIRAL INFECTIONS IN THE POSTTRANSPLANT PATIENT

by Richard E. Champlin, MD

M. D. Anderson Cancer Center, Houston, Texas

Infection is a common and often life-threatening problem in the first year after blood and bone marrow transplantation. Multiple bacterial, fungal and viral organisms are implicated, many not serious pathogens except in settings of compromised immune function. Strategies for preventing and treating gram-negative and gram-positive bacterial infections, fungal infections and herpes virus infections such as cytomegalovirus receive much attention; im-

proved management of these infections contributes to recent decreases in transplant-related mortality. The importance of common respiratory viruses, such as respiratory syncytial virus (RSV), influenza, parainfluenza, rhinoviruses, adenoviruses and coronaviruses, in causing severe illness in transplant recipients is less well understood.

- continued on page 5

### Table of Contents:

- Message from the Scientific Advisory Committee Chair ..... 2
- Message from the Scientific Director ..... 3
- ABMTR Initiates Study of Autotransplants for Neuroblastoma ..... 4
- Recent IBMTR/ABMTR Publications ..... 4
- IBMTR/ABMTR Member Profile: Richard E. Champlin, MD ..... 5
- IBMTR Celebrates Silver Anniversary ..... 6
- Foundation & Corporate Support of the IBMTR/ABMTR ..... 7
- IBMTR/ABMTR Corporate Membership Program ..... 7
- Statistical Center Personnel ..... 8
- ABMTR Advisory Committee Listing ..... 8

## IBMTR/ABMTR ANNUAL PARTICIPANTS' MEETING in Keystone, Colorado on January 8-14, 1998

by D'Etta Waldoch Severson, CMP, IBMTR/ABMTR Associate Director-International Programs

The 1998 Annual Participants' Meeting will combine a stimulating scientific program, 13 Working Committee meetings, a beautiful venue and some of the best skiing available in Colorado. Plenary and Simultaneous Scientific Sessions will be presented by more than 75 speakers representing 10 countries. Topics include evaluation of minimal residual disease, ex vivo expansion of stem cells, biology of dendritic cells, immunotherapy in the transplant setting, cord blood and peripheral blood allografts and posttransplant infections. Sessions will be held in the morning and evening, allowing time in the afternoon for participants to enjoy a variety of winter recreational activities at Keystone.

The 1998 Keynote Address, *The Other Side of Health Care—A Physician Treated by Transplantation*, will be given by Dr. Richard Boxer on Sunday, January 11, at the opening reception. Dr. Boxer, a national leader in health care reform and a practicing urologist, received an autotransplant for non-Hodgkin lymphoma at the University of Nebraska in Omaha. On Monday, January 12, the late afternoon reception will be combined with an IBMTR/ABMTR Poster Session. The \$500 Mortimer M. Bortin Research Award will be given for the best abstract submitted.

Data Management Workshops will be held on Friday, January 9. Sessions on scoring common toxicities, and overviews of statistical analyses, high-

dose therapies and audit survival tactics will provide practical guidelines for those working with clinical data and the Statistical Center. \$500 grants from the US Department of Defense will be awarded to 30 eligible data managers to offset travel costs associated with attending the Workshops. StemCell Technologies Inc will offer three full-day training sessions at Keystone, January 10-12. The fee for participating in each session is \$400. Those interested may contact Ellen Low at ☎ 800-667-0322 or ☎ 604-877-0713, or stemsoft@stemcell.com.

Friday evening and Saturday, January 9-10, are devoted to a series of excellent corporate-supported Satellite Sessions. Breakfast on Sunday, Monday and Tuesday will feature Satellite Poster Sessions, and a luncheon Satellite Session will be held on Monday.

The IBMTR/ABMTR Steering Committees will meet for the first time at Keystone, as well as the Executive, Advisory and Working Committees. The five-day meeting will conclude on Wednesday, January 14, at noon.

### Register Early!


More than 500 participants are expected to attend the 1998 Annual Meeting at Keystone. Participants are encouraged to make hotel reservations soon.

**For meeting information, contact  
D'Etta at the Statistical Center:  
☎ 414-456-8377 or fax: 414-456-6530**

The ABMTR Newsletter is funded by an unrestricted educational grant from ICN Pharmaceuticals, Inc.



**Message from  
the Scientific  
Advisory  
Committee  
Chair**

  
James O. Armitage, MD  
Chair, Scientific Advisory  
Committee

**The ABMTR Continues As a Unique Resource  
for Studying the Growing Use of Autologous Transplantation**

The Autologous Blood & Marrow Transplant Registry (ABMTR) continues to grow. Currently, 220 participating centers in the United States, Canada, Mexico and South America provide data to the Registry. More than 100 physicians from these centers volunteer their time to serve on one or more ABMTR Working Committees, to plan and conduct studies using these data.

In the past year, ABMTR centers registered over 7,000 new patients. The total number of transplants available for study exceeds 30,000. The distribution of diseases treated by those transplants is shown below.

These data are being used to conduct an increasing number of studies. The ABMTR has active investigations in autotransplants for breast cancer, non-Hodgkin and Hodgkin lymphoma and ovarian cancer. Disease-specific Report Forms are recently complete or near completion for multiple myeloma, neuroblastoma, lung cancer and CNS tumors. Data col-

lected on these forms will allow additional studies in the near future. The Registry continues to be a unique resource for studying the impact of high-dose therapy on management of patients with diverse disorders.

This issue of the Newsletter focuses on RSV (respiratory syncytial virus) and other community respiratory viral infections in the bone marrow transplant setting, an increasingly recognized problem in immune suppressed patients. Understanding the epidemiology and manifestations of these infections in the posttransplant patient is important to allow early treatment. Registry studies to provide insight into the prevalence and natural history of community respiratory infections are planned. The Newsletter also summarizes a new ABMTR study on autotransplants for neuroblastoma, funded in part by the Eppley Foundation for Research in New York.

On behalf of the Registry, I want to express thanks to all those whose efforts make this program a success.



ABMTR Advisory Committee Chair, James O. Armitage, MD, is Professor and Chairman, Department of Medicine, University of Nebraska Medical Center, Omaha. Dr. Armitage served as President of the American Society for Clinical Oncology (1996-1997).

**Distribution of autotransplants performed between 1989 and 1996, registered with the ABMTR by 220 teams in North and South America**

Disease	Totals, %
Breast cancer	10,556 (35)
Non-Hodgkin lymphoma	7,653 (25)
Hodgkin lymphoma	3,593 (12)
Acute myelogenous leukemia	2,330 (8)
Acute lymphoblastic leukemia	590 (2)
Chronic myelogenous leukemia	271 (1)
Multiple myeloma	1,715 (6)
Neuroblastoma	735 (2)
Ovarian cancer	695 (2)
Testicular cancer	452 (1)
Brain tumor	370 (1)
Lung cancer	128 (<1)
Bone sarcoma	118 (<1)
Other cancer	1,189 (4)
<b>Total</b>	<b>30,395</b>

## The IBMTR/ABMTR Statistical Center Celebrates Achievements: 1972-1997

This year was a very special one for the IBMTR/ABMTR Statistical Center. First, we celebrated the 25<sup>th</sup> anniversary of the IBMTR. On September 13 over 200 physicians and scientists from around the world joined us at the Medical College of Wisconsin for our 25<sup>th</sup> Anniversary Educational Symposium on *New Directions in Blood Cell and Bone Marrow Transplants*. Speakers addressed issues of stem biology, alternative sources of stem cells for transplantation, gene therapy and xenotransplantation. Almost 300 friends and supporters shared a gala dinner program that evening, featuring comments by Dan Rutz of CNN News and a keynote speech by Wisconsin First Lady Sue Ann Thompson (see p. 6). We were very pleased to have three of the IBMTR's founders join us for the celebration: Dr. Robert Good of All Children's Hospital, St. Petersburg, Florida; Professor Georges Mathé of the Institut de Cancerologie et d'Immunologie, Villejuif, France; and Dr. George W. Santos of The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Second, I am happy to announce, the National Institutes of Health intends to award an R24 grant to support the IBMTR and ABMTR for 1998-2003. This grant will provide about 60 percent of the funds needed for our scientific and educational programs. The remaining funds must come from foundation, corporate and individual donations.

Third, accrual to the database reached an all-time high. The Statistical Center received about 7,000 initial Report Forms for transplant recipients during the past year, an increase of more than 2,000 compared to the year before!

Finally, five IBMTR/ABMTR studies were accepted for presentation at this year's annual meeting of the American Society of Hematology (ASH), December 5-9, 1997, San Diego, California:

**Dr. Julie Vose (University of Nebraska, Omaha) will present results of autotransplants in patients with aggressive non-Hodgkin lymphoma failing primary induction therapy.** This study of 221 patients failing to achieve a first complete remission with conventional therapy demonstrates 100-day mortality of  $17 \pm 5\%$  (95% confidence interval) with 3-year progression-free and overall survival of  $32 \pm 6\%$  and  $40 \pm 7\%$ , respectively. The only predictor of autotransplant outcome was sensitivity to prior chemotherapy. Patients with resistant disease had a 3-year probability of survival of only  $19 \pm 12\%$  compared to  $48\% \pm 13\%$  for those with sensitive (partial response) disease.

**Dr. Martin S. Tallman (Northwestern University, Chicago) will present a study of the effect of high-dose cytarabine, given for consolidation of acute myelogenous leukemia in first remission, on outcome of subsequent HLA-identical sibling transplants.** The study includes 77 patients receiving no postremission therapy prior to transplant, 151 receiving high-dose cytarabine and 239 receiving other consolidation therapy including cytarabine at standard dose. Preliminary analyses indicate no differences in relapse, transplant-related mortality or survival.

**Dr. Stella Davies (University of Minnesota, Minneapolis) will present a comparison of total body irradiation (TBI) or busulfan with cyclophosphamide for pretransplant conditioning in children transplanted in first or second remission.** Multivariate analyses show increased treatment-related mortality and lower leukemia-free survival in the children receiving TBI.

**Dr. Jakob Passweg (Kantonsspital Basel, Switzerland) will present an analysis of bone marrow transplant for severe aplastic anemia using unrelated or HLA-mismatched related donors.** Five-year probabilities of survival in this cohort of 240 patients transplanted between 1985 and 1995 are  $37 \pm 7\%$ .

**Dr. Philip Rowlings (Medical College of Wisconsin, Milwaukee) will present 8 cases of Hodgkin Disease developing after an allogeneic bone marrow transplant for leukemia or aplastic anemia.** The observed-to-expected (in the general population) incidence ratio of Hodgkin Disease in transplant recipients was 6.31 (95% confidence interval 2.7-12). In contrast to other posttransplant lymphoproliferative disorders, these tumors developed relatively late and were not associated with T-cell depletion of donor marrow, use of antilymphocyte globulin or donor-recipient mismatch. In situ hybridization studies suggested presence of Epstein Barr virus in at least half of these cases.

These studies indicate the diversity and importance of issues addressed using the IBMTR/ABMTR database. Thank you for your continued participation in IBMTR/ABMTR research and educational programs. Through your help, we have been able to make a significant impact on the success of blood and marrow transplantation over the past 25 years.

## Message from the Scientific Director

Mary M. Horowitz,  
MD, MS  
Scientific Director



Mary M. Horowitz,  
MD, MS is  
Scientific Director  
of the IBMTR/ABMTR  
and Professor of  
Medicine at the Medical  
College of Wisconsin

# ABMTR INITIATES STUDY OF AUTOTRANSPLANTS FOR NEUROBLASTOMA

By Philip A. Rowlings, MD, MS, IBMTR/ABMTR Assistant Scientific Director

Neuroblastoma is the most common extra-cranial solid tumor of children accounting for 8%-10% of childhood malignancies. In the United States, between 500 and 1,000 children are diagnosed with neuroblastoma each year. Eighty-five percent are less than six years old at the time of diagnosis. Stage of disease and age at diagnosis are the major determinants of treatment outcome. Clinical staging of neuroblastoma is based on the extent of the primary tumor and sites of metastases. A set of uniform criteria for diagnosis, staging, and response to therapy were recently published (1). About 40% of children are cured with surgery, radiation and/or chemotherapy. Conventional treatments fail in the remaining 60%.

Published results of autotransplants in relatively small numbers of patients with high risk neuroblastoma are encouraging, showing disease-free survival rates of 30-50% (2). The ABMTR database has information for over 700 autotransplants for neuroblastoma. By analyzing large numbers of patients, the study should provide a more precise estimate of outcome in groups defined by well-characterized prognostic factors.

The study will also examine patient-, disease- and treatment-related variables for their association with transplant outcome. Of particular interest is the relative efficacy of high-dose conditioning regimens and approaches to graft purging. Also, because ABMTR centers provide continuing follow-up information on long-term survivors, the study will attempt to define the risk of late effects such as second cancers. In collaboration with the Pediatric Oncology Group, a quality of life questionnaire will also be developed to assess functional status of long-term survivors of autotransplants for neuroblastoma. Finally, in collaboration with the IBMTR, the study will compare the outcome of autologous and allogeneic transplants for neuroblastoma.

The first step in this study, development of a Disease-Specific Report Form for data collection was recently completed, with the help of a generous grant from the New York-based Eppley Foundation for Research. Centers who have submitted information regarding their neuroblastoma patients on older versions of the Report Forms will be asked to submit a supplemental form to provide all of

the information required for the planned studies. We encourage you to submit the brief supplemental form as quickly as possible.

The study, which is under the auspices of the IBMTR/ABMTR Pediatric Cancer Working Committee (Chair, Bruce Camitta), will be chaired by Naynesh R. Kamani, MD, Director, Pediatric Bone Marrow Transplantation at the University of Texas Health Science Center in San Antonio. Individuals who wish to participate in this study or have questions may contact the IBMTR/ABMTR Statistical Center or Dr. Naynesh Kamani, Director, Pediatric Bone Marrow Transplantation, Division of Hematology/Oncology/Immunology, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284, ☎ (210) 704-3450 or fax (210) 704-2396, email: nkamani@srhcc.org.

1. Brodeur G, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol* 11:1466-1477, 1993.

2. Kamani NR. Autotransplants for neuroblastoma. *Bone Marrow Transplant* 17:301-304, 1996.

## RECENT SCIENTIFIC REPORTS FROM THE IBMTR/ABMTR

Curtis RE, Rowlings PA, Deeg HJ, Shriner DA, Socié G, Travis LB, Horowitz MM, Witherspoon RP, Hoover RN, Sobocinski KA, Fraumeni JF Jr, Boice JD Jr. **Solid cancers after bone marrow transplantation.** *New Engl J Med* 336:897-904, 1997.

Szydlo R, Goldman JM, Klein JP, Gale RP, Ash RC, Bach FH, Bradley BA, Casper JT, Flomenberg N, Gajewski JL, Gluckman E, Henslee-Downey PJ, Hows JM, Jacobsen N, Kolb H-J, Lowenberg B, Masaoka T, Rowlings PA, Sondel PM, van Bekkum DW, van Rood JJ, Vowels MR, Zhang MJ, Horowitz MM. **Results of allogeneic bone marrow transplants for leukemia using donors other than HLA-identical siblings.** *J Clin Oncol* 15:1767-1777, 1997.

Antman KH, Rowlings PA, Vaughan WP, Pelz CJ, Fay JW, Fields KK, Freytes CO, Gale RP, Hillner BE, Holland HK, Kennedy MJ, Klein JP, Lazarus HM, McCarthy PL Jr, Saez R, Spitzer G, Stadtmauer EA, Williams SF, Wolff S, Sobocinski KA, Armitage JO, Horowitz MM. **High-dose chemotherapy with autologous hematopoietic stem cell support for breast cancer in North America.** *J Clin Oncol* 15:1870-1879, 1997.

Passweg JR, Socié G, Hinterberger W, Bacigalupo A, Biggs JC, Camitta BM, Champlin RE, Gale RP, Gluckman E, Gordon-Smith EC, Hows JM, Klein JP, Nugent ML, Pasquini R, Rowlings PA, Speck B, Tichelli A, Zhang MJ, Horowitz MM, Bortin MM. **Bone marrow transplantation for severe aplastic anemia: Has outcome improved?** *Blood* 90:858-864, 1997.

Zhang MJ, Baccarani M, Gale RP, McGlave PB, Atkinson K, Champlin RE, Dicke KA, Giralt S, Gluckman E, Goldman JM, Klein JP, Herzig RH, Masaoka T, O'Reilly RJ, Rozman C, Rowlings PA, Sobocinski KA, Speck B, Zwaan FE, Horowitz MM. **Survival of patients with chronic myelogenous leukaemia relapsing after bone marrow transplantation: Comparison with patients receiving conventional chemotherapy.** *Br J Haematol*, 1997. In press.

Lee SJ, Kuntz KM, Horowitz MM, McGlave PB, Goldman JM, Sobocinski KA, Hegland J, Kollman C, Parsons SK, Weinstein MC, Weeks JC, Antin JH. **A decision analysis of unrelated donor bone marrow transplantation for chronic myelogenous leukemia.** *Ann Int Med*, 1997. In press.

Gale RP, Hehlmann R, Zhang MJ, Hasford J, Goldman JM, Heimpel H, Hochhaus A, Klein JP, Kolb H-J, McGlave PB, Passweg JR, Rowlings PA, Sobocinski KA, Horowitz MM and the German CML Study Group. **Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia.** *Blood*, 1997. In press.

Waters TM, Bennett C, Pajean TS, Sobocinski KA, Klein JP, Rowlings PA, Horowitz MM. **Economic analyses of bone marrow and blood stem cell transplantation for leukemias and lymphoma: What do we know?** *Bone Marrow Transplant*, 1997. In press.

Passweg JR, Tiberghien P, Cahn J-Y, Vowels MR, Camitta BM, Gale RP, Herzig RH, Hoelzer D, Horowitz MM, Ifrah N, Klein JP, Marks DI, Ramsay NKC, Rowlings PA, Weisdorf DJ, Zhang MJ, Barrett AJ. **Graft versus leukemia effects in T-lineage and B-lineage acute lymphoblastic leukemia.** *Bone Marrow Transplant*, 1997. In press.

*Reprints available on request*

**Community Respiratory Viral Infections...** (continued from page 1)

Infection with community respiratory viruses in immune competent persons is common though generally not serious, the most frequent syndrome being the "common cold." Except in the elderly and newborn, community respiratory virus infections generally involve only the upper respiratory tract and are self-limited in immune competent individuals.

A recent study at the M.D. Anderson Cancer Center (MDACC), examining nasal and throat specimens in leukemia and transplant patients presenting with respiratory symptoms, demonstrated community respiratory viruses in 27%. Viral prevalence in this study mirrored that in the community except that RSV was more common than might be expected. RSV was, in fact, the most common respiratory virus isolate. RSV infections occurred primarily in the winter and early spring. In contrast to respiratory virus infections in immune competent persons, such infections in transplant recipients frequently progressed to pneumonia after an upper respiratory prodrome. In MDACC studies, RSV was associated with pneumonia in about half of patients infected in the first year after an allogeneic bone marrow transplant; more than half of RSV pneumonias were fatal.

Strategies for preventing morbidity and mortality from community respiratory viruses require better awareness of their prevalence, prevention of nosocomial transmission, im-

munization and early diagnosis and treatment. Several studies demonstrate that respiratory viruses are frequently transmitted nosocomially, often from persons with only mild symptoms of illness. Strict adherence to infection control measures, that include contact isolation and prevention of exposure to persons with even mild respiratory illnesses,

***"...successful treatment [of community respiratory virus infections] requires early diagnosis and intervention."***

can decrease nosocomial risk. Immunization is available only for influenza virus; patients, family members and health care workers should be vaccinated yearly. Passive immunization with immune globulin may be helpful for some viruses, including RSV. Effective antivirals are available for influenza A (amantadine, rimantidine) and RSV (ribavirin). However, successful treatment requires early diagnosis and intervention. This requires awareness of the prevalence of these viruses in the community and appropriate investigation of respiratory symptoms.

Although it is well-proven that community respiratory viruses can cause severe pulmo-

nary infection and death in transplant recipients, their overall contribution to early and late mortality after blood and marrow transplantation is still unclear. Most studies are limited by small numbers, inadequate sampling and restriction to patients with severe respiratory symptoms. The IBMTR/ABMTR will be exploring this area over the next few years, first by examining the seasonal incidence of fatal and non-fatal respiratory infections. We are particularly interested in whether interstitial pneumonias reported as idiopathic are associated with known patterns of viral prevalence in the community. With better understanding of the natural history of these disorders, hopefully progress can be made in prevention, diagnosis and treatment strategies.

**Suggested Reading:**

Whimbey E, Englund JA, Ljungman P (ed). Proceedings of a Symposium: Community respiratory viral infections in the immunocompromised host. *Am J Med* 1997;102 (3A).

Whimbey E, Champlin RE, Couch RB, et al. Community respiratory virus infections among hospitalized adult bone marrow transplant recipients. *Clin Infect Dis* 1996;22:778-782.

Wendt CH, Hertz MI. Respiratory syncytial virus and parainfluenza virus infections in the immunocompromised host. *Sem Respir Infect* 1995;10:224-231.

**IBMTR/ABMTR MEMBER PROFILE: Richard E. Champlin, MD**



Richard E. Champlin, MD is Professor of Medicine and Chairman of the Department of Hematology at the University of Texas M.D. Anderson Cancer Center in Houston, where he is also Chief, Section of Blood and Bone Marrow Transplantation. He is a fellow of the American College of Physicians, and a member of the American Society of Hematology, and the American Society for Clinical

Oncology. Dr. Champlin was the first President of the Council of Donor Transplant and Collection Centers of the National Marrow Donor Program, appointed Chairman, Bone Marrow Transplant Committee of the National Cancer Center Network in 1995 and serves as Chairman of the Scientific

Affairs Committee of the American Society of Blood and Marrow Transplantation.

Dr. Champlin has been associated with the International Bone Marrow Transplant Registry (IBMTR) for many years and serves on the IBMTR's Executive Committee and Scientific Advisory Committee. He also serves on the Executive Committee and Scientific Advisory Committee of the Autologous Blood and Marrow Transplant Registry (ABMTR).

An international expert in leukemia and bone marrow transplantation, he is Chair of the IBMTR's Histocompatibility, Alternative Donors, and Stem Cell Sources Working Committee and co-chair of the Chronic Lymphocytic Leukemia Working Committee, a joint scientific committee of the IBMTR and ABMTR.



## IBMTR CELEBRATES SILVER ANNIVERSARY

In its 25th year of existence as a productive scientific organization, the International Bone Marrow Transplant Registry (IBMTR) took time out on September 13th for its silver Anniversary Celebration, "Sharing Knowledge - Sharing Hope." Commemorative events included a scientific symposium at the Medical College of Wisconsin attended by more than 200 members of the Milwaukee area transplant and oncology community, Registry founders, Executive and Advisory Committee members, and international representatives from many participating teams.

Speakers included Irving Weissman (Stanford University School of Medicine, Palo Alto, California) speaking on the biology of the hematopoietic stem cell, Mary Horowitz (Medical College of Wisconsin, Milwaukee) speaking on alternative stem cell sources, Malcolm Brenner (St. Jude's Children's Research Hospital, Memphis, Tennessee) speaking on gene therapy, and Megan Sykes (Harvard Medical School, Boston, Massachusetts) speaking on xenotransplantation. Perspectives on the history of the IBMTR and the field of transplantation and a vision for the future were shared by three of the Registry's founding members, Dr. Robert Good of All Children's Hospital, St. Petersburg, Florida; Professor Georges Mathé of the Institut de Cancerologie et d'Immunologie, Villejuif, France; and Dr. George W. Santos of The Johns Hopkins University School of Medicine, Baltimore, Maryland.

The symposium was followed by a spectacu-

lar gala dinner at the Milwaukee Art Museum on Saturday evening, attended by almost 300 Registry friends and supporters. A video presentation, sponsored and produced by Rockwell Automation Allen-Bradley Company of Milwaukee, a founding supporter of the Registry, provided a moving perspective on the Registry's history, and the importance of its work to patients. Dan Rutz, Managing Editor for CNN Health and Medical News, and Mrs. Sue Ann Thompson, First Lady of the State of Wisconsin and a cancer survivor, gave thought-provoking commentaries on cancer care.

Most importantly, the program honored the thousands of transplant recipients and their families. They have, by participating in clinical research and sharing their information with the medical community, played the most important role in the progress made over the past 25 years. Some of these patients were present to share in the Anniversary Dinner. Others had their stories told through a photograph display developed by local artists and premiered at the event. This exhibit will be displayed throughout Southeast Wisconsin and at international scientific meetings.

Our heartfelt thanks go out to the many sponsors and supporters whose generosity and participation made the 25<sup>th</sup> Anniversary Celebration of the IBMTR a memorable occasion and to all whose contributions have made the past 25 years of scientific work possible.

**The International Bone Marrow Transplant Registry (IBMTR) celebrated its 25<sup>th</sup> anniversary September 13, 1997 with an educational symposium, featuring nationally and internationally known cancer researchers, followed by a gala dinner.**



(Photo) Mary M. Horowitz, MD, MS, Scientific Director of the IBMTR, poses with IBMTR founders: (left to right) Robert L. Truitt, PhD, Professor of Pediatrics, Medical College of Wisconsin; George W. Santos, MD, The Johns Hopkins University School of Medicine, Baltimore, MD; Prof. Georges Mathé, Institut de Cancerologie et d'Immunologie, Paris; Robert A. Good, MD, PhD, All Children's Hospital, St. Petersburg, FL; and Robert Peter Gale, MD, PhD, chair of the IBMTR Scientific Advisory Committee and Bone Marrow and Stem Cell Transplant Director, Salick Health Care, Los Angeles.

## IBMTR Founder: Alfred A. Rimm, PhD

An article in our 25th Anniversary Newsletter reviewed the history of the IBMTR and ABMTR. However, in my column I amazingly (and embarrassingly) failed to cite contributions of one of the Registry's founders: Alfred A. Rimm. In retrospect I understand why: Al was such a central figure in the IBMTR/ABMTR for so long he became part of the Registry's identity. Mort Bortin never considered Al a "founder"; he *was* the Registry.

Al entered the bone marrow transplant world as Mort's statistical collaborator in murine transplant studies. Their early studies dealt with issues like radiation chimeras, graft-vs-host disease, graft-vs-leukemia and the like. Re-reading these articles today, I am amazed how the central issues Mort and Al raised are the focus of current research. I am also reluctant to try to quantify progress in understanding some issues Mort and Al identified in 1970 (I am referring to substance rather than techniques).

Al volunteered to help Mort with statistical analyses of the early ACS/NIH Bone Marrow Transplant Registry. He also helped bring Mort and his collaborators from Mount Sinai Hospital in Milwaukee to the Medical College of Wisconsin (the current site of the Statistical Center). The first IBMTR/ABMTR-related publication I found by Al is from 1972 making this year the 25th anniversary of Al's involvement with us. This publication was followed by almost 75 more in which Al and his colleagues provided statistical support for IBMTR/ABMTR analyses.

Al's contributions to our organization are too numerous to list. I am especially grateful for three: (1) introducing us to new, innovative techniques for statistical analyses, (2) input to our grant submissions, and (3) recruiting Mary Horowitz. Statisticians are, on average (or perhaps modally), odd. But not Al: doesn't everyone survive weeks on champagne and apples? And I suppose most folks have 4-sided reversible Scotch plaid ties (something to do with kabalah?).

Al left the Medical College of Wisconsin in 1993 to head the Department of Epidemiology and Biostatistics at Case Western Reserve University. Their gain is our loss.

-- Robert Peter Gale, MD, PhD  
IBMTR Scientific Advisory  
Committee Chair

## FOUNDATION AND CORPORATE SUPPORT OF THE IBMTR / ABMTR

All of us at the IBMTR/ABMTR Statistical Center thank the many contributors who have joined our international collaboration for research in blood and marrow transplantation. Private support for the Registries continues to be vitally important since federal grants cover only 60 percent of the Statistical Center's budget. We gratefully acknowledge the support of the Medical College of Wisconsin; the National Cancer Institute; the National Institute of Allergy and Infectious Disease; the National Heart, Lung and Blood Institute; the Department of Defense; and the generosity of the following foundations and corporations:

### Non-Federal Support Listing for the IBMTR / ABMTR (Grant Awards Since 1995)

- |   |   |  |
|---|---|--|
| <i>Aastron Biosciences</i>                      | <i>Deborah J. Dearholt Memorial Fund</i>                        | <i>Northwestern Mutual Life Insurance Company Foundation</i>                   |
| <i>Activated Cell Therapy, Inc.</i>             | <i>The Eppley Foundation for Research</i>                       | <i>Novartis Pharmaceuticals, Inc.</i>  |
| * <i>Alpha Therapeutic Corporation</i>          | <i>ESSEX Pharma GmbH (Germany)</i>                              | * <i>Ortho Biotech Inc.</i>  |
| <i>Alpha Therapeutic GmbH</i>                   | <i>Fujisawa USA</i>   | <i>John Oster Family Foundation</i>  |
| * <i>American Oncology Resources</i>            | <i>Genentech, Inc.</i>  | <i>Jane &amp; Lloyd Pettit Foundation</i>                                      |
| * <i>Amgen, Inc.</i>                            | <i>Glaxo Wellcome, Inc.</i>                                     | <i>Alirio Pfiffer Bone Marrow Transplantation Support Association (Brazil)</i> |
| <i>Amgen Europe AG</i>                          | <i>Hewlett-Packard Company</i>                                  | * <i>Pfizer Inc.</i>   |
| <i>Anonymous</i>                                | <i>Hoechst Marion Roussel, Inc.</i>                             | <i>Pharmacia and Upjohn</i>  |
| <i>Astra Arcus AB</i>                           | * <i>ICN Pharmaceuticals, Inc.</i>                              | * <i>Principal Mutual Life Insurance Company</i>                               |
| * <i>Astra USA</i>                              | * <i>Immunex Corporation</i>                                    | <i>QLT PhotoTherapeutics, Inc.</i>   |
| * <i>Baxter Healthcare Corporation</i>          | * <i>Janssen Pharmaceutica</i>                                  | <i>Quantum Health Resources</i>  |
| * <i>Bayer Corporation</i>                      | <i>The Kettering Family Foundation</i>                          | <i>RGK Foundation</i>  |
| <i>Biochem Pharma</i>                           | <i>Kirin Brewery Company (Japan)</i>                            | <i>Roche Laboratories</i>  |
| <i>Biogen</i>                                   | <i>Robert J. Kleberg, Jr. &amp; Helen C. Kleberg Foundation</i> | <i>Rockwell Automation/Allen-Bradley Co.</i>                                   |
| <i>BioWhittaker, Inc.</i>                       | <i>Herbert H. Kohl Charities</i>                                | <i>RPR Gencell</i>   |
| <i>BIS Laboratories</i>                         | <i>Lederle International</i>                                    | * <i>SangStat Medical Corporation</i>  |
| * <i>Blue Cross and Blue Shield Association</i> | <i>Life Technologies, Inc.</i>                                  | <i>Schering-Plough International</i>   |
| <i>The Lynde and Harry Bradley Foundation</i>   | * <i>The Liposome Company</i>                                   | <i>Walter Schroeder Foundation, Inc.</i>                                       |
| * <i>Bristol-Myers Squibb Company</i>           | <i>Nada and Herbert P. Mahler Charities</i>                     | * <i>Searle</i>  |
| <i>Cell Therapeutics, Inc.</i>                  | * <i>MDS Nordion</i>  | <i>SEQUUS Pharmaceuticals</i>  |
| * <i>CellPro, Inc.</i>                          | <i>Medical SafeTEC</i>  | <i>Stackner Family Foundation</i>  |
| * <i>Centeon</i>                                | * <i>MGI Pharma, Inc.</i>                                       | <i>The Starr Foundation</i>  |
| <i>Center for Advanced Studies in Leukemia</i>  | * <i>Milliman &amp; Robertson, Inc.</i>                         | <i>Joan and Jack Stein Foundation</i>  |
| * <i>Chimeric Therapies, Inc.</i>               | <i>Milstein Family Foundation</i>                               | <i>StemCell Technologies Inc</i>   |
| * <i>Chiron Therapeutics</i>                    | <i>The Milwaukee Foundation/</i>                                | <i>SyStemix</i>  |
| <i>Cigna Health Care</i>                        | <i>Elsa Schoeneich Medical Research Fund</i>                    | <i>Therakos</i>  |
| * <i>COBE BCT Inc.</i>                          | <i>NCGS and Associates, Inc.</i>                                | <i>TS Scientific and Planer Products</i>                                       |
| * <i>Coram Healthcare</i>                       | <i>NeXstar Pharmaceuticals, Inc.</i>                            | <i>Laboratories Wyeth France</i>   |
| <i>Coulter Corporation</i>                      | <i>Samuel Roberts Noble Foundation</i>                          | * <i>Wyeth-Ayerst Laboratories</i>   |
| <i>Charles E. Culpeper Foundation</i>           |   | <i>Xoma Corporation</i>  |
| <i>Eleanor Naylor Dana Charitable Trust</i>     |   |  |

\* *Corporate Member*

### IBMTR / ABMTR CORPORATE MEMBERSHIP PROGRAM

Several corporations have joined the IBMTR/ABMTR Corporate Membership Program (see above). The annual membership program provides member organizations with informational materials on blood and bone marrow transplantation developed by the IBMTR/ABMTR Information Resource Service.

The program includes subscriptions to the *Statistical Center Report on Survival Statistics for Blood and Marrow Transplants*, *IBMTR and ABMTR Newsletters*, the worldwide *IBMTR/ABMTR Directory of Blood and Marrow Transplant Teams*, and the *IBMTR/ABMTR Summary Slides on State-of-the-Art in Blood and Marrow Transplantation* as well as invitations to our meetings and educational forums and access to the IBMTR/ABMTR databases for simple analyses. These resources are useful for marketing managers, medical directors, research directors, product managers, case managers or transplant coordinators.

For additional information on the Corporate Membership Program, please contact Susan Ladwig, Associate Director of Development ☎ (414) 456-8363, Fax: (414) 456-6530.

By

**Susan Ladwig, MA**  
**Associate Director**  
**of Development,**  
**Statistical Center**

### A Special Thank You

to our  
1998 Annual  
**IBMTR / ABMTR**  
**Meeting Supporters**

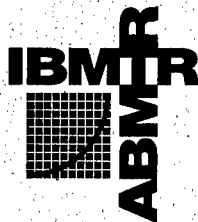
- AASTROM BIOSCIENCES  
AMGEN, INC.  
BAXTER HEALTHCARE, INC.  
BIOTECH GROUP  
BIOCHEM PHARMA  
BIS LABORATORIES  
BRISTOL-MYERS SQUIBB  
ONCOLOGY  
CELL THERAPEUTICS, INC.  
CELLPRO, INC.  
CENTEON  
CHIRON THERAPEUTICS, INC.  
COBE BCT  
FUJISAWA USA  
ICN PHARMACEUTICALS,  
INC.  
IMMUNEX CORPORATION  
ISHAGE  
THE LIPOSOME COMPANY,  
INC.  
MEDICAL SAFETEC  
MEDIMMUNE, INC.  
NEXSTAR PHARMACEUTICALS  
NOVARTIS PHARMACEUTICALS  
ORTHO BIOTECH INC.  
PFIZER INC.  
PHARMACIA & UPJOHN  
ROCHE LABORATORIES  
SANGSTAT MEDICAL  
CORPORATION  
SCHERING-PLOUGH  
CORPORATION  
SEARLE  
SEQUUS  
PHARMACEUTICALS, INC.  
STEMCELL TECHNOLOGIES  
INC  
SYSTEMIX  
THERAKOS  
WYETH-AYERST  
LABORATORIES

**STATISTICAL  
CENTER  
PERSONNEL**

**MARY M. HOROWITZ, MD, MS**  
Scientific Director  
**PHILIP A. ROWLINGS, MD, MS**  
Assistant Scientific Director

**JOHN P. KLEIN, PhD**  
Statistical Director  
**MEI-JIE ZHANG, PhD**  
Assistant Professor/Biostatistician  
**KATHLEEN A. SOBOCINSKI, MS**  
Associate Statistical Director

**MELODEE L. NUGENT, MA**  
Information Specialist  
**SANDRA C. MURPHY, MS**  
Biostatistician  
**JUDY VEUM STONE, MS**  
Biostatistician



*The ABMTR Newsletter is funded by an unrestricted educational grant from ICN Pharmaceuticals, Inc.*

**BARBARA A. McGARY, BS**  
Manager of Information Systems  
**BARBARA B. LIU, MS**  
Database Programs Manager  
**SHARON K. NELL**  
Communications Coordinator  
**JANE E. REBRO**  
Assistant Communications Coordinator  
**DIANE J. KNUTSON**  
Systems Coordinator  
**HEMANT A. PATANI**  
Research Assistant

**CLAUDIA A. ABEL**  
Data Coordinator  
**ANGELA S. KUMMEROW**  
Data Coordinator  
**HONGYU TIAN**  
Data Coordinator  
**PATRICIA A. VESPALEC**  
Data Coordinator  
**BARBARA H. BORTIN, MS**  
Data Entry Assistant  
**YING HU**  
Data Entry Assistant

**KAVITA A. PATANI**  
Data Entry Assistant  
**ANN G. PERELES**  
Data Entry Assistant  
**LILY QIAN**  
Data Entry Assistant  
**JANELLE M. STANO**  
Data Entry Assistant  
**TERI WILLIAMS**  
Data Entry Assistant

**D'ETTA WALDOCH SEVERSON, CMP**  
Associate Director, International Programs  
**LAURIE L. SCHWEITZER**  
Conference Registration Manager

**SUSAN U. LADWIG, MA**  
Associate Director of Development  
**LISA J. LEHRMANN**  
Program Coordinator  
**LINDA M. SCHNEIDER**  
Desktop Publishing Specialist

**KIM R. HYLER**  
Administrative Assistant  
**JEAN M. EDER**  
Staff Assistant  
**JANNINE H. WALLDAN**  
Clerical Assistant

**ABMTR Advisory Committee**

**James O Armitage, MD**  
(Chair)  
University of Nebraska  
Medical Center  
Omaha, NE USA

**Karen Antman, MD**  
Columbia University  
New York, NY USA

**Frederick R Appelbaum, MD**  
Fred Hutchinson  
Cancer Research Center  
Seattle, WA USA

**Charles S August, MD**  
Miami Children's Hospital  
Miami, FL USA

**Karl G Blume, MD**  
Stanford University  
Medical Center  
Stanford, CA USA

**Bruce Camitta, MD**  
Medical College  
of Wisconsin  
Milwaukee, WI USA

**Richard E Champlin, MD**  
MD Anderson  
Cancer Center  
Houston, TX USA

**Paul A Chervenick, MD**  
H. Lee Moffitt  
Cancer Center  
Tampa, FL USA

**Peter F Coccia, MD**  
University of Nebraska  
Medical Center  
Omaha, NE USA

**Karel A Dicke, MD, PhD**  
Arlington Cancer Center  
Arlington, TX USA

**Gerald J Elfenbein, MD**  
H. Lee Moffitt  
Cancer Center  
Tampa, FL USA

**Joseph W Fay, MD**  
Baylor University  
Medical Center  
Dallas, TX USA

**Robert Peter Gale, MD, PhD**  
Salick Health Care, Inc.  
Los Angeles, CA USA

**John Graham-Pole, MD**  
University of Florida  
Gainesville, FL USA

**Subhash C Gulati, MD**  
New York Hospital/Cornell  
Medical Center  
New York, NY USA

**Geoffrey P Herzig, MD**  
Roswell Park  
Cancer Institute  
Buffalo, NY USA

**Roger H Herzig, MD**  
University of Louisville  
Louisville, KY USA

**Mary M Horowitz, MD, MS**  
Medical College  
of Wisconsin  
Milwaukee, WI USA

**David D Hurd, MD**  
Wake Forest University  
Cancer Center  
Winston-Salem, NC USA

**Sundar Jagannath, MD**  
University of Arkansas  
Medical School  
Little Rock, AK USA

**Herbert Kaizer, MD**  
Rush Presbyterian  
St. Luke's Medical Center  
Chicago, IL USA

**Armand Keating, MD**  
University of Toronto  
Toronto, Ontario, CANADA

**John P Klein, PhD**  
Medical College  
of Wisconsin  
Milwaukee, WI USA

**Hillard M Lazarus, MD**  
University Hospital  
of Cleveland  
Cleveland, OH USA

**Carole B Miller, MD**  
Johns Hopkins  
Oncology Center  
Baltimore, MD USA

**Lee M Nadler, MD**  
Dana-Farber  
Cancer Institute  
Boston, MA USA

**Gordon L Phillips, MD**  
Markey Cancer Center  
Lexington, KY USA

**Norma KC Ramsay, MD**  
University of Minnesota  
Minneapolis, MN USA

**Robert C Seeger, MD**  
Children's Hospital  
of Los Angeles  
Los Angeles, CA USA

**Elizabeth J Shpall, MD**  
University of Colorado  
Health Sciences Center  
Denver, CO USA

**Gary L Spitzer, MD**  
Gerogetown University  
Medical Center  
Washington DC USA

**Patrick J Stiff, MD**  
Loyola University  
Maywood, IL USA

**William P Vaughan, MD**  
University of Alabama  
at Birmingham  
Birmingham, AL USA

**Julie M Vose, MD**  
University of Nebraska  
Medical Center  
Omaha, NE USA

**Roy S Weiner, MD**  
Tulane University  
School of Medicine  
New Orleans, LA USA

**Daniel J Weisdorf, MD**  
University of Minnesota  
Minneapolis, MN USA

**Stephanie F Williams, MD**  
University of Chicago  
Medical Center  
Chicago, IL USA

**Steven N Wolff, MD**  
Vanderbilt University  
Medical Center  
Nashville, TN USA



International Bone Marrow Transplant Registry  
Autologous Blood & Marrow Transplant Registry

*Sharing Knowledge.*

*Sharing Hope.*

**Welcome to the IBMTR/ABMTR**

Home of a worldwide effort to improve the  
results of blood and bone marrow transplants.

MISSION STATEMENT  
PERSONNEL DIRECTORY  
TRANSPLANT CENTERS  
NEWSLETTERS  
MEETING INFORMATION  
PUBLICATIONS  
COMMITTEES  
DATA COLLECTION  
INFORMATION SERVICES  
CORPORATE MEMBERSHIP  
PROGRAM  
WE NEED YOUR SUPPORT!

**New Update**

- [1999 IBMTR/ABMTR & ASBMT Annual Meeting/Registration Information.](#)
- [Global Transplant Center Locations and Contacts.](#)

Supported through an unrestricted educational grant from [Searle](#).

## **INFORMATION SERVICES**

### **FAQs**

**MISSION STATEMENT**

**PERSONNEL DIRECTORY**

**TRANSPLANT CENTERS**

**NEWSLETTERS**

**MEETING INFORMATION**

**PUBLICATIONS**

**COMMITTEES**

**DATA COLLECTION**

**INFORMATION SERVICES**

**FAQs**

**Disease - Specific Reports**

**Information Request**

**Report of Survival Statistics**

**Summary Slides**

**Other related Web Sites**

**CORPORATE MEMBERSHIP**

**PROGRAM**

**WE NEED YOUR SUPPORT!**

### **Blood and Marrow Transplants A Basic Introduction**

#### **1. What is bone marrow?**

Bone marrow is a substance found in the hollow bones of the hips, legs and arms. Special cells in the bone marrow called "stem cells" or "hematopoietic stem cells" produce all circulating blood cells including red cells which carry oxygen, white cells which make up the body's immune system and platelets which prevent bleeding.

#### **2. Why are transplants needed?**

Some people have diseases that alter or destroy the bone marrow. Others have diseases that can only be cured with high doses of radiation and drugs (sometimes called high-dose chemotherapy.) These high-dose treatments kill cancer cells but also kill normal bone marrow stem cells. Once the stem cells are destroyed, blood production stops. Blood or bone marrow transplants restore stem cells destroyed by disease or treatment.

#### **3. What is the difference between bone marrow and blood stem cell transplants?**

All transplants supply hematopoietic stem cells to restore blood production. When the stem cells are collected directly from bone marrow, the transplant is called a bone marrow transplant. When the stem cells are collected from the blood, the transplant is called a blood stem cell transplant or a peripheral blood stem cell transplant.

#### **4. What is the difference an allogeneic and an autologous transplant?**

Allogeneic transplants use blood or bone marrow cells from another person, usually a sibling but sometimes another relative or an unrelated donor. Autologous transplants use the patient's own blood or bone marrow cells which are removed prior to high-dose therapy, frozen and later returned.

### **Frequently Asked Questions**

#### **1. How many transplants are done and for what indications?**

There is no central repository registering ALL blood and marrow transplants. However, using data from worldwide surveys of transplant activity and data we collect here at the IBMTR/ABMTR, we periodically estimate the number of blood and marrow transplants performed worldwide and in North America. See 1998 Summary Slides for these figures (1 and 7).

**Reproduced From  
Best Available Copy**

## 2. Where is the best place to go for a transplant?

There is no one answer to this question. The decision about where to have a transplant done depends on many factors: geographic proximity and accessibility, experience of the center with a particular disease or type of transplant, a patient's comfort with the expertise and the personality of the treating physicians and the facility, requirements of particular insurance plans and others. Some resources for information that might help in this decision are listed below.

The **National Marrow Donor Program (NMDP)** has a directory of participating transplant centers that describes each center, summarizes its areas of expertise and provides contact information. It also gives some center-specific outcome information.

The **Oncology Nursing Society** has a directory called, "Bone Marrow Transplant Nursing Resource Directory". In this directory they list U.S. transplant centers by state and give limited details such as: how many transplants were performed for 1996, contact names and numbers, and how long the program has been opened. Please note, all transplant centers are not listed in this directory. They survey all institutions and only include those who respond to their survey. The Oncology Nursing Society can be reached at 412-921-7373 or visit their website at [www.ons.org](http://www.ons.org).

 **TOP**

**NEXT** 

**Reproduced From  
Best Available Copy**

## INFORMATION SERVICES

### FAQs

- [MISSION STATEMENT](#)
- [PERSONNEL DIRECTORY](#)
- [TRANSPLANT CENTERS](#)
- [NEWSLETTERS](#)
- [MEETING INFORMATION](#)
- [PUBLICATIONS](#)
- [COMMITTEES](#)
- [DATA COLLECTION](#)
- [INFORMATION SERVICES](#)
- [FAQs](#)
- [Disease - Specific Reports](#)
- [Information Request](#)
- [Report of Survival Statistics](#)
- [Summary Slides](#)
- [Other related Web Sites](#)
- [CORPORATE MEMBERSHIP PROGRAM](#)
- [WE NEED YOUR SUPPORT!](#)

The **BMT Newsletter** has an issue entitled, "Choosing a BMT Center." This issue provides insight into what to look for in a transplant center.

**BMT LINK** is another source for information on choosing a transplant center. They have a pamphlet, "A Survivors Guide to a Transplant". There is a section which deals with choosing a center. It lists questions which might help one decide on where to go for a transplant.

### 3. I would like information about a particular disease.

A patient's most important resource for information is his or her physician. There is no substitute for a open and frank conversation with one's doctor. We encourage patients to talk to their physicians frequently and to seek clarification on confusing issues. Before acting on information obtained through this or other websites, the information should be discussed with a physician familiar with the patient's medical situation.

All IBMTR/ABMTR publications are available upon request. Please check our Publication List.

The IBMTR/ABMTR December 1998 Newsletter includes figures on outcomes of transplants for the most common indications.

The **BMT Newsletter** also highlights specific diseases in many of its issues.

**InfoLink** is a website produced by the IBMTR/ABMTR, the National Marrow Donor Program and the American Society for Blood and Marrow Transplantation. It includes articles written by transplant experts at both basic and technical levels.

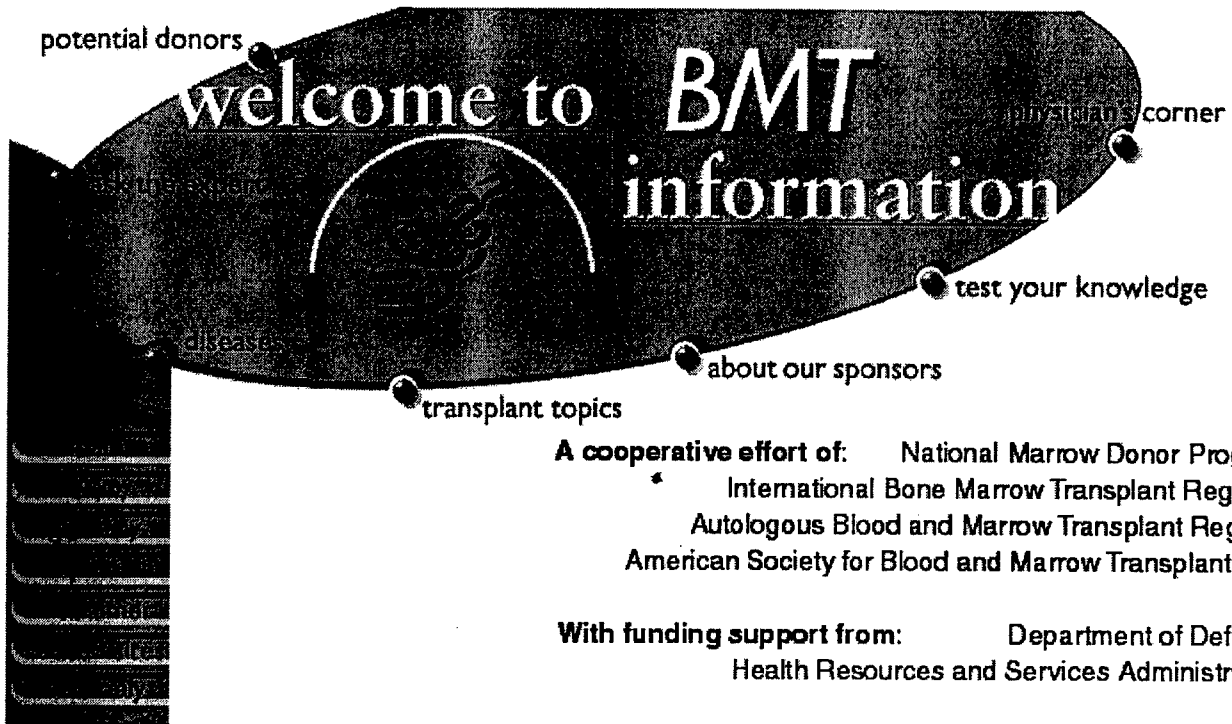
### 4. How can I request specific information from the IBMTR/ABMTR database?

This information is most appropriate for physicians and clinical investigators making treatment decisions or planning clinical studies. Please fill out the [IBMTR/ABMTR Information Request Form](#).

[▲ TOP](#)

[◀ BACK](#)

**Reproduced From  
Best Available Copy**



**A cooperative effort of:** National Marrow Donor Program  
International Bone Marrow Transplant Registry/  
Autologous Blood and Marrow Transplant Registry  
American Society for Blood and Marrow Transplantation

**With funding support from:** Department of Defense  
Health Resources and Services Administration

Viewing Preference Text Only With Images

*Last Revised 10/15/98*

[Potential Donors](#) | [Ask the Expert](#) | [Diseases](#) | [Transplant Topics](#) | [About our Sponsors](#) | [Test your Knowledge](#) | [Physician's Corner](#)  
[Main](#) | [Survey](#) | [Glossary](#) | [Q & A](#) | [Disclaimer](#) | [Related Sites](#) | [View Images](#)

---

## Autologous Blood and Bone Marrow Transplantation for Breast Cancer

Philip A. Rowlings, MBBS, M.S., FRACP, FRCPA  
Assistant Scientific Director, IBMTR/ABMTR

Mary Horowitz, M.D., M.S.  
Scientific Director, IBMTR/ABMTR

[Introduction](#) | [Current Data](#) | [Clinical Trials](#) | [Published Papers](#)

### Introduction

[Basic](#) | [Technical](#)

Breast cancer is the second most common cause of cancer deaths in North America. The American Cancer Society estimates that more than 180,000 new cases of breast cancer were diagnosed in 1996 (1). Fortunately, many women are cured of their disease through surgery with or without radiation therapy, chemotherapy, or hormone treatments after surgery. Unfortunately, the disease returns in many women, either at the same or another site. Still other women have metastasis—disease outside the breast and lymph nodes—at the time of diagnosis, which cannot be cured with surgery. So, scientists continue to look for effective treatments for women with recurrent or high-risk breast cancer.

A treatment used currently for women with recurrent breast cancer is high-dose chemotherapy followed by transplantation of the patient's own bone marrow or blood cells. This is called autologous transplant or *autotransplant*. This treatment, however, is controversial for patients with breast cancer. The therapy is expensive, and there is little information comparing the results of autotransplant with the results of standard chemotherapy. This controversy about autotransplants has caused legal problems between patients wishing to have the treatment and insurance companies refusing to pay for this treatment.

In response to the controversy, the U.S. Congress asked the General Accounting Office to write a report about the treatment. This report is entitled "Coverage of Autologous Bone Marrow Transplantation for Breast Cancer" (2). The report analyzed the financial and political issues that affect the use of new technologies for health care in the United States. But this report did not reach any conclusions about the use of autotransplants for patients with breast cancer.

The National Cancer Institute is trying to compare the results of autotransplants with those of standard therapy by sponsoring several large clinical trials in cancer centers throughout the United States. In these trials, patients are randomly assigned to different types of treatment and their outcomes are compared. Patients enrolling in these trials have a 50-50 chance of receiving a transplant. Randomized trials are the best way to determine whether one treatment is better than another. These trials are especially appropriate in evaluating treatments such as autotransplants for breast cancer, in which the true benefit is unknown. Several studies show that patients treated in clinical trials have better outcomes than those treated outside of trials, regardless of which treatment they receive. However, many patients and their physicians hesitate to get involved in these trials because they do not want to be assigned to the standard therapy (3).

Despite the controversy, the use of autotransplants for patients with breast cancer has greatly increased in the past 6 years. Data reported to the Autologous Blood and Marrow Transplant Registry (ABMTR) show that about 3,500 autotransplants were done in 1995 for patients with breast cancer.

## References

1. Cancer Facts and Figures - 1996. American Cancer Society.

[Return to article](#)

2. Unites States General Accounting Office: Report to the Honorable Ron Wyden, U.S. Senate, Health Insurance "Coverage of Autologous Bone Marrow Transplantation for Breast Cancer." April 1996. GAO/HEHS-96-83.

[Return to article](#)

3. Gradishar WJ, Tallman MS, Abrams JS. High-dose chemotherapy of breast cancer. Ann Intern Med 125:599-604, 1996.

[Return to article](#)

[Return to Top](#)

## Current Data

### Background

[Basic](#) | [Technical](#)

High-dose chemotherapy combined with autotransplant is being used more and more often to treat breast cancer in women who have a high risk of their breast cancer continuing or recurring. Two organizations keeping track of information about transplants for breast cancer and other diseases are the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR) of North America. According to data from these organizations, breast cancer is now the most common reason for blood cell or bone marrow transplantation.

Currently, most reports published about autotransplants include only a few patients and do not compare results with standard chemotherapy. Only one small study has been published of women with metastatic breast cancer treated with either standard dose or high-dose chemotherapy (1). This study included only women with newly diagnosed metastatic breast cancer. It showed a longer survival period for patients who had autotransplants. However, the results of larger trials and other clinical studies are not yet available. Until these results are published, most questions about the advantages of autotransplant cannot be answered. In the meantime, data about the safety of autotransplants and the outcome of patients having this treatment are available from the ABMTR and other sources.

### What Is the ABMTR?

The Autologous Blood and Marrow Transplant Registry (ABMTR) of North America is an organization of more than 200 transplant institutions in the United States, Canada, and Central and South America. These institutions report data about autotransplants to a Statistical Center at the Medical College of Wisconsin. The ABMTR began to collect data in 1992. About half of the autotransplants done in North America for patients with all diseases are registered with the ABMTR (2,3). (Click [here](#) for a list of participating centers.)

### Trends in Autotransplants and Deaths for Patients with Breast Cancer

From 1989 to 1995, the number of autotransplants increased by almost six times. At first, autotransplants were done primarily for patients with metastatic disease. More recently, autotransplants

have been done more often for women with primary breast cancer (stage II, stage III, and inflammatory disease). Most important, the percentage of patients who had died by 100 days after treatment decreased from 18% (1989) to 5% (1995).

### **Outcome for Patients with High-Risk Primary Breast Cancer**

Figure 1 shows the estimates of survival time after autotransplant in patients with stage II, stage III, and inflammatory breast cancer. The chances that a woman with stage II breast cancer will still be living 3 years after autotransplant are about 75%. For women with stage III breast cancer, the chance is 70%. For those with inflammatory breast cancer, the chance is about 50%.

For a woman with stage II breast cancer, the chance that she will still be living *and her disease will not have progressed* 3 years after autotransplant is about 65%. For women with stage III breast cancer, this chance is 60%. For those with inflammatory breast cancer, the chance is 40%. In 1995, only 4% of patients undergoing autotransplant had died by 100 days after treatment.

### **Outcome for Patients with Metastatic Breast Cancer**

A patient's survival after autotransplant for metastatic breast cancer is often predicted by how the disease responds to standard dose chemotherapy before the patient has the transplant (Fig. 1, Fig. 2). The way that breast cancer responds to standard dose therapy is classified in one of three ways: 1) complete disappearance, 2) partial disappearance (in which the size of disease is reduced by at least half), or 3) resistant. For a woman whose metastatic cancer disappears completely after standard chemotherapy, the chance that she will still be alive 3 years after having an autotransplant is about 45%. For women with only partial disappearance after standard dose chemotherapy, the chance of surviving 3 years after autotransplant is about 30%. For those with resistant metastatic cancer, the chance of surviving 3 years is about 15%.

For a woman whose metastatic cancer disappears completely after standard chemotherapy, the chance that she will still be living *and her disease will not have progressed* 3 years after autotransplant is about 30%. For women with partial disappearance, this chance is about 15%. For those with resistant metastatic breast cancer, this chance is about 5%. In 1995, 6% of patients with metastatic breast cancer who underwent autotransplant died by 100 days after treatment.

### **Autotransplants Versus Standard Dose Therapy for Patients with Breast Cancer**

Scientists are not certain whether the results reported for patients undergoing autotransplant are better than those reported for patients having standard dose therapy. Currently, comparing the results of these two treatments can cause several problems. A bias in the selection of patients for study may occur. This bias can happen because patients planning to have an autotransplant often undergo extensive medical tests before the procedure. These tests can detect hidden diseases and exclude from the study any patients who might have poor results (4). In addition, patients who undergo autotransplants are often chosen because their lungs, heart and kidneys are functioning well. These factors are likely to lead to better results.

If scientists are to compare the results of autotransplant and standard dose therapy in a useful way, they must analyze the data and carefully adjust it for factors that affect the patient, the disease, and the transplant. The best way to do this is in large randomized trials in which all patients are evaluated and followed carefully, regardless of the therapy they are assigned. Several studies suggest that people treated in randomized trials have better outcomes than people receiving the same treatment outside of trials.

### **References**

1. Bezwoda WR, Seymour L, Dansey RD: High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: A randomized trial. *Journal of Clinical Oncology* 13:2483-2489, 1995.



[Return to article](#)

2. National Hospital Discharge Survey for 1990 and 1991. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control. National Center for Health Statistics. Hospital Care Statistics Branch, 6525 Belcrest Road, Hyattsville, MD, 20782.

[Return to article](#)

3. Graves EJ: Detailed diagnoses and procedures, National Hospital Discharge Survey, 1989. Vital and Health Statistics- Series 13: Data From the National Health Survey. 108:1-236, 1991.

[Return to article](#)

4. Crump M, Goss PE, Prince M, Girouard C: Outcome of extensive evaluation before adjuvant therapy in women with breast cancer and 10 or more positive axillary lymph nodes. Journal of Clinical Oncology. 14:66-69, 1996.

[Return to article](#)

## Captions

Fig. 1. The probability of survival after autotransplant for patients with breast cancer, 1989-1995.

Fig. 2. The probability of survival after autotransplant for patients with metastatic breast cancer based on the sensitivity of the disease to standard chemotherapy before transplant, 1989-1995.

## Links to other resources of use to physicians and other health professionals caring for patients with breast cancer.

A comprehensive information service is provided by the NIH PDQ Search Service at [http://cancernet.nci.nih.gov/trials/pdq\\_search.html](http://cancernet.nci.nih.gov/trials/pdq_search.html)

[Return to Top](#)

## Clinical Trials

### Basic | [Technical](#)

A *randomized clinical trial* (or Phase III trial) is an experiment done on human beings to evaluate the results of two or more therapies. Patients participating in the trials are randomly assigned to one of the therapies being studied. The outcomes of the patients receiving each type of treatment are then analyzed and compared.

---

### Trial:

Comparison of high-dose chemotherapy and autotransplant versus standard dose chemotherapy in women with stage II and IIIA breast cancer and at least ten positive axillary nodes (NCI Clinical Trial #CLB-9082 INT-0163)

### Description:

This Phase III trial is sponsored by the National Cancer Institute. The trial will compare the results of two groups of women undergoing treatment for stage II or IIIA breast cancer who have at least ten positive axillary nodes. The two treatments are:

1. High-dose chemotherapy with autotransplant and radiotherapy of the chest wall
2. Standard dose chemotherapy and radiotherapy of the chest wall after initial chemotherapy

### Purposes:

To compare the survival rates of women with stage II or IIIA breast cancer who undergo these two treatments

To compare the toxic effects of these two treatments

---

**Trial:**

Randomized study of adjuvant chemotherapy versus adjuvant chemotherapy followed by high-dose chemotherapy and autotransplant in women with stage II or III breast cancer at high risk of recurrence (NCI Clinical Trial #EST-2190 INT-0121)

**Description:**

This Phase III trial is sponsored by the National Cancer Institute. The trial will compare the results of two types of treatment for women with stage II or stage III breast cancer who are at high risk of recurrence. The two treatments are:

1. Adjuvant chemotherapy
2. Adjuvant chemotherapy followed by high-dose chemotherapy and autotransplant

**Purposes:**

To compare the sites and rates of recurrent cancer, the survival rates, and toxicity of these two treatments in women with stage II or III breast cancer and ten or more positive lymph nodes

To evaluate the rate and degree of contamination of bone marrow by breast cancer cells at the time patients enter the study and after they undergo chemotherapy

To document the changes in psychosocial function in patients during treatment and compare their recovery of this function after treatment

To establish a bank of tumor samples for future laboratory study

---

**Trial:**

Comparison of conventional chemotherapy versus high-dose chemotherapy and autotransplant in women with metastatic breast cancer whose disease responds to conventional chemotherapy (NCI Clinical Trial #E-PBT01 NCI-T90-0180D)

**Description:**

This Phase III trial is sponsored by the National Cancer Institute. It will compare the results of two treatments in women with metastatic breast cancer whose disease responds to conventional chemotherapy. The two treatments are:

1. Conventional chemotherapy
2. High-dose chemotherapy and autotransplant

**Purposes:**

To compare the survival rates of patients with metastatic breast cancer whose disease responds to conventional chemotherapy and who undergo these two treatments

To compare the financial costs and toxicity of these two treatments

To evaluate the patients' quality of life associated with these two treatments

---

**Trial:**

Randomized study of autologous transplant versus transplantation of peripheral blood stem cells

in patients with high-risk breast carcinoma (NCI Clinical Trial #FHCRC-772.1 NCI-H94-0370)

**Description:**

This Phase III trial is sponsored by the National Cancer Institute. The trial will determine which source of blood cells grafts faster in patients with high-risk or advanced breast cancer. The two sources of cells are:

1. Autologous bone marrow
2. Peripheral blood stem cells stimulated with granulocyte colony-stimulating factor (G-CSF)

**Purposes:**

To determine which of these two sources of stem cells leads to a faster graft in patients with high-risk or advanced breast cancer who are given G-CSF after undergoing transplant

To compare the rate and duration of infection, requirements for transfusion, the length of hospital stay, and the rate of complications between patients in these two groups

To compare the total cost of hospitalization between these two groups of patients

To evaluate long-term engraftment in the two treatment groups

To evaluate hidden tumor cells in peripheral blood and bone marrow, and to evaluate T-cell populations in collections of peripheral blood stem cells

---

**Trial:**

Randomized study of high-dose chemotherapy versus conventional chemotherapy followed by chemotherapy combined with autotransplant in women with primary breast cancer involving four to nine axillary nodes (NCI Clinical Trial #S-9623 SWOG-9623)

**Description:**

This Phase III trial is sponsored by the National Cancer Institute. It will compare the results of two treatments in women with primary breast cancer involving four to nine lymph nodes. The two treatments are:

1. Intensive sequential doses of three types of chemotherapy
2. Conventional chemotherapy followed by chemotherapy combined with autotransplant

**Purposes:**

To compare survival rates between women undergoing these two treatments

To compare the toxic effects associated with these treatments

[Return to Top](#)

---

[Potential Donors](#) | [Ask the Expert](#) | [Diseases](#) | [Transplant Topics](#) | [About our Sponsors](#) | [Test your Knowledge](#) | [Physician's Corner](#)  
[Main](#) | [Survey](#) | [Glossary](#) | [Q & A](#) | [Disclaimer](#) | [Related Sites](#) | [Text Only](#)

Welcome to BMTInformation at [www.bmtinfo.org](http://www.bmtinfo.org)

[Potential Donors](#) | [Ask the Expert](#) | [Diseases](#) | [Transplant Topics](#) | [About our Sponsors](#) | [Test your Knowledge](#) | [Physician's Corner](#)  
[Main](#) | [Survey](#) | [Glossary](#) | [Q & A](#) | [Disclaimer](#) | [Related Sites](#) | [View Images](#)

---

## Autologous Blood and Bone Marrow Transplantation for Breast Cancer

Philip A. Rowlings, MBBS, M.S., FRACP, FRCPA  
Assistant Scientific Director, IBMTR/ABMTR

Mary Horowitz, M.D., M.S.  
Scientific Director, IBMTR/ABMTR

[Introduction](#) | [Current Data](#) | [Clinical Trials](#) | [Published Papers](#)

### Introduction

[Basic](#) | [Technical](#)

Breast cancer is the second most common cause of cancer deaths in North America, and the American Cancer Society estimates that more than 180,000 new cases of breast cancer were diagnosed in 1996 (1). Many women with breast cancer are cured after local surgery with or without radiotherapy. Many others, however, have a recurrence of disease (either locally or at distant sites) after primary surgery or present with metastatic disease at diagnosis. Therefore, better treatments for patients with high-risk primary and advanced breast cancer continue to be investigated.

The role of high-dose chemotherapy with autologous hematopoietic stem cell support (autotransplant) as treatment for breast cancer remains controversial. The rationale for autotransplants is the dose-response relationship between many chemotherapy drugs and breast cancer, suggesting that increasing doses beyond the limits of bone marrow toxicity may increase cures. The controversy results from the high cost of autotransplants and the paucity of data comparing outcome with standard dose therapy. There have been legal disputes between patients wishing to undergo the procedure and third-party payers refusing to reimburse the costs. Some of these disputes have received extensive exposure.

Responding to the controversy, the U.S. Congress commissioned the General Accounting Office (GAO) to review this area. Its findings are summarized in a report entitled "Coverage of Autologous Bone Marrow Transplantation for Breast Cancer" (2). The GAO report made some recommendations about the financial and political issues governing dissemination of new technologies and health care in the United States. It produced no conclusions regarding use of autotransplants for patients with breast cancer. To determine the relative efficacy of autotransplants and standard therapy, several large trials sponsored by the National Cancer Institute are being conducted by the U.S. cooperative oncology groups. Accrual of patients into these trials is slower than expected, however, because patients and physicians are reluctant to accept randomization to standard dose therapy. A careful review of the continued relevance and necessity of these trials was recently published (3).

Despite the controversy, use of autotransplants for patients with breast cancer has increased dramatically over the past 6 years. According to data reported to the Autologous Blood and Marrow Transplant Registry (ABMTR), which receives information on 40% to 50% of all transplants done in North America, about 3,500 autotransplants were done in 1995 for patients with breast cancer, making this disease the single most common indication for blood or marrow transplant of any kind (autologous or

allogeneic).

### References

1. Cancer Facts and Figures - 1996. Atlanta: American Cancer Society.

[Return to article](#)

2. United States General Accounting Office: Report to the Honorable Ron Wyden, U.S. Senate, Health Insurance "Coverage of Autologous Bone Marrow Transplantation for Breast Cancer." April 1996. GAO/HEHS-96-83.

[Return to article](#)

3. Gradishar WJ, Tallman MA, Abrams JS: High-dose chemotherapy of breast cancer. Ann Intern Med 125:599-604, 1996.

[Return to article](#)

[Return to Top](#)

## Current Data on Autotransplants for Patients with Breast Cancer

[Basic](#) | [Technical](#)

### Background

High-dose chemotherapy (either with or without radiation therapy) with autologous hematopoietic stem cell support (autotransplant) is increasingly used to treat breast cancer. According to data reported to the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR) of North America, breast cancer is now the most common indication for hemopoietic stem cell transplant of any kind, either autologous or allogeneic. Published reports of autotransplants include relatively few patients, and substantial reporting biases are likely to exist (see selected list of references). Only one randomized study has been published. This study included 90 women with newly diagnosed metastatic breast cancer treated with either standard dose therapy or two courses of high-dose chemotherapy with stem cell support (1). This study showed a statistically significant advantage in both survival and disease-free survival for patients receiving autotransplants versus those receiving conventional dose chemotherapy. However, the 3-year survival in the autotransplant group was only 20%, suggesting that few women are cured with this approach. The study has been criticized because of its small sample size and choice of regimens. Until results of larger randomized trials or other carefully controlled clinical studies are available, most questions regarding the comparative efficacy of autotransplant versus standard dose therapy will remain unanswered. However, considerable data are available from the ABMTR and other sources regarding the safety and outcomes of high-dose treatment.

### What Is the ABMTR?

The Autologous Blood and Marrow Transplant Registry of North America (ABMTR) is a voluntary organization of more than 200 transplant centers in the United States, Canada, and Central and South America. ABMTR centers report data on consecutive autotransplants to a Statistical Center at the Medical College of Wisconsin. The Statistical Center also collects data for allogeneic blood and bone marrow transplants (allotransplants) from centers participating in the International Bone Marrow Transplant Registry (IBMTR), a similar but independent organization of allotransplant centers worldwide. The ABMTR began collecting data in 1992. Data were collected retrospectively for patients receiving autotransplants between 1989 and 1992, and prospectively thereafter. Based on data collected by the Center for Disease Control Hospital Surveys (2,3), about half of autotransplants done in North America for all diseases are registered with the ABMTR. (Click [here](#) for a list of participating centers.)

### Trends in Autotransplants and Mortality for Patients with Breast Cancer

**Table 1** lists data reported to the ABMTR on almost 7,000 women receiving autotransplants for breast cancer. The number of autotransplants increased almost sixfold from 1989 to 1995. The disease stage at the time of transplant also changed significantly: while most autotransplants in 1989 were for metastatic disease, now more than half are done as adjuvant therapy for primary breast cancer (stages II, III and inflammatory disease). Stem cells collected from the blood are now the most common form of hematopoietic support. Most importantly, 100-day mortality decreased significantly from 18% in 1989-90 to 5% in 1995.

Table 1. Trends in autotransplants for breast cancer reported to the ABMTR 1989-1995.

### **Outcome in High-Risk Primary Breast Cancer**

Kaplan-Meier estimates of survival after autotransplants for stages II, III and inflammatory breast cancer are shown in Figure 1. Three-year probabilities of survival after autotransplant are about 75% for women with stage II, 70% for women with stage III, and about 50% (range 40%-64%) for women with inflammatory breast cancer. Three-year probabilities of progression-free survival after autotransplant are about 65% for women with stage II, 60% for women with stage III, and 40% for women with inflammatory breast cancer. In 1995, the 100-day mortality rate was 4%.

### **Outcome in Metastatic Breast Cancer**

Survival after autotransplant for metastatic breast cancer is predominantly determined by the responsiveness of the disease to standard dose therapy before transplant. Response is usually categorized as complete (disappearance of all known disease for 4 or more weeks), partial (a 50% or greater reduction in the size of measurable disease), or resistant (any response less than partial). Figures 1 and 2 show Kaplan-Meier estimates of survival after autotransplant for women with metastatic breast cancer according to disease-responsiveness before transplant. Three-year probabilities of survival after autotransplant are about 45% for women with complete response, 30% for women with partial response, and 15% for women with resistant metastatic breast cancer. Three-year probabilities of progression-free survival after autotransplant are about 30% for women with complete response, 15% for women with partial response and 5% for women with resistant metastatic breast cancer. In 1995, the 100-day mortality rate was 6%.

### **Autotransplants Versus Standard Dose Therapy for Breast Cancer**

It is uncertain whether the results above are superior to those obtained in similar women using standard dose therapy. Comparing historical results with conventional therapy has caused several problems. Selection biases may occur since patients considered for autotransplant often have extensive medical evaluations before the procedure. This may detect occult metastatic disease in women with primary breast cancer and exclude from adjuvant transplant trials those patients who are likely to have poorer outcomes (4). Additionally, autotransplants are often restricted to women with good performance status and near-normal pulmonary, cardiac and renal function. Conversely, results of autotransplants might be expected to be worse compared to standard dose therapy when patients are treated as part of phase I studies with experimental and potentially toxic protocols. Meaningful comparisons of autotransplant versus standard dose therapy require careful adjustment for differences in factors related to the patient, the disease, and transplant, ideally in large randomized clinical trials.

### **References**

1. Bezwoda WR, Seymour L, Dansey RD: High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: A randomized trial. *Journal of Clinical Oncology* 13:2483-2489, 1995.

[Return to article](#)

2. National Hospital Discharge Survey for 1990 and 1991. U.S. Department of Health and Human Services, Public Health Service, Center for Disease Control. National Center for Health Statistics. Hospital Care Statistics Branch, 6525 Belcrest Road, Hyattsville, MD, 20782.

[Return to article](#)

3. Graves EJ: Detailed diagnoses and procedures, National Hospital Discharge Survey, 1989. Vital and Health Statistics - Series 13: Data from the National Health Survey. 108:1-236, 1991.

[Return to article](#)

4. Crump M, Goss PE, Prince M, Girouard C: Outcome of extensive evaluation before adjuvant therapy in women with breast cancer and 10 or more positive axillary lymph nodes. Journal of Clinical Oncology 14:66-69, 1996.

[Return to article](#)

## Captions

Fig. 1. Probability of survival after autotransplants for breast cancer, 1989-1995.

Fig. 2. Probability of survival after autotransplants for metastatic breast cancer according to pretransplant chemosensitivity, 1989-1995.

## Links to other resources of use to physicians and other health professionals caring for patients with breast cancer.

A comprehensive information service is provided by the NIH PDQ Search Service at [http://cancernet.nci.nih.gov/trials/pdq\\_search.html](http://cancernet.nci.nih.gov/trials/pdq_search.html)

[Return to Top](#)

## Clinical Trials

[Basic](#) | [Technical](#)

For details about enrolling a patient in one of these trials, contact the Chairpersons listed at the end of each trial summary. The details listed are correct as of the date given at the end of the title.

Additional Phase I and II trials are listed with the PDQ search service and are also conducted at individual transplant institutions.

### Trials

- [CLB-9082 INT-0163](#)
- [EST-2190 INT-0121](#)
- [E-PBT01 NCI-T90-0180D](#)
- [FHCRC-772.1 NCI-H94-0370](#)
- [S-9623 SWOG-9623](#)

### CLB-9082 INT-0163

NCI HIGH PRIORITY CLINICAL TRIAL --- Phase III Randomized Comparison of High-Dose Chemotherapy with Autologous Marrow and Peripheral Stem Cell Support vs Standard-Dose Chemotherapy Following Adjuvant Chemotherapy in Women with Stage II/IIIA Breast Cancer with at Least 10 Positive Axillary Nodes (Summary Last Modified 09/96)  
STATUS: Active AGE RANGE: over 18

NCI-sponsored, NCI cooperative group program

#### OBJECTIVES:

I. Compare disease-free and overall survival of women with stage II/IIIA breast cancer randomized to

receive high-dose cyclophosphamide/cisplatin/carmustine with autologous bone marrow/peripheral stem cell support plus chest wall irradiation vs. conventional doses of the same drugs plus chest wall irradiation, administered after 4 courses of adjuvant cyclophosphamide/doxorubicin/fluorouracil (CAF).

II. Compare the toxic effects of these 2 regimens.

PROTOCOL ENTRY CRITERIA:

--Disease Characteristics--

Histologically confirmed adenocarcinoma of the breast

Pathologically confirmed stage IIA, IIB, or IIIA (i.e., T1-3, N1-2, M0)

10-or more positive axillary nodes required

Absence of distant metastases, evidenced by:

- Negative bone scan
- Negative bilateral bone marrow aspirate/biopsy
- Negative CT of head, chest, abdomen, pelvis

Hormone receptor status:

- Any estrogen receptor (ER) or progesterone receptor (PR) status accepted, including unknown
- Knowledge of ER and PR status desired

No bilateral breast cancer

--Prior/Concurrent Therapy--

Biologic therapy:

Not specified

Chemotherapy:

No prior chemotherapy

Endocrine therapy:

Not specified

Radiotherapy:

No prior radiotherapy

Surgery:

- Radical or modified radical mastectomy or lumpectomy with level I/II axillary dissection required
- Preferably within 2 weeks prior to initiating cyclophosphamide/doxorubicin/fluorouracil (CAF)
- Not more than 8 weeks prior to initiating CAF (10 weeks with permission of the study chairman)
- Negative resection margins required
- Lymphatic and vascular involvement permitted

--Patient Characteristics--

Age:

- Over 18
- No upper limit, but over physiologic 50 expected to tolerate treatment less well

Sex:

Women only

Menopausal status:



Pre-, post-, or perimenopausal

Performance status:

CALGB 0 or 1

Karnofsky 80%-100%

Hematopoietic:

ANC at least 1,800/mL

Platelets at least 100,000/mL

Hemoglobin greater than 10 g/dL

Bone marrow cellularity at least 30%

Hepatic:

Bilirubin not more than 1.5 times normal

AST not more than 1.5 times normal

Renal:

Creatinine less than 1.8 mg/dL

BUN not more than 1.5 times normal

Cardiovascular:

Left ventricular ejection fraction (LVEF) on MUGA at least 45% at rest and at least 5% increase with exercise (exercise test not required if LVEF is at least 55%)

EKG required within 90 days prior to entry

No uncontrolled or significant cardiovascular disease, i.e.:

No myocardial infarction within 1 year

No congestive heart failure

Pulmonary:

FVC at least 60% of predicted

FEV1 at least 60% of predicted

DLCO at least 60% of predicted

Other:

No previous or concomitant second malignancy except:

Curatively treated cervical cancer

Nonmelanomatous skin cancer

Negative viral titers, e.g.:

HIV

HBsAg

Hepatitis C

No serious medical/psychiatric condition that would:

Preclude protocol therapy

Prevent informed consent

Companion quality-of-life study (CLB-9066) must be offered

PROTOCOL CHAIRPERSONS

William P. Peters, Chair Ph: 313-833-0715

Director

Barbara Ann Karmanos Cancer Institute

110 East Warren Avenue

Detroit, MI 48201-1379

Cancer and Leukemia Group B Primary lead CLB-9082

James J. Vredenburgh, Co-Chair Ph: 919-684-6707  
Duke University Medical Center  
P.O. Box 3961  
Durham, NC 27710  
Cancer and Leukemia Group B Primary lead CLB-9082

Elizabeth J. Shpall, Chair Ph: 303-372-9000  
University of Colorado Cancer Center  
Bone Marrow Transplant Program  
Campus Box B190  
4200 East Ninth Avenue  
Denver, CO 80262  
Southwest Oncology Group Secondary lead SWOG-9114

Michael Crump, Chair Ph: 416-340-3793  
Toronto General Hospital  
M-L 2-018  
200 Elizabeth Street  
Toronto, Ontario M5G 2C4  
Canada  
NCIC-Clinical Trials Group Secondary lead CAN-NCIC-MA13

[Return to Clinical Trials](#)

[Return to Top](#)

### **EST-2190 INT-0121**

NCI HIGH PRIORITY CLINICAL TRIAL --- Phase III Randomized Study of Adjuvant CAF (Cyclophosphamide/Doxorubicin/Fluorouracil) vs Adjuvant CAF Followed by Intensification with High-Dose Cyclophosphamide/Thiotepa plus Autologous Stem Cell Rescue in Women with Stage I/III Breast cancer at High Risk of Recurrence (Summary Last Modified 02/96)  
STATUS: Active AGE RANGE: 15 to 60

#### **SPONSORSHIP**

NCI-sponsored, NCI cooperative group program

#### **OBJECTIVES:**

- I. Compare sites and rates of recurrence, disease-free survival, overall survival, and toxicity of adjuvant chemotherapy with CAF (cyclophosphamide, doxorubicin, fluorouracil) vs. adjuvant CAF followed by marrow ablation with cyclophosphamide/thiotepa and autologous stem cell rescue in women with stage II/III breast cancer and 10 or more positive lymph nodes.
- II. Evaluate prospectively the incidence and degree of occult marrow contamination with breast cancer cells at the time of study entry and following CAF chemotherapy by analyzing samples of marrow using a panel of monoclonal antibodies specific for breast cancer.
- III. Document the changes in psychosocial function that occur during treatment on either regimen, and compare post-treatment recovery of psychosocial function.
- IV. Establish a bank of paraffin-embedded tumor samples for future laboratory study.

#### **PROTOCOL ENTRY CRITERIA:**

--Disease Characteristics--

Biopsy-proven epithelial carcinoma of the breast with at least 10 involved lymph nodes

Stage II/III disease

Synchronous bilateral breast cancer eligible provided primaries occurred within 6 weeks of each other

Contralateral intraductal cancer eligible

The following conditions exclude:

T4 disease

Apocrine, adenoidcystic, or squamous carcinoma

Inflammatory carcinoma of the breast

Lesions fixed to skin or chest wall

Peau d'orange skin changes

Asynchronous bilateral infiltrating breast cancer

Radical or modified radical mastectomy or breast-sparing surgery with axillary dissection required within 12 weeks of entry

Negative surgical margins required

Type of procedure, number of nodes examined, number of positive nodes, and tumor size must be reported

Breast-sparing surgery must have included wide excision (i.e., removal of gross tumor plus normal breast tissue)

Bone marrow aspirate, bilateral core biopsy, and bone scan must be negative for tumor

Aspiration and biopsy not required for patients who received 1 or 2 courses of any doxorubicin-based chemotherapy prior to entry

Hormone receptor status:

Estrogen and progesterone receptor status must be determined by either biochemical or immunohistochemical assays

--Prior/Concurrent Therapy--

Biologic therapy:

No prior therapy with colony-stimulating factors for breast cancer

Chemotherapy:

1 or 2 prior courses of any doxorubicin-based chemotherapy allowed provided documentation of treatment is available

Endocrine therapy:

No prior hormonal therapy for breast cancer except up to 21 days of tamoxifen that is stopped prior to entry

Prior postmenopausal estrogen therapy allowed but must be discontinued prior to entry

Radiotherapy:

No prior radiotherapy

Postoperative radiotherapy required on study

Surgery:

Surgery completed no more than 12 weeks prior to entry

Surgery completed no more than 12 weeks prior to start of chemotherapy in patients who receive one or two courses of doxorubicin-based chemotherapy prior to randomization

--Patient Characteristics--

Age:  
15 to 60

Sex:  
Women only

Menopausal status:  
Pre- or postmenopausal

Performance status:  
ECOG 0 or 1

Hematopoietic:  
(obtained within 2 weeks prior to entry)  
WBC at least 4,000/mL  
Platelets at least 100,000/mL

Hepatic:  
(obtained within 2 weeks prior to entry)  
Bilirubin no more than 1.2 times normal  
AST (or ALT) no more than 1.2 times normal  
Alkaline phosphatase no more than 1.2 times normal

Renal:  
Not specified

Cardiovascular:  
Left ventricular ejection fraction (by MUGA) at least 50% or equal to or greater than the lower limit of institutional normal  
No prior angina pectoris requiring nitrate therapy  
No myocardial infarction within 6 months  
No uncontrolled congestive heart failure  
No uncontrolled hypertension  
No major ventricular arrhythmia

Pulmonary:  
FEV1 at least 60% of predicted  
DLCO (corrected) at least 60% of predicted  
Lung volume at least 60%  
Lung volume not required if uncorrected FEV1 and DLCO greater than 80%  
No symptomatic obstructive or restrictive lung disease

Other:  
No symptomatic CNS disease of any etiology  
No insulin-dependent diabetes mellitus  
No uncompensated major thyroid dysfunction  
No uncompensated major adrenal dysfunction  
No HIV positivity  
No prior malignancy within 5 years except:  
    In situ breast cancer (lobular or ductal)  
    Inactive nonmelanomatous skin cancer  
    In situ cervical cancer  
No pregnant or nursing women  
Assessment of insurance coverage required

PROTOCOL CHAIRPERSONS

Martin Stuart Tallman, Chair Ph: 312-908-8697  
Northwestern University Hematology/Oncology  
Suite 700  
233 East Erie Street  
Chicago, IL 60611  
Eastern Cooperative Oncology Group Primary lead EST-2190

William P. Vaughan, Chair Ph: 205-934-1908  
Bone Marrow Transplantation Program  
University of Alabama at Birmingham  
541 Tinsley Harrison Tower  
1900 University Boulevard  
UAB Station  
Birmingham, AL 35294-0006  
Cancer and Leukemia Group B Secondary lead CLB-9496

Charles F. LeMaistre, Chair Ph: 210-593-3801  
South Texas Cancer Institute  
7700 Floyd Curl Drive  
San Antonio, TX 78229  
Southwest Oncology Group Secondary lead SWOG-9061

[Return to Clinical Trials](#)

[Return to Top](#)

### **E-PBT01 NCI-T90-0180D**

NCI HIGH PRIORITY CLINICAL TRIAL --- Phase III Randomized Comparison of Conventional CMF Maintenance vs High-Dose Combination Chemotherapy plus Autologous Bone Marrow and Peripheral Stem Cell Rescue in Women with Metastatic Breast Cancer Responding to Conventional Induction Chemotherapy (Summary Last Modified 06/96)  
STATUS: Active AGE RANGE: 18 to 60

NCI-sponsored, NCI cooperative group program

#### **OBJECTIVES**

I. Compare time to failure and overall survival of patients with metastatic breast cancer responding after 4-6 courses of conventional induction chemotherapy who are randomly assigned to 24 months of conventional maintenance chemotherapy with CMF (cyclophosphamide/methotrexate/fluorouracil) vs. high-dose chemotherapy with cyclophosphamide/thiotepa/carboplatin followed by autologous bone marrow and peripheral stem cell rescue.

II. Compare the toxicity of these 2 regimens.

III. Compare the financial costs of these 2 regimens.

IV. Evaluate the quality of life associated with these 2 treatments.

#### **PROTOCOL ENTRY CRITERIA**

--Disease Characteristics--

Histologically documented adenocarcinoma of the breast

Metastatic or recurrent disease

No leptomeningeal or brain metastases  
Inflammatory breast cancer requires distant metastases  
Adequate hepatic function (see below) required with liver metastases  
Metastases to ipsilateral regional lymph nodes (supraclavicular or cervical) only may be treated by mastectomy or locoregional radiotherapy

Hormonal receptor status:

Estrogen receptor (ER)-negative or unknown  
ER-positive (at least 10 fmol/mg cytosol protein) bone/soft tissue disease eligible only if progressed on at least 1 hormone manipulation in the adjuvant or metastatic setting  
ER-positive, visceral disease eligible without prior hormone therapy

Bidimensionally measurable or evaluable disease, as follows:

Not irradiated or progressed since radiotherapy

Evaluable disease defined as:

Blastic and mixed blastic/lytic lesions with no anticipated need for palliative radiotherapy during first 3 courses  
Pure osteolytic lesions  
Positive bone scan as only evidence of metastasis permitted provided patient has analgesic requirement or decreased performance status  
Evidence must be unequivocal if bone x-ray is negative  
Hepatic metastases greater than 2 cm on CT or MRI or of any size if biopsy-proven  
Abdominal or pelvic mass on CT or MRI  
Multinodular or confluent lung or skin metastases  
Cytologically positive pleural effusion

No large third-space fluid accumulation that cannot be drained

No large pericardial effusion

--Prior/Concurrent Therapy--

Biologic therapy:

Not specified

Chemotherapy:

One course of induction therapy as specified in the protocol allowed prior to entry  
No other chemotherapy for metastatic disease, except patient may have relapsed after primary treatment for stage IV disease by virtue of metastasis only to ipsilateral supraclavicular nodes  
At least 6 months between adjuvant chemotherapy and recurrence

Endocrine therapy:

Prior hormone manipulation required for bone or visceral metastasis unless rapidly progressing

At least 4 weeks since or no benefit from oophorectomy for metastatic or recurrent disease

Radiotherapy:

None to pelvic bones or lower spine  
No anticipated requirement for palliation during first 3 courses

Surgery:

At least 2 weeks since major surgery

--Patient Characteristics--

Age:

18 to 60

Sex:

Women only

Menopausal status:

Premenopausal or postmenopausal

Performance status:

ECOG 0 or 1

Hematopoietic:

ANC at least 1,500/mL

Platelets at least 100,000/mL

Hepatic:

Bilirubin not greater than 2.0 mg/dL

AST/alkaline phosphatase not greater than 2 times normal

If liver function compromised by metastatic disease:

Bilirubin not greater than 5.0 mg/dL

AST not greater than 600 U/mL

Renal:

After hydration:

Creatinine not greater than 1.5 mg/dL and/or

Creatinine clearance at least 60 mL/min

Cardiovascular:

No significant cardiovascular disease, i.e.:

No congestive heart failure

No myocardial infarction within 3 months

No arrhythmia requiring medication

No poorly controlled hypertension (diastolic over 100 mm Hg)

Pulmonary:

No significant non-neoplastic pulmonary disease

Other:

No active infection

No active peptic ulcer disease

No brittle insulin-dependent diabetes mellitus

No hospitalization for psychiatric illness, including severe depression or psychosis

No current alcohol or drug abuse

No pregnant or nursing women

Not HIV seropositive and no clinical evidence of AIDS

No active second malignancy within 10 years except:

Curatively treated nonmelanomatous skin cancer

In situ cervical carcinoma

PROTOCOL CHAIRPERSONS

Edward Allen Stadtmauer, Chair Ph: 215-662-7806

University of Pennsylvania Cancer Center

6 Penn Tower

3400 Spruce Street

Philadelphia, PA 19104

Eastern Cooperative Oncology Group Primary lead E-PBT01

James N. Ingle, Chair Ph: 507-284-2511  
Mayo Clinic  
Division of Medical Oncology  
200 First Street Southwest  
Rochester, MN 55905  
North Central Cancer Treatment Group Secondary lead NCCTG-913201

Kenneth F. Mangan, Chair Ph: 215-707-2847  
Temple University Hospital  
Bone Marrow Transplant Program  
Department of Medicine  
3322 North Broad Street  
Philadelphia, PA 19140  
Southwest Oncology Group Secondary lead SWOG-9412

Edward Allen Stadtmauer, Chair Ph: 215-662-7806  
University of Pennsylvania Cancer Center  
6 Penn Tower  
3400 Spruce Street  
Philadelphia, PA 19104  
Philadelphia Bone Marrow Transplant Group Secondary lead PBT-1

[Return to Clinical Trials](#)

[Return to Top](#)

### **FHCRC-772.1 NCI-H94-0370**

Phase III Randomized Study of Autologous Bone Marrow vs G-CSF-Stimulated Peripheral Blood Stem Cell Transplantation for High-Risk Breast Carcinoma (Summary Last Modified 06/94)  
STATUS: Active AGE RANGE: no greater than 65

#### **SPONSORSHIP**

NCI-sponsored, NCI grant supported

#### **OBJECTIVES**

- I. Determine which stem cell source, autologous bone marrow (AuBM) or autologous peripheral blood stem cells (PBSC) mobilized with granulocyte colony-stimulating factor (G-CSF), results in more rapid engraftment in patients with high-risk or advanced breast carcinoma given post-transplant G-CSF.
- II. Compare the rate and duration of infection, transfusion requirements, days of hospitalization, and rate of transplant-related complications between patients receiving PBSC vs. AuBM.
- III. Compare the total cost of hospitalization when using PBSC vs. AuBM.
- IV. Evaluate long-term engraftment in the two treatment groups.
- V. Evaluate occult tumor cells in peripheral blood and marrow, and evaluate T-cell populations in PBSC collections.

#### **PROTOCOL ENTRY CRITERIA**

--Disease Characteristics--

High-risk breast carcinoma that has failed conventional therapy or has a greater than 50% chance for



relapse, i.e.:

- Stage II with more than 10 positive nodes
- Stage III
- Stage IV

No evidence of marrow involvement on biopsy

Marrow positive only by immunocytochemistry allowed

No rapidly progressing disease requiring immediate therapy

No carcinomatous meningitis or untreated CNS disease

Hormone receptor status:

Not specified

--Prior/Concurrent Therapy--

Biologic therapy:

Not specified

Chemotherapy:

No more than 3 prior courses of myelosuppressive chemotherapy for metastatic disease

Endocrine therapy:

Not specified

Radiotherapy:

No prior pelvic irradiation

Surgery:

Not specified

--Patient Characteristics--

Age:

No greater than 65

Menopausal status:

Not specified

Sex:

Not specified

Performance status:

Karnofsky 70%-100%

Hematopoietic:

ANC at least 1,500/mL

Platelets at least 150,000/mL

Marrow cellularity at least 60% of normal

No history of prolonged neutropenia (ANC below 500 for more than 30 days) after conventional-dose chemotherapy

Hepatic:

Bilirubin no greater than 1.5 mg/dL

Renal:

Creatinine no greater than 1.5 mg/dL  
No history of severe cyclophosphamide-induced hemorrhagic cystitis

Cardiovascular:

LVEF at least 45%

Other:

No HIV antibody

Willing to undergo multiple aphereses

Marrow available or patient willing to undergo marrow harvest

PROTOCOL CHAIRPERSONS

William I. Bensinger, Chair Ph: 206-667-4933

Fred Hutchinson Cancer Research Center

1124 Columbia Street

Seattle, WA 98104

Fred Hutchinson Cancer Research Center Primary lead FHCRC-772.1

[Return to Clinical Trials](#)

[Return to Top](#)

**S-9623 SWOG-9623**

Phase III Randomized Study of Intensive Sequential Doxorubicin, Paclitaxel, and Cyclophosphamide vs Doxorubicin/Cyclophosphamide Followed by STAMP I or STAMP V Combination Chemotherapy with Autologous Stem Cell Rescue in Women with Primary Breast Cancer and 4-9 Involved Axillary Lymph Nodes (Summary Last Modified 08/96)

STATUS: Active AGE RANGE: adult

NCI-sponsored, NCI cooperative group program

OBJECTIVES

I. Compare disease-free and overall survival following intensive sequential chemotherapy with doxorubicin, paclitaxel, and cyclophosphamide versus standard dose doxorubicin/cyclophosphamide followed by high-dose STAMP I (cyclophosphamide/cisplatin/carmustine) or STAMP V (cyclophosphamide/carboplatin/thiotepa) and autologous peripheral blood progenitor cell or bone marrow rescue in women with operable breast cancer and 4-9 positive axillary lymph nodes.

II. Compare the toxic effects associated with these regimens.

PROTOCOL ENTRY CRITERIA

--Disease Characteristics--

Histologically confirmed adenocarcinoma of the breast with 4-9 histologically involved axillary lymph nodes

No known T4, N3, or M1 disease

Prior breast-sparing surgery or modified radical mastectomy plus axillary lymph node dissection required

Surgical margins negative for invasive or noninvasive ductal carcinoma

At least 10 nodes sampled

No more than 12 weeks since definitive surgery

Synchronous bilateral breast carcinoma eligible, provided:  
One breast meets the eligibility criteria  
Other breast has fewer than 10 involved nodes and is not N3 or T4

Hormone receptor status:  
Not specified

--Prior/Concurrent Therapy--

Biologic therapy:  
Not specified

Chemotherapy:  
No prior chemotherapy

Endocrine therapy:  
Not specified

Radiotherapy:  
No prior radiotherapy to the breast

Surgery:  
See Disease Characteristics

--Patient Characteristics--

Age:  
Adult

Sex:  
Women only

Menopausal status:  
Any status

Performance status:  
SWOG 0 or 1

Hematopoietic:  
WBC at least 3,000/mL  
ANC at least 1,000/mL  
Platelets at least 100,000/mL

Hepatic:  
Bilirubin no greater than 1.5 times normal  
AST no greater than 1.5 times normal

Renal:  
Creatinine clearance at least 60 mL/min

Cardiovascular:  
Left ventricular ejection fraction at rest at least 45% by MUGA  
EKG abnormalities require patient clearance by cardiologist  
No uncontrolled or significant cardiac disease  
No congestive heart failure  
No second- or third-degree heart block or other serious cardiac conduction abnormality  
No atrial or ventricular arrhythmia

No requirement for medication known to affect cardiac conduction unless:  
Given for reasons other than heart failure or arrhythmia  
Patient cleared by a cardiologist

**Pulmonary:**

FVC and FEV1 at least 60% of predicted  
DLCO at least 60%

**Other:**

No HIV antibody  
Known HBsAg and hepatitis C status required  
No serious medical or psychiatric illness that precludes informed consent or study participation  
No second malignancy within 5 years except adequately treated:  
    Nonmelanomatous skin cancer  
    In situ cervical cancer  
No pregnant or nursing women  
Effective contraception required of fertile women

**PROTOCOL CHAIRPERSONS**

Scott I. Bearman, Chair Ph: 303-372-9000  
University of Colorado Cancer Center  
Box B-190  
4200 East Ninth Avenue  
Denver, CO 80262  
Southwest Oncology Group Primary lead S-9623

Clifford A. Hudis, Chair Ph: 212-639-6483  
Memorial Sloan-Kettering Cancer Center  
Box # 206  
1275 York Avenue  
New York, NY 10021  
Cancer and Leukemia Group B Secondary lead CLB-S9623

William Costin Wood, Chair Ph: 404-248-3301  
Emory University Hospital  
Suite B206  
1365 Clifton Road NE  
Atlanta, GA 30322  
Eastern Cooperative Oncology Group Secondary lead E-S9623

[Return to Clinical Trials](#)

[Return to Top](#)

---

[Potential Donors](#) | [Ask the Expert](#) | [Diseases](#) | [Transplant Topics](#) | [About our Sponsors](#) | [Test your Knowledge](#) |  
[Physician's Corner](#)  
[Main](#) | [Survey](#) | [Glossary](#) | [Q & A](#) | [Disclaimer](#) | [Related Sites](#) | [Text Only](#)

**Welcome to BMTInformation at [www.bmtinfo.org](http://www.bmtinfo.org)**

[Potential Donors](#) | [Ask the Expert](#) | [Diseases](#) | [Transplant Topics](#) | [About our Sponsors](#) | [Test your Knowledge](#) | [Physician's Corner](#)  
[Main](#) | [Survey](#) | [Glossary](#) | [Q & A](#) | [Disclaimer](#) | [Related Sites](#) | [View Images](#)

## Selected list of recently published literature on autotransplants for patients with breast cancer by topics

Issues have been raised by the numerous published studies of small series of patients treated with autotransplants for breast cancer. Recently published data (authors, title and journal) are listed below according to topic.

- [A. Conditioning regimens used for autotransplant in women with Primary Breast Cancer](#)
- [B. Conditioning regimens used for autotransplant in women with Recurrent or Metastatic Breast Cancer](#)
- [C. Radiation therapy following autotransplant.](#)
- [D. Immune modulation posttransplant to induce antitumor activity.](#)
- [E. Detection of residual tumor cells in the stem cell source.](#)
- [F. Purging of stem cell source to remove residual breast cancer cells.](#)
- [G. Toxicity of autotransplants for breast cancer.](#)
- [H. Safety of autotransplants for breast cancer.](#)
- [I. Legal and financial issues.](#)
- [J. Randomized trials involving autotransplants for breast cancer.](#)
- [K. Prognostic factors in autotransplants for metastatic breast cancer.](#)
- [L. Double \(Tandem\) autotransplants for breast cancer.](#)
- [M. Pharmacokinetic monitoring in autotransplants for breast cancer.](#)
- [N. Quality of life after autotransplants for breast cancer.](#)
- [O. Hemopoietic stem cell sources for autotransplants for breast cancer.](#)
- [P. Autotransplants as outpatients.](#)
- [Q. Change in disease stage with extensive evaluation](#)

### A. Conditioning regimens used for autotransplant in women with Primary Breast Cancer

deMagalhaes-Silverman M. Rybka WB. Lembersky B. Bloom EJ. Lister J. Pincus SM. Voloshin M. Wilson J. Ball ED.  
 High-dose cyclophosphamide, carboplatin, and etoposide with autologous stem cell rescue in patients with breast cancer.  
 American Journal of Clinical Oncology. 19(2):169-73, 1996 Apr.

Broun ER. Sledge GW. Einhorn LH. Tricot GJ.  
 High-dose carboplatin and mitoxantrone with autologous bone marrow support in the treatment of advanced breast cancer.  
 American Journal of Clinical Oncology. 16(1):9-13, 1993 Feb.

Spitzer TR. Cirenza E. McAfee S. Foelber R. Zarzin J. Cahill R. Mazumder A.  
 Phase I-II trial of high-dose cyclophosphamide, carboplatin and autologous bone marrow or peripheral blood stem cell rescue.  
 Bone Marrow Transplantation. 15(4):537-42, 1995 Apr.

Somlo G. Doroshow JH. Forman SJ. Leong LA. Margolin KA. Morgan RJ Jr.

Raschko JW. Akman SA. Ahn C. Nagasawa S. et al.  
High-dose doxorubicin, etoposide, and cyclophosphamide with stem cell reinfusion in patients with metastatic or high-risk primary breast cancer.  
City of Hope Bone Marrow Oncology Team.  
*Cancer*. 73(6):1678-85, 1994 Mar 15.

Somlo G. Doroshow JH. Forman SJ. Leong LA. Margolin KA. Morgan RJ Jr. Raschko JW. Akman SA. Ahn C. Sniecinski I.  
High-dose cisplatin, etoposide, and cyclophosphamide with autologous stem cell reinfusion in patients with responsive metastatic or high-risk primary breast cancer.  
*Cancer*. 73(1):125-34, 1994 Jan 1.

de Graaf H. Willemse PH. de Vries EG. Sleijfer DT. Mulder PO. van der Graaf WT. Smit Sibinga CT. van der Ploeg E. Dolsma WV. Mulder NH.  
Department of Internal Medicine, University Hospital Groningen, The Netherlands.  
Intensive chemotherapy with autologous bone marrow transfusion as primary treatment in women with breast cancer and more than five involved axillary lymph nodes.  
*European Journal of Cancer*. 30A(2):150-3, 1994.

Mulder NH. Mulder PO. Sleijfer DT. Willemse PH. van der Ploeg E. Dolsma WV. de Vries EG.  
Department of Medical Oncology, University Hospital Groningen, The Netherlands.  
Induction chemotherapy and intensification with autologous bone marrow reinfusion in patients with locally advanced and disseminated breast cancer.  
*European Journal of Cancer*. 29A(5):668-71, 1993.

Peters WP. Ross M. Vredenburg JJ. Meisenberg B. Marks LB. Winer E. Kurtzberg J. Bast RC Jr. Jones R. Shpall E. et al.  
High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer.  
*Journal of Clinical Oncology*. 11(6):1132-43, 1993 Jun.

TMJ: a well-tolerated high-dose regimen for the adjuvant chemotherapy of high risk breast cancer.  
*Journal of Medicine*. 25(3-4):241-50, 1994.

[Back to top](#)

## **B. Conditioning regimens used for autotransplant in women with Recurrent or Metastatic Breast Cancer**

deMagalhaes-Silverman M. Rybka WB. Lembersky B. Bloom EJ. Lister J. Pincus SM. Voloshin M. Wilson J. Ball ED.  
High-dose cyclophosphamide, carboplatin, and etoposide with autologous stem cell rescue in patients with breast cancer.  
*American Journal of Clinical Oncology*. 19(2):169-73, 1996 Apr.

Kalaycioglu ME. Lichtin AE. Andresen SW. Tuason L. Bolwell BJ.  
High-dose busulfan and cyclophosphamide followed by autologous bone marrow transplantation and/or peripheral blood progenitor cell rescue for metastatic breast cancer.  
*American Journal of Clinical Oncology*. 18(6):491-4, 1995 Dec.

Broun ER. Sledge GW. Einhorn LH. Tricot GJ.  
High-dose carboplatin and mitoxantrone with autologous bone marrow support  
in the treatment of advanced breast cancer.  
American Journal of Clinical Oncology. 16(1):9-13, 1993 Feb.

Mulder NH. Dolsma WV. Mulder PO. De Vries EG. Willemse PH. Sleijfer  
DT. Hospers GA. Van der Graaf WT.  
Anticancer Research. 15(4):1565-8, 1995 Jul-Aug.

Lazarus HM. Gray R. Ciobanu N. Winter J. Weiner RS.  
Phase I trial of high-dose melphalan, high-dose etoposide and autologous  
bone marrow re-infusion in solid tumors: an Eastern Cooperative Oncology Group (ECOG) study.  
Bone Marrow Transplantation. 14(3):443-8, 1994 Sep.

Weaver CH. Bensinger WI. Appelbaum FR. Lilleby K. Sandmaier B.  
Brunvand M. Rowley S. Petersdorf S. Rivkin S. Gooley T. et al.  
Phase I study of high-dose busulfan, melphalan and thiotepa with  
autologous stem cell support in patients with refractory malignancies.  
Bone Marrow Transplantation. 14(5):813-9, 1994 Nov.

Vaughan WP. Reed EC. Edwards B. Kessinger A.  
High-dose cyclophosphamide, thiotepa and hydroxyurea with autologous  
hematopoietic stem cell rescue: an effective consolidation chemotherapy  
regimen for early metastatic breast cancer.  
Bone Marrow Transplantation. 13(5):619-24, 1994 May.

Bowers C. Adkins D. Dunphy F. Harrison B. LeMaistre CF. Spitzer G.  
Dose escalation of mitoxantrone given with thiotepa and autologous bone  
marrow transplantation for metastatic breast cancer.  
Bone Marrow Transplantation. 12(5):525-30, 1993 Nov.

Klumpp TR. Mangan KF. Glenn LD. Macdonald JS.  
Phase II pilot study of high-dose busulfan and CY followed by autologous  
BM or peripheral blood stem cell transplantation in patients with advanced  
chemosensitive breast cancer.  
Bone Marrow Transplantation. 11(4):337-9, 1993 Apr.

Somlo G. Doroshow JH. Forman SJ. Leong LA. Margolin KA. Morgan RJ Jr.  
Raschko JW. Akman SA. Ahn C. Nagasawa S. et al.  
High-dose doxorubicin, etoposide, and cyclophosphamide with stem cell  
reinfusion in patients with metastatic or high-risk primary breast cancer.  
City of Hope Bone Marrow Oncology Team.  
Cancer. 73(6):1678-85, 1994 Mar 15.

Somlo G. Doroshow JH. Forman SJ. Leong LA. Margolin KA. Morgan RJ Jr.  
Raschko JW. Akman SA. Ahn C. Sniecinski I.  
High-dose cisplatin, etoposide, and cyclophosphamide with autologous stem  
cell reinfusion in patients with responsive metastatic or high-risk  
primary breast cancer.  
Cancer. 73(1):125-34, 1994 Jan 1.

Schrier DM. Stemmer SM. Johnson T. Kasliwal R. Lear J. Matthes S.  
Taffs S. Dufton C. Glenn SD. Butchko G. et al.  
High-dose 90Y Mx-diethylenetriaminepentaacetic acid (DTPA)-BrE-3 and  
autologous hematopoietic stem cell support (AHSCS) for the treatment of  
advanced breast cancer: a phase I trial.  
Cancer Research. 55(23 Suppl):5921s-5924s, 1995 Dec 1.

Mulder NH. Mulder PO. Sleijfer DT. Willemse PH. van der Ploeg E. Dolsma WV. de Vries EG.  
Department of Medical Oncology, University Hospital Groningen, The Netherlands.  
Induction chemotherapy and intensification with autologous bone marrow reinfusion in patients with locally advanced and disseminated breast cancer.  
European Journal of Cancer. 29A(5):668-71, 1993.

Saez RA. Selby GB. Slease RB. Epstein RB. Mandanas RA. Confer DL.  
Autologous bone marrow transplantation for metastatic breast cancer.  
Journal - Oklahoma State Medical Association. 87(9):405-10, 1994 Sep.

Stemmer SM. Cagnoni PJ. Shpall EJ. Bearman SI. Matthes S. Dufton C. Day T. Taffs S. Hami L. Martinez C. Purdy MH. Arron J. Jones RB.  
High-dose paclitaxel, cyclophosphamide, and cisplatin with autologous hematopoietic progenitor-cell support: a phase I trial.  
Journal of Clinical Oncology. 14(5):1463-72, 1996 May.

Patrone F. Ballestrero A. Ferrando F. Brema F. Moraglio L. Valbonesi M. Basta P. Ghio R. Gobbi M. Sessarego M.  
Four-step high-dose sequential chemotherapy with double hematopoietic progenitor-cell rescue for metastatic breast cancer.  
Journal of Clinical Oncology. 13(4):840-6, 1995 Apr.

Ghalie R. Richman CM. Adler SS. Cobleigh MA. Korenblit AD. Manson SD. McLeod BC. Taylor SG 4th. Valentino LA. Wolter J. et al.  
Treatment of metastatic breast cancer with a split-course high-dose chemotherapy regimen and autologous bone marrow transplantation.  
Journal of Clinical Oncology. 12(2):342-6, 1994 Feb.

O'Brien ME. Talbot DC. Smith IE.  
Carboplatin in the treatment of advanced breast cancer: a phase II study using a pharmacokinetically guided dose schedule.  
Journal of Clinical Oncology. 11(11):2112-7, 1993 Nov.

Williams SF. Gilewski T. Mick R. Bitran JD.  
High-dose consolidation therapy with autologous stem-cell rescue in stage IV breast cancer: follow-up report.  
Journal of Clinical Oncology. 10(11):1743-7, 1992 Nov.

Antman K. Ayash L. Elias A. Wheeler C. Hunt M. Eder JP. Teicher BA. Critchlow J. Bibbo J. Schnipper LE. et al.  
A phase II study of high-dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy [see comments].  
Journal of Clinical Oncology. 10(1):102-10, 1992 Jan.

Fields KK. Elfenbein GJ. Perkins JB. Janssen WE. Ballester OF. Hiemenz JW. Zorsky PE. Kronish LE. Foody MC.  
High-dose ifosfamide/carboplatin/etoposide: maximum tolerable doses, toxicities, and hematopoietic recovery after autologous stem cell reinfusion.  
Seminars in Oncology. 21(5 Suppl 12):86-92, 1994 Oct.

Fields KK. Elfenbein GJ. Perkins JB. Hiemenz JW. Janssen WE. Zorsky PE. Ballester OF. Kronish LE. Foody MC.  
Two novel high-dose treatment regimens for metastatic breast cancer--ifosfamide, carboplatin, plus etoposide and mitoxantrone plus



thiotepa: outcomes and toxicities.  
Seminars in Oncology. 20(5 Suppl 6):59-66, 1993 Oct.

[Return to top](#)

### **C. Radiation therapy following autotransplant.**

Marks LB. Rosner GL. Prosnitz LR. Ross M. Vredenburgh JJ. Peters WP.  
The impact of conventional plus high dose chemotherapy with autologous  
bone marrow transplantation on hematologic toxicity during subsequent  
local-regional radiotherapy for breast cancer.  
Cancer. 74(11):2964-71, 1994 Dec 1.

Shah AB. Hartsell WF. Ghalie R. Kaizer H.  
Patterns of failure following bone marrow transplantation for metastatic  
breast cancer: the role of consolidative local therapy.  
International Journal of Radiation Oncology, Biology, Physics. 32(5):1433-8, 1995 Jul 30.

Mundt AJ. Sibley GS. Williams S. Rubin SJ. Heimann R. Halpern H. Weichselbaum RR.  
Patterns of failure of complete responders following high-dose  
chemotherapy and autologous bone marrow transplantation for metastatic  
breast cancer: implications for the use of adjuvant radiation therapy  
International Journal of Radiation Oncology, Biology, Physics. 30(1):151-60, 1994 Aug 30.

Marks LB. Halperin EC. Prosnitz LR. Ross M. Vredenburgh JJ. Rosner  
GL. Peters W.  
Post-mastectomy radiotherapy following adjuvant chemotherapy and  
autologous bone marrow transplantation for breast cancer patients with  
greater than or equal to 10 positive axillary lymph nodes.  
Cancer and Leukemia Group B  
International Journal of Radiation Oncology, Biology, Physics.  
23(5):1021-6, 1992.

[Return to top](#)

### **D. Immune modulation posttransplant to induce antitumor activity.**

Yamasaki S. Kan N. Mise K. Harada T. Ichinose Y. Moriguchi Y. Kodama  
H. Satoh K. Ohgaki K. Tobe T.  
Cellular interaction against autologous tumor cells between IL-2-cultured  
lymphocytes and fresh peripheral blood lymphocytes in patients with breast  
cancer given immuno-chemotherapy.  
Biotherapy. 6(1):63-71, 1993.

Lazarus HM. Winton EF. Williams SF. Grinblatt D. Champion M. Cooper  
BW. Gunn H. Manfreda S. Isaacs RE.  
Phase I multicenter trial of interleukin 6 therapy after autologous bone  
marrow transplantation in advanced breast cancer.  
Bone Marrow Transplantation. 15(6):935-42, 1995 Jun.

Head JF. Elliott RL. McCoy JL.  
Evaluation of lymphocyte immunity in breast cancer patients.  
Breast Cancer Research & Treatment. 26(1):77-88, 1993.

McCulloch PG. MacIntyre A.  
Effects of surgery on the generation of lymphokine-activated killer cells

in patients with breast cancer.  
British Journal of Surgery. 80(8):1005-7, 1993 Aug.

Baxevanis CN. Dedoussis GV. Papadopoulos NG. Missitzis I. Stathopoulos GP. Papamichail M.  
Tumor specific cytolysis by tumor infiltrating lymphocytes in breast cancer.  
Cancer. 74(4):1275-82, 1994 Aug 15.

Dadmarz R. Sgagias MK. Rosenberg SA. Schwartzentruber DJ.  
CD4+ T lymphocytes infiltrating human breast cancer recognise autologous tumor in an MHC-class-II restricted fashion  
Cancer Immunology, Immunotherapy. 40(1):1-9, 1995 Jan.

Kennedy MJ. Vogelsang GB. Jones RJ. Farmer ER. Hess AD. Altomonte V. Huelskamp AM. Davidson NE.  
Phase I trial of interferon gamma to potentiate cyclosporine-induced graft-versus-host disease in women undergoing autologous bone marrow transplantation for breast cancer  
Journal of Clinical Oncology. 12(2):249-57, 1994 Feb.

Kennedy MJ. Vogelsang GB. Beveridge RA. Farmer ER. Altomonte V. Huelskamp AM. Davidson NE.  
Phase I trial of intravenous cyclosporine to induce graft-versus-host disease in women undergoing autologous bone marrow transplantation for breast cancer.  
Journal of Clinical Oncology. 11(3):478-84, 1993 Mar.

[Return to top](#)

#### **E. Detection of residual tumor cells in the stem cell source.**

Brugger W. Bross KJ. Glatt M. Weber F. Mertelsmann R. Kanz L.  
Mobilization of tumor cells and hematopoietic progenitor cells into peripheral blood of patients with solid tumors.  
Blood. 83(3):636-40, 1994 Feb 1.

Simpson SJ. Vachula M. Kennedy MJ. Kaizer H. Coon JS. Ghalie R. Williams S. Van Epps D.  
Detection of tumor cells in the bone marrow, peripheral blood, and apheresis products of breast cancer patients using flow cytometry.  
Experimental Hematology. 23(10):1062-8, 1995 Sep.

Fields KK. Elfenbein GJ. Trudeau WL. Perkins JB. Janssen WE. Moscinski LC.  
Clinical significance of bone marrow metastases as detected using the polymerase chain reaction in patients with breast cancer undergoing high-dose chemotherapy and autologous bone marrow transplantation.  
Journal of Clinical Oncology. 14(6):1868-76, 1996 Jun.

Datta YH. Adams PT. Drobyski WR. Ethier SP. Terry VH. Roth MS.  
Sensitive detection of occult breast cancer by the reverse-transcriptase polymerase chain reaction.  
Journal of Clinical Oncology. 12(3):475-82, 1994 Mar.

[Return to top](#)

## F. Purging of stem cell source to remove residual breast cancer cells.

Shpall EJ. Stemmer SM. Hami L. Franklin WA. Shaw L. Bonner HS. Bearman SI. Peters WP. Bast RC Jr. McCulloch W. et al. Amifostine (WR-2721) shortens the engraftment period of 4-hydroperoxycyclophosphamide-purged bone marrow in breast cancer patients receiving high-dose chemotherapy with autologous bone marrow support. *Blood*. 83(11):3132-7, 1994 Jun 1.

Shpall EJ. Stemmer SM. Bearman SI. Myers S. Purdy M. Jones RB. New strategies in marrow purging for breast cancer patients receiving high-dose chemotherapy with autologous bone marrow transplantation. *Breast Cancer Research & Treatment*. 26 Suppl:S19-23, 1993.

Myklebust AT. Godal A. Juell S. Pharo A. Fodstad O. Comparison of two antibody-based methods for elimination of breast cancer cells from human bone marrow. *Cancer Research*. 54(1):209-14, 1994 Jan 1.

Kennedy MJ. Davis J. Passos-Coelho J. Noga SJ. Huelskamp AM. Ohly K. Davidson NE. Administration of human recombinant granulocyte colony-stimulating factor (filgrastim) accelerates granulocyte recovery following high-dose chemotherapy and autologous marrow transplantation with 4-hydroperoxycyclophosphamide-purged marrow in women with metastatic breast cancer. *Cancer Research*. 53(22):5424-8, 1993 Nov 15.

Dietzfelbinger HF. Kuhn D. Zafferani M. Hanauske AR. Rastetter JW. Berdel WE. Removal of breast cancer cells from bone marrow by in vitro purging with ether lipids and cryopreservation. *Cancer Research*. 53(16):3747-51, 1993 Aug 15.

Ingram SS. Samulski T. Dodge R. Prosnitz LR. Peters P. Vredenburg J. The effects of hyperthermia in bone marrow purging of breast cancer. *International Journal of Hyperthermia*. 12(1):21-9, 1996 Jan-Feb.

[Return to top](#)

## G. Toxicity of autotransplants for breast cancer

Stemmer SM. Stears JC. Burton BS. Jones RB. Simon JH. White matter changes in patients with breast cancer treated with high-dose chemotherapy and autologous bone marrow support. *Ajnr: American Journal of Neuroradiology*. 15(7):1267-73, 1994 Aug.

Todd NW. Peters WP. Ost AH. Roggli VL. Piantadosi CA. Pulmonary drug toxicity in patients with primary breast cancer treated with high-dose combination chemotherapy and autologous bone marrow transplantation. *American Review of Respiratory Disease*. 147(5):1264-70, 1993 May.

Pittman KB. To LB. Bayly JL. Olweny CL. Abdi EA. Carter ML. Malycha P. Gill PG. Walsh J. Ward GG. et al. Non-haematological toxicity limiting the application of sequential high

dose chemotherapy in patients with advanced breast cancer.  
Bone Marrow Transplantation. 10(6):535-40, 1992 Dec.

Marks LB. Rosner GL. Prosnitz LR. Ross M. Vredenburgh JJ. Peters WP.  
The impact of conventional plus high dose chemotherapy with autologous  
bone marrow transplantation on hematologic toxicity during subsequent  
local-regional radiotherapy for breast cancer.  
Cancer. 74(11):2964-71, 1994 Dec 1.

Lewkow LM. Hooker JL. Movahed A.  
Cardiac complications of intensive dose mitoxantrone and cyclophosphamide  
with autologous bone marrow transplantation in metastatic breast cancer.  
International Journal of Cardiology. 34(3):273-6, 1992 Mar.

Patz EF Jr. Peters WP. Goodman PC.  
Pulmonary drug toxicity following high-dose chemotherapy with autologous  
bone marrow transplantation: CT findings in 20 cases.  
Journal of Thoracic Imaging. 9(2):129-34, 1994 Spring.

Khawly JA. Rubin P. Petros W. Peters WP. Jaffe GJ.  
Retinopathy and optic neuropathy in bone marrow transplantation for breast cancer.  
Ophthalmology. 103(1):87-95, 1996 Jan.

[Return to top](#)

## **H. Safety of autotransplants for breast cancer**

Holland HK. Dix SP. Geller RB. Devine SM. Heffner LT. Connaghan DG.  
Hillyer CD. Hughes LL. Miller RL. Moore MR. Winton EF. Wingard JR.  
Minimal toxicity and mortality in high-risk breast cancer patients  
receiving high-dose cyclophosphamide, thiotepa, and carboplatin plus  
autologous marrow/stem-cell transplantation and comprehensive supportive care.  
Journal of Clinical Oncology. 14(4):1156-64, 1996 Apr.

[Return to top](#)

## **I. Legal and financial issues**

Wynstra NA.  
Breast cancer. Selected legal issues.  
Cancer. 74(1 Suppl):491-511, 1994 Jul 1.

Hillner BE. Smith TJ. Desch CE.  
Efficacy and cost-effectiveness of autologous bone marrow transplantation  
in metastatic breast cancer. Estimates using decision analysis while  
awaiting clinical trial results.  
JAMA. 267(15):2055-61, 1992 Apr 15.

Eddy DM.  
High-dose chemotherapy with autologous bone marrow transplantation for the  
treatment of metastatic breast cancer.  
Journal of Clinical Oncology. 10(4):657-70, 1992 Apr.

Peters WP. Rogers MC.  
Variation in approval by insurance companies of coverage for autologous  
bone marrow transplantation for breast cancer.

New England Journal of Medicine. 330(7):473-7, 1994 Feb 17.

Cutler CM. Udvarhelyi IS. Winkenwerder W.  
Variations in insurance coverage for autologous bone marrow transplantation for breast cancer.  
New England Journal of Medicine. 331(5):329-30, 1994 Aug 4.

Erbas JK.  
Variations in insurance coverage for autologous bone marrow transplantation for breast cancer  
New England Journal of Medicine.  
331(5):330, 1994 Aug 4.

Templeton KM.  
Variations in insurance coverage for autologous bone marrow transplantation for breast cancer.  
New England Journal of Medicine.  
331(5):330, 1994 Aug 4.

Wingard JR.  
Variations in insurance coverage for autologous bone marrow transplantation for breast cancer.  
New England Journal of Medicine. 331(5):330, 1994 Aug 4.

Krause KJ.  
Variations in insurance coverage for autologous bone marrow transplantation for breast cancer.  
New England Journal of Medicine.  
331(5):330, 1994 Aug 4.

Khanna V.  
Variations in insurance coverage for autologous bone marrow transplantation for breast cancer.  
New England Journal of Medicine.  
331(5):330-1, 1994 Aug 4.

[Return to top](#)

## **J. Randomized trials involving autotransplants for breast cancer**

Bezwodna WR. Seymour L. Dansey RD.  
High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial.  
Journal of Clinical Oncology. 13(10):2483-9, 1995 Oct.

Rutqvist LE.  
Randomized adjuvant breast cancer trials in Sweden.  
Cancer. 74(3 Suppl):1156-9, 1994 Aug 1.

Osborne CK.  
Current trials and future directions of the Southwest Oncology Group Breast Cancer Committee.  
Cancer. 74(3 Suppl):1135-8, 1994 Aug 1.

Wood WC.  
Current trials and future directions of the Eastern Cooperative Oncology Group Breast Cancer Committee.

Cancer. 74(3 Suppl):1132-4, 1994 Aug 1.

Hurd DD. Peters WP.

Randomized, comparative study of high-dose (with autologous bone marrow support) versus low-dose cyclophosphamide, cisplatin, and carmustine as consolidation to adjuvant cyclophosphamide, doxorubicin, and fluorouracil for patients with operable stage II or III breast cancer involving 10 or more axillary lymph nodes (CALGB Protocol 9082). Cancer and Leukemia Group B. Monographs - National Cancer Institute. (19):41-4, 1995.

[Return to top](#)

### **K. Prognostic factors in autotransplants for metastatic breast cancer**

Rowlings PA. Antman KS. Horowitz MM. Williams SF. Lazarus HM. Fields KK. Pelz CJ. Sobocinski KA. Armitage JO. for the Breast Cancer Working Committee of the Autologous Blood and Marrow Transplant Registry-North America.

Prognostic factors in autotransplants for metastatic breast cancer. Blood. 88(10): 618a, abstract 2459, 1995 Nov 15.

Dunphy FR. Spitzer G. Fornoff JE. Yau JC. Huan SD. Dicke KA. Buzdar AU. Hortobagyi GN.

Factors predicting long-term survival for metastatic breast cancer patients treated with high-dose chemotherapy and bone marrow support. Cancer. 73(8):2157-67, 1994 Apr 15.

Ayash LJ. Wheeler C. Fairclough D. Schwartz G. Reich E. Warren D. Schnipper L. Antman K. Frei E 3rd. Elias A.

Prognostic factors for prolonged progression-free survival with high-dose chemotherapy with autologous stem-cell support for advanced breast cancer. Journal of Clinical Oncology. 13(8):2043-9, 1995 Aug.

[Return to top](#)

### **L. Double (Tandem) autotransplants for breast cancer**

Broun ER. Sridhara R. Sledge GW. Loesch D. Kneebone PH. Hanna M. Hromas R. Cornetta K. Einhorn LH.

Tandem autotransplantation for the treatment of metastatic breast cancer. Journal of Clinical Oncology. 13(8):2050-5, 1995 Aug.

Ayash LJ. Elias A. Wheeler C. Reich E. Schwartz G. Mazanet R. Tepler I. Warren D. Lynch C. Gonin R. et al.

Double dose-intensive chemotherapy with autologous marrow and peripheral-blood progenitor-cell support for metastatic breast cancer: a feasibility study.

Journal of Clinical Oncology. 12(1):37-44, 1994 Jan.

Bitran JD. Samuels B. Klein I. Hanauer S. Johnson L. Martinec J. Harris E. Kempler J. White W. Tandem high-dose chemotherapy supported by hemopoietic progenitor cells yields prolonged survival in stage IV breast cancer.

Bone Marrow Transplantation. 17; 157-162, 1996

[Return to top](#)

### **M. Pharmacokinetic monitoring in autotransplants for breast cancer**

Jones RB. Matthes S. Dufton C. Bearman SI. Stemmer SM. Meyers S. Shpall EJ.  
Pharmacokinetic/pharmacodynamic interactions of intensive  
cyclophosphamide, cisplatin, and BCNU in patients with breast cancer.  
Breast Cancer Research & Treatment. 26 Suppl:S11-7, 1993.

Chen TL. Passos-Coelho JL. Noe DA. Kennedy MJ. Black KC. Colvin OM. Grochow LB.  
Nonlinear pharmacokinetics of cyclophosphamide in patients with metastatic  
breast cancer receiving high-dose chemotherapy followed by autologous bone  
marrow transplantation  
Cancer Research. 55(4):810-6, 1995 Feb 15.

O'Brien ME. Talbot DC. Smith IE.  
Carboplatin in the treatment of advanced breast cancer: a phase II study  
using a pharmacokinetically guided dose schedule.  
Journal of Clinical Oncology. 11(11):2112-7, 1993 Nov.

[Return to top](#)

## **N. Quality of life after autotransplants for breast cancer.**

Ahles TA. Tope DM. Furstenberg C. Hann D. Mills L.  
Psychologic and neuropsychologic impact of autologous bone marrow transplantation.  
Journal of Clinical Oncology. 14(5):1457-62, 1996 May.

McQuellon RP. Muss HB. Hoffman SL. Russell G. Craven B. Yellen SB.  
Patient preferences for treatment of metastatic breast cancer: a study of  
women with early-stage breast cancer.  
Journal of Clinical Oncology. 13(4):858-68, 1995 Apr.

[Return to top](#)

## **O. Hemopoetic stem cell sources for autotransplants for breast cancer.**

de Graaf H. Mulder NH. Willemse PH. van der Graaf WT. Sleijfer DT.  
Zijlstra JG. Elias M. Sibinga CT. Vellenga E. de Vries EG.  
The additive effect of peripheral blood stem cells, harvested with  
low-dose cyclophosphamide, to autologous bone marrow reinfusion on  
hematopoietic reconstitution after ablative chemotherapy in breast cancer  
patients with localized disease.  
Anticancer Research. 15(6B):2851-6, 1995 Nov-Dec.

Elias AD. Ayash L. Anderson KC. Hunt M. Wheeler C. Schwartz G.  
Tepler I. Mazanet R. Lynch C. Pap S. et al.  
Mobilization of peripheral blood progenitor cells by chemotherapy and  
granulocyte-macrophage colony-stimulating factor for hematologic support  
after high-dose intensification for breast cancer.  
Blood. 79(11):3036-44, 1992 Jun 1.

Myers SE. Mick R. Williams SF.  
High-dose chemotherapy with autologous stem cell rescue in women with  
metastatic breast cancer with involved bone marrow: a role for peripheral  
blood progenitor transplant.  
Bone Marrow Transplantation. 13(4):449-54, 1994 Apr.

Kritz A. Crown JP. Motzer RJ. Reich LM. Heller G. Moore MP. Hamilton

N. Yao TJ. Heelan RT. Schneider JG. et al.  
Beneficial impact of peripheral blood progenitor cells in patients with metastatic breast cancer treated with high-dose chemotherapy plus granulocyte-macrophage colony-stimulating factor. A randomized trial. *Cancer*. 71(8):2515-21, 1993 Apr 15.

[Return to top](#)

### **P. Autotransplants as outpatients.**

Peters WP. Ross M. Vredenburg JJ. Hussein A. Rubin P. Dukelow K. Cavanaugh C. Beauvais R. Kasprzak S.  
The use of intensive clinic support to permit outpatient autologous bone marrow transplantation for breast cancer. *Seminars in Oncology*. 21(4 Suppl 7):25-31, 1994 Aug.

[Return to top](#)

### **Q. Change in disease stage with extensive evaluation**

Crump M. Goss PE. Prince M. Girouard C.  
Outcome of extensive evaluation before adjuvant therapy in women with breast cancer and 10 or more positive axillary lymph nodes. *Journal of Clinical Oncology*. 14(1):66-9, 1996 Jan.

[Return to top](#)

---

[Potential Donors](#) | [Ask the Expert](#) | [Diseases](#) | [Transplant Topics](#) | [About our Sponsors](#) | [Test your Knowledge](#) | [Physician's Corner](#)  
[Main](#) | [Survey](#) | [Glossary](#) | [Q & A](#) | [Disclaimer](#) | [Related Sites](#) | [Text Only](#)

**Welcome to BMTInformation at [www.bmtinfo.org](http://www.bmtinfo.org)**



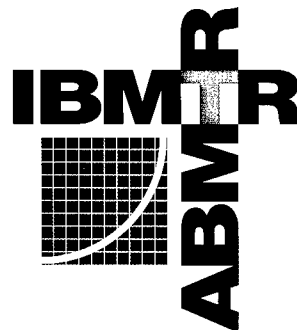
# BMTnet

BLOOD & MARROW  
TRANSPLANTATION

---

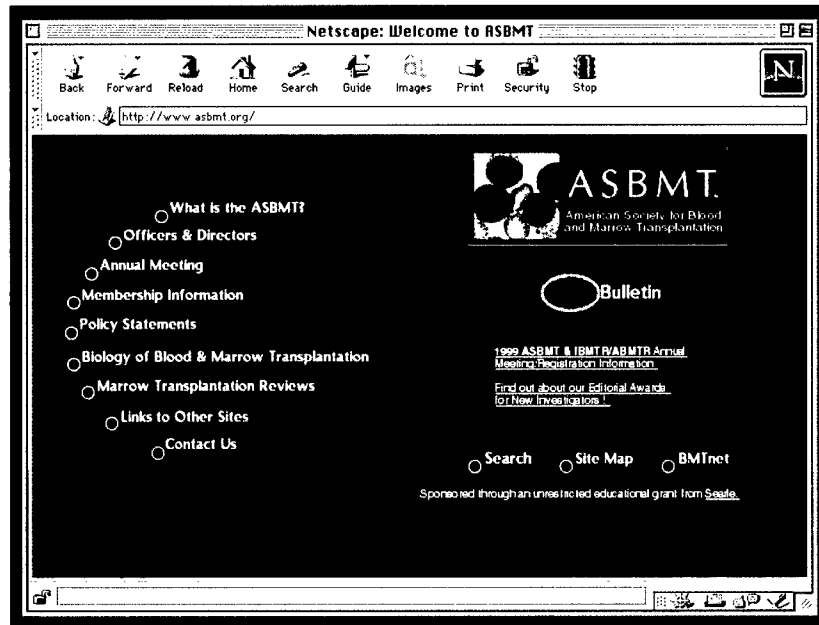
# *ONLINE*

---



# ASBMT

American Society for Blood and Marrow Transplantation



The web site at [www.asbmt.org](http://www.asbmt.org) advances the mission of ASBMT — to represent and serve blood and marrow transplantation investigators, clinicians and the patients they care for.

Features of the web site include:

- ASBMT policy statements, including Guidelines for Clinical Centers and Guidelines for Training.
- Searchable full texts of articles in ASBMT periodicals, Biology of Blood and Marrow Transplantation and Marrow Transplantation Reviews.
- ASBMT officers and directors, including direct e-mail links.
- Investigator awards, editorial awards and other ASBMT programs and recognitions.
- ASBMT Annual Meeting program, registration and housing information.
- Membership application information.
- Links to other BMT sites, including medical and patient advocacy organizations and government agencies.

The web site will continue to evolve with new features and functions that serve the communications needs of ASBMT members.

## **ASBMT**

The American Society for Blood and Marrow Transplantation is the leading individual membership organization promoting research, education and clinical practice in the field of blood and marrow transplantation.

ASBMT promotes high-quality BMT clinical care, clinical guidelines and standards, rapid advancement of the BMT field through basic and clinical research and an annual scientific meeting, scholarly publication through its *Biology of Blood and Marrow Transplantation* journal, effective representation of BMT to legislators and government regulators, representation of BMT interests to managed care and health plan administrators, and public and professional awareness and understanding of blood and marrow transplantation.

## **IBMTR/ABMTR**

*Sharing Knowledge. Sharing Hope.*

The International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplantation Registry (ABMTR) are voluntary organizations of basic and clinical scientists collaborating in an effort to address important issues in blood and marrow transplantation. We are not a donor registry — we gather information on results of blood and marrow transplants. This information is used to guide clinical decisions and identify ways to improve transplant outcomes.

The IBMTR is an international study group engaged in ongoing investigation of allogeneic and syngeneic (identical twin) transplantation for more than 25 years. The ABMTR began collecting data from centers in North America and South America in 1991 on transplants using autologous bone marrow and/or blood cells.

The IBMTR/ABMTR Statistical Center is a division of the Health Policy Institute of the Medical College of Wisconsin in Milwaukee.

## **BMTnet**

BMTnet is a cooperative effort among BMT organizations to coordinate web sites serving the blood and marrow transplantation field. BMTnet and its component web sites are supported by an unrestricted educational grant from Searle.

www.asbmt.org

**ASBMT**  
Annual Meeting 1999  
SCIENTIFIC AGENDA

Click date for program info

IBMT/ABMT February							ABMT March						
S	M	T	W	T	F	S	S	M	T	W	T	F	S
7	8	9	10	11	12	13	7	8	9	10	11	12	13
14	15	16	17	18	19	20	14	15	16	17	18	19	20
21	22	23	24	25	26	27	21	22	23	24	25	26	27
28							28	29	30	31			

March						
S	M	T	W	T	F	S
	1	2	3	4	5	6
7	8	9	10	11	12	13

Click on a calendar date for Annual Meeting program information.

www.ibmtr.org

**IBMTR**  
TRANSPLANT CENTERS  
U.S.A.

Click on state for list of Centers

- MI Michigan
- MT Montana
- NC North Carolina
- ND North Dakota
- NH New Hampshire
- NJ New Jersey
- NM New Mexico
- NV Nevada
- NY New York
- OH Ohio
- OK Oklahoma
- OR Oregon
- PA Pennsylvania
- PB Puerto Rico
- SC South Carolina
- SD South Dakota
- TN Tennessee
- TX Texas
- UT Utah
- VA Virginia
- WI Wisconsin
- WV West Virginia

Click on a state for a list of transplant centers.

**ASBMT**  
Policy Statements

Guidelines for Clinical Centers

The following "Guidelines for Clinical Centers" were adopted by the American Society of Blood and Marrow Transplantation on May 21, 1995, and published in *Biology of Blood and Marrow Transplantation*, Volume 1, pages 54-55, 1995.

**Objective**  
The primary objective of the American Society of Blood and Marrow Transplantation (ASBMT) is to ensure the highest quality of medical practice in hematopoietic transplantation medicine. To this end, the following guidelines describe recommendations for centers performing blood and/or marrow transplantation for the treatment of human disease.

**Program Size**  
To ensure continuing proficiency in a transplant program, a minimum number of 10 transplants should have been performed during the previous year. If the program performs only one type of graft (autologous or allogeneic), at least 10 transplants of that type must be performed per annum; programs performing both allogeneic and autologous transplants should perform a minimum of 10 transplants of each kind per annum.

Guidelines for Clinical Centers  
 Objective  
 Program Size  
 Staff  
 Data Acquisition & Quality Assurance  
 Facilities

Guidelines for Training

Instant access to "Guidelines for Clinical Centers" and "Guidelines for Training."

**IBMTR**  
INFORMATION SERVICES  
Summary Slides

ANNUAL NUMBER OF BLOOD AND MARROW TRANSPLANTS WORLDWIDE 1970-1997

NUMBER OF TRANSPLANTS

YEAR

Autologous

Allogeneic

MISSION STATEMENT  
PERSONNEL DIRECTORY  
TRANSPLANT CENTERS  
NEWSLETTERS  
MEETING INFORMATION  
PUBLICATIONS  
COMMITTEES  
DATA COLLECTION  
FAQs  
Disease-Specific Reports  
Information Request  
Report of Survival Statistics  
Summary Slide Edition  
Other related Web Sites  
CORPORATE MEMBERSHIP PROGRAM  
WE NEED YOUR SUPPORT!

Slide series illustrates trends in blood and marrow transplantation.

# IBMTR/ABMTR

International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry



The web site at [www.ibmtr.org](http://www.ibmtr.org) serves the mission of IBMTR/ABMTR — to gather and disseminate information on results of blood and marrow transplants to aid clinical decisions and to identify ways to improve transplant outcomes.

Features of the web site include:

- Locations and contact information for transplant centers participating in the IBMTR/ABMTR.
- IBMTR/ABMTR studies in progress.
- Statistical summary slides, featuring data on the current status of blood and marrow transplantation.
- Full text of current and highlights of past IBMTR and ABMTR newsletters.
- IBMTR/ABMTR publications list.
- IBMTR and ABMTR Report Forms that can be printed directly from the web site.
- IBMTR/ABMTR Annual Meeting program, registration and housing information.
- Information on how to contact IBMTR/ABMTR Executive, Advisory and Working Committee members and the Statistical Center personnel, including many direct e-mail links.

New features and functions will be added, including Working Committee discussion rooms, on-line IBMTR/ABMTR registration forms, and other information service features, including disease-specific reports and survival data.

# ***WHAT?***

BMT information and resources on the Internet.

# ***WHEN?***

NOW.

This new web service is online, ready to serve you.

# ***WHY?***

To provide valuable information and reference materials, and to enhance communication among BMT clinicians, investigators and other health care professionals.

# ***WHERE?***

At: **www.bmntnet.org** — a comprehensive, central resource of blood and marrow transplantation topics.

**www.asbmt.org** — the new web site of the American Society for Blood and Marrow Transplantation (ASBMT)

**www.ibmtr.org** — the new web site of the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR)

Supported by an unrestricted educational grant from Searle.

**www.searleoncology.com**

**IBMTR/ABMTR Presentations on Breast Cancer at  
National and International Meetings  
1994-1998**

November 1994

4th International Meeting of the Canadian Bone Marrow Transplant Group Ottawa, Canada  
P.A. Rowlings: BMT: What can we learn from the IBMTR/ABMTR database?

Chemotherapy Foundation Symposium XII New York, USA  
K. Fields: High dose chemotherapy with BMT in treatment of breast cancer

First International Cancer Congress Hong Kong  
K. Antman: High dose chemotherapy for breast cancer

January 1995

Second Symposium on Autotransplants Keystone, USA  
M.M. Horowitz: Overview of autologous transplantation

First Annual Meeting of the American Society for Blood & Marrow Transplantation Keystone, USA  
H. Sutton: Healthcare economics, reform and BMT  
M.M. Horowitz: Outcomes assessment in BMT

February 1995

20th Annual Topics and Advances in Internal Medicine San Diego, USA  
R.E. Corringham: High dose chemotherapy in established breast cancer treatment

March 1995

High Dose Chemotherapy with Stem Cell Support for the Treatment of Breast Cancer Bethesda, USA  
M.M. Horowitz: Use of the ABMTR database

April 1995

Meeting of the United Network of Organ Sharing New Orleans, USA  
G.J. Elfenbein: Autologous BMT for breast cancer

May 1995

Future Directions in Stem Cell Transplantation Teaneck, USA  
M.M. Horowitz: Use of autologous and allogeneic marrow transplantation: An overview from the IBMTR

August 1995

International Society for Experimental Hematology

Düsseldorf, Germany

P.A. Rowlings: Prognostic factors in autotransplants for metastatic breast cancer

September 1995

6th Uruguayan Congress of Haematology

Montevideo, Uruguay

P.A. Rowlings: Autologous BMT, peripheral stem cells and their clinical applications

November 1995

Columbian Society for Oncology

Cali, Columbia

W.P. Vaughan: Advances in autologous and allogeneic BMT

Meeting of the Ecuador National Cancer Institute

Quito, Ecuador

W.P. Vaughan: Advances in BMT

December 1995

American Society of Hematology

Seattle, USA

P.A. Rowlings: Prognostic factors in autotransplants for metastatic breast cancer

January 1996

1996 IBMTR/ABMTR Participants' Meeting

Keystone, USA

K. Antman: Autotransplants for breast cancer

J.O. Armitage: ABMTR update

Keystone Symposium on Blood Cell and Bone Marrow Transplants

Keystone, USA

M.M. Horowitz: Analyzing transplant outcomes: comparison with other therapies

J.O. Armitage: Do autotransplants uniquely cure cancer?

R.P. Gale: How do autotransplants cure cancer?

K. Antman: Breast cancer workshop

February 1996

Blue Cross and Blue Shield Technology Center Forum

Chicago, USA

M.M. Horowitz: Outcomes of autologous transplants for breast cancer

Cancer Care for Non-Oncologists

Irvine, USA

R.O. Dillman: Biotherapy for cancer

Blue Cross and Blue Shield Technology Center Forum

Chicago, IL

M.M. Horowitz: High dose chemotherapy versus autotransplants for breast cancer and multiple myeloma



March 1996

California Society of Hospital Pharmacists

Newport Beach, USA

R.O. Dillman: New directions in stem cell transplants

4th International Symposium on Blood Cell Transplantation

Adelaide, South Australia

K.A. Antman: Blood cell transplants for breast cancer

Association of Cancer Executives

Philadelphia, USA

R.O. Dillman: Update on autologous BMT

22nd Annual Meeting of the European Group for Blood & Marrow Transplantation

Vienna, Austria

M.M. Horowitz: Challenges in using observational data to compare transplant and non-transplant treatment

April 1996

First South American Transplantation Meeting

Buenos Aires, Argentina

P.A. Rowlings: Autotransplant for metastatic breast cancer

4th International Symposium on Blood Cell Transplantation

Adelaide, South Australia

K.A. Antman: Blood cell transplants for breast cancer

Association of Cancer Executives

Philadelphia, USA

R.O. Dillman: Update on autologous BMT

May 1996

American Society of Clinical Oncology

Philadelphia, USA

J.K. Erban: Effect of legislation mandating coverage for BMT for breast cancer

H.M. Lazarus: Outcome of autotransplants in older adults

Experimental and Clinical Approaches in Oncology: Approaching the 21st Century

Teaneck, USA

M.M. Horowitz: Use of blood and marrow transplant in cancer treatment

Societat Catalana de Hematologia

Barcelona, Spain

A. Julia: Indications of transplantation

June 1996

Advances in Haematology

London, UK

M.M. Horowitz: Use of blood and marrow transplantation in cancer treatment

Indian Society of Hematology Meeting

Bombay, India

A.G. Mundia: Stem cell transplants in solid tumors

August 1996

8th International Symposium on Autologous Marrow and Blood Transplantation

Arlington, USA

P.A. Rowlings: ABMTR results

P.A. Rowlings: Clinical studies in metastatic disease

D. Weisdorf: Comparison of unrelated donor BMT versus autologous BMT

Joint Statistical Meetings

Chicago, USA

J.P. Klein: Modeling multistate survival illustrated in bone marrow transplantation

September 1996

Meeting of the American Academy of Insurance Medicine

Kansas City, USA

M.M. Horowitz: Outcome of blood and marrow transplantation

October 1996

Oncology Nursing Conference 1996

Santo Domingo, Dominican Republic

C. Meneghetti: High dose chemotherapy and autologous BMT for breast cancer treatment

22nd Annual Meeting of the Brazilian Society of Hematology and Hemotherapy

Porto Alegre, Brazil

D.G. Tabak: BMT in the Mercosul - A Brazilian perspective

November 1996

Second Uruguayan Congress on BMT and PBSC Transplants

Montevideo, Uruguay

G. Milone: Advances in breast cancer treatment: BMT results

Conference of the Society of Blood Transfusion Hematology

Ho Chi Minh City, Vietnam

K.H. Lin: BMT in Taiwan

Meeting of the Polish Society of Hematology

Poznan, Poland

J. Hansz: Past, present and future of hematopoietic cell transplantation

March 1997

I Encontro sobre Transplante de Medula Ossea e Hemopatias Malignas Curitiba, Brazil

S. Pavlovsky: The Argentine Group for Bone Marrow Transplantation experience  
M.M. Horowitz: Chemotherapy vs. autologous vs. allogeneic BMT: Which is the best treatment?  
M.M. Horowitz: Breast cancer - ABMTR data  
A. Sumoza: BMT in Venezuela  
K.A. Sobocinski: Analysis of transplant data

Annual Meetings of the BMT and Hematology Societies of Taiwan Kaohseoug, Taiwan

C.H. Tzeng: An update on BMT and PBSCT

23rd Annual Meeting of the European Group for Blood and Marrow Transplantation Aix-les-Bains, France

K. Antman: High-dose therapy for breast cancer in North America

German Stem Cell Meeting Berlin, Germany

W. Hinterberger: Implications of posttransplant consolidative immunotherapy and immune modulation

1997 Blood Cell and Marrow Transplantation Multidisciplinary Symposium Dallas, USA

P.A. Rowlings: Patient outcomes

April 1997

Canadian Apheresis Group Annual Meeting and Stem Cell Symposium Quebec City, Canada

A. Keating: Overview of PBSC transplants

Brazilian College of Breast Surgeons Rio de Janeiro, Brazil

D.G. Tabak: The role of BMT in the treatment of breast cancer

Bone Marrow Transplant Symposium Graifswald, Germany

G. Dolken: High-dose chemotherapy as an adjuvant therapy for high-risk breast cancer

May 1997

Second National PBSCT Congress Istanbul, Turkey

F. Arpaci: High-dose treatment in patients with solid tumors

American Society for Clinical Oncology Denver, USA

M.M. Horowitz: Prognostic factors for outcome of autotransplants in women with high-risk breast cancer.

June 1997

VIII National Congress of the Italian Society of Hemapheresis Trieste, Italy

A. Iacone: Background of Hemapheresis

August 1997

Aplastic Anemia Foundation of America International Patient Conference Philadelphia, USA

M.M. Horowitz: Bone marrow transplant research and treatment in the United States and Europe

November 1997

Dept. of Defense Breast Cancer Research Meeting

Washington, DC, USA

M.M. Horowitz: High-dose chemotherapy and blood or BMT for patients with high-risk breast cancer

Bone Marrow Transplantation for the Treatment of Autoimmune Disease

Worcester, USA

P.A. Rowlings: Standardized data collection for high-dose therapy and autologous stem cell transplants

January 1998

1998 IBMTR/ABMTR Participants' Meeting

Keystone, USA

C. Bennett: Cost analysis of autologous stem cell transplants: preliminary results

March 1998

Osaka Hematopoietic Stem Cell Transplantation Seminar

Osaka, Japan

M.M. Horowitz: Autologous transplantation: ABMTR results

60th Meeting of the Japanese Society of Hematology

Osaka, Japan

M.M. Horowitz: Increasing use of hematopoietic stem cell transplantation: IBMTR/ABMTR results

Kanto Bone Marrow Transplantation Seminar

Tokyo, Japan

M.M. Horowitz: Use of registry data in statistical analysis of bone marrow transplantation results

24th Annual Meeting of the European Group for Blood and Marrow Transplantation

Courmayeur, Italy

J.P. Klein: Comparing diseases and outcome measures: clinical and methodological problems

May 1998

Transplantation in Hematology and Oncology

Münster, Germany

M.M. Horowitz: Status of blood and marrow transplantation

July 1998

Ninth International Symposium on Autologous Blood and Marrow Transplantation

Dallas, USA

G.J. Elfenbein: Autotransplants for solid tumors

P.L. McCarthy: Autotransplants in men with breast cancer

R.L. Powles: Long term effects following autologous BMT: the London experience

September 1998

Second Balkan International Congress of Oncology Meeting

Izmir, Turkey

F. Arpaci: High dose therapy: why and when

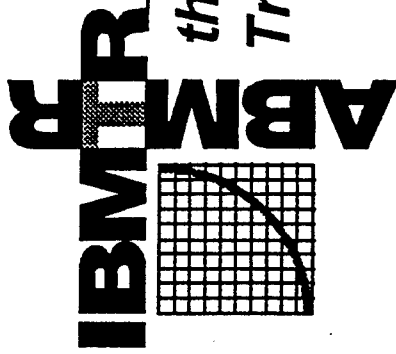
F. Arpaci: What is the best BMT strategy in patients with hematological malignancies and solid tumors?

8th Argentine Cancerology Congress & 5th Conference on Oncology Nursing

Buenos Aires, Argentina

G.J. Elfenbein: High dose therapy followed by autologous hematopoietic SCT for high risk breast cancer

# **AUTOTRANSPLANTS FOR BREAST CANCER**



*A Report from*

*the Autologous Blood and Marrow  
Transplant Registry-North America*

## **BREAST CANCER**

- 180,000 new cases/year in U.S.
- 50% under age 65
- 20-25% "high-risk"  
(Stage II/III with  $\geq 10$  nodes; metastatic)
- > 20,000 potential autotransplant recipients

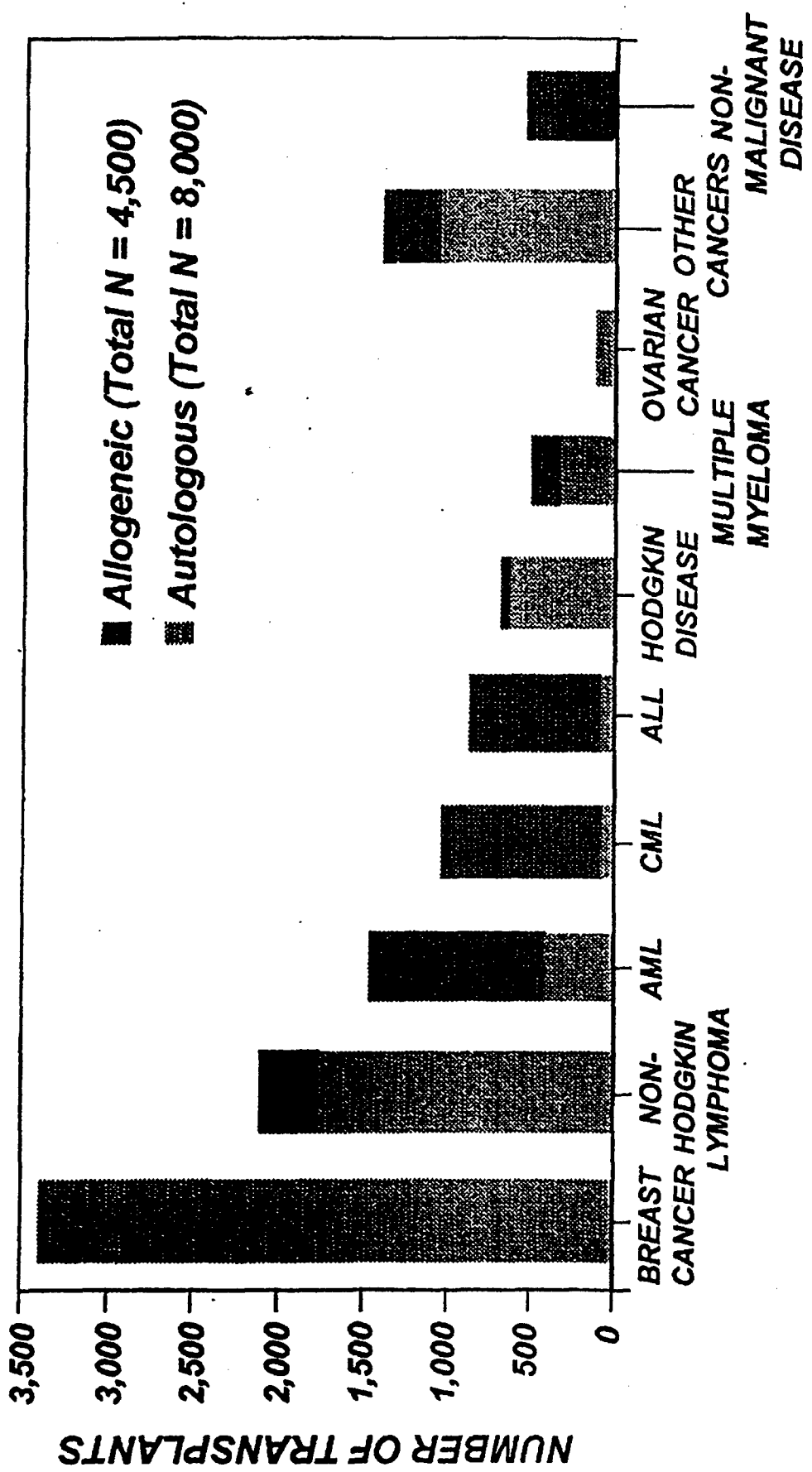
# **RATIONALE FOR AUTOTRANSPLANTS IN BREAST CANCER**

- *Experimental and clinical evidence  
for dose-response*

- *Dose limited by myelosuppression*

# INDICATIONS FOR BLOOD AND MARROW TRANSPLANTATION IN NORTH AMERICA

1995

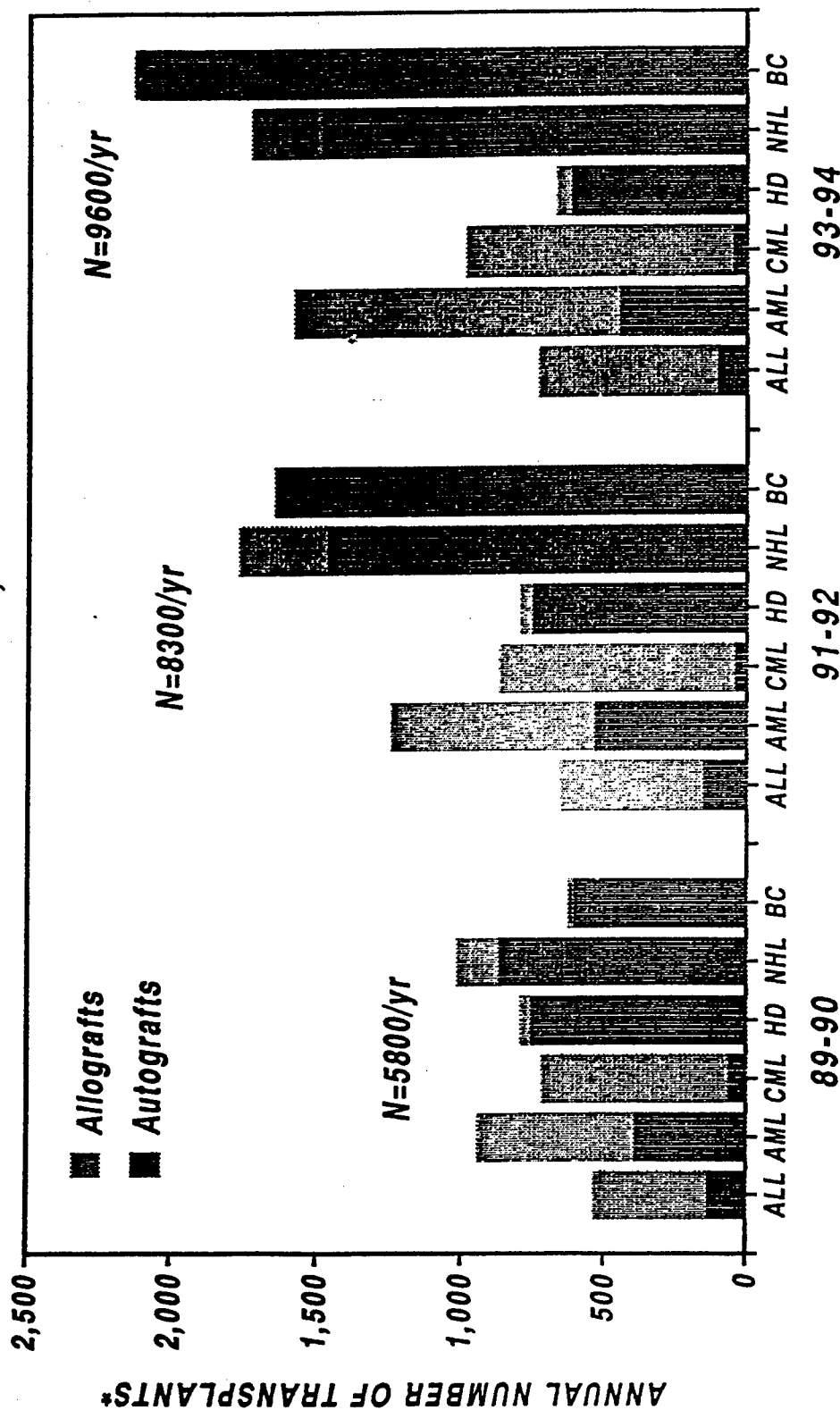




KBC96 2

*Overview of 5886 autotransplants for  
breast cancer performed between  
January 1989 and June 1995*

# ALLO- AND AUTOTRANSPLANTS North America, 1989-94



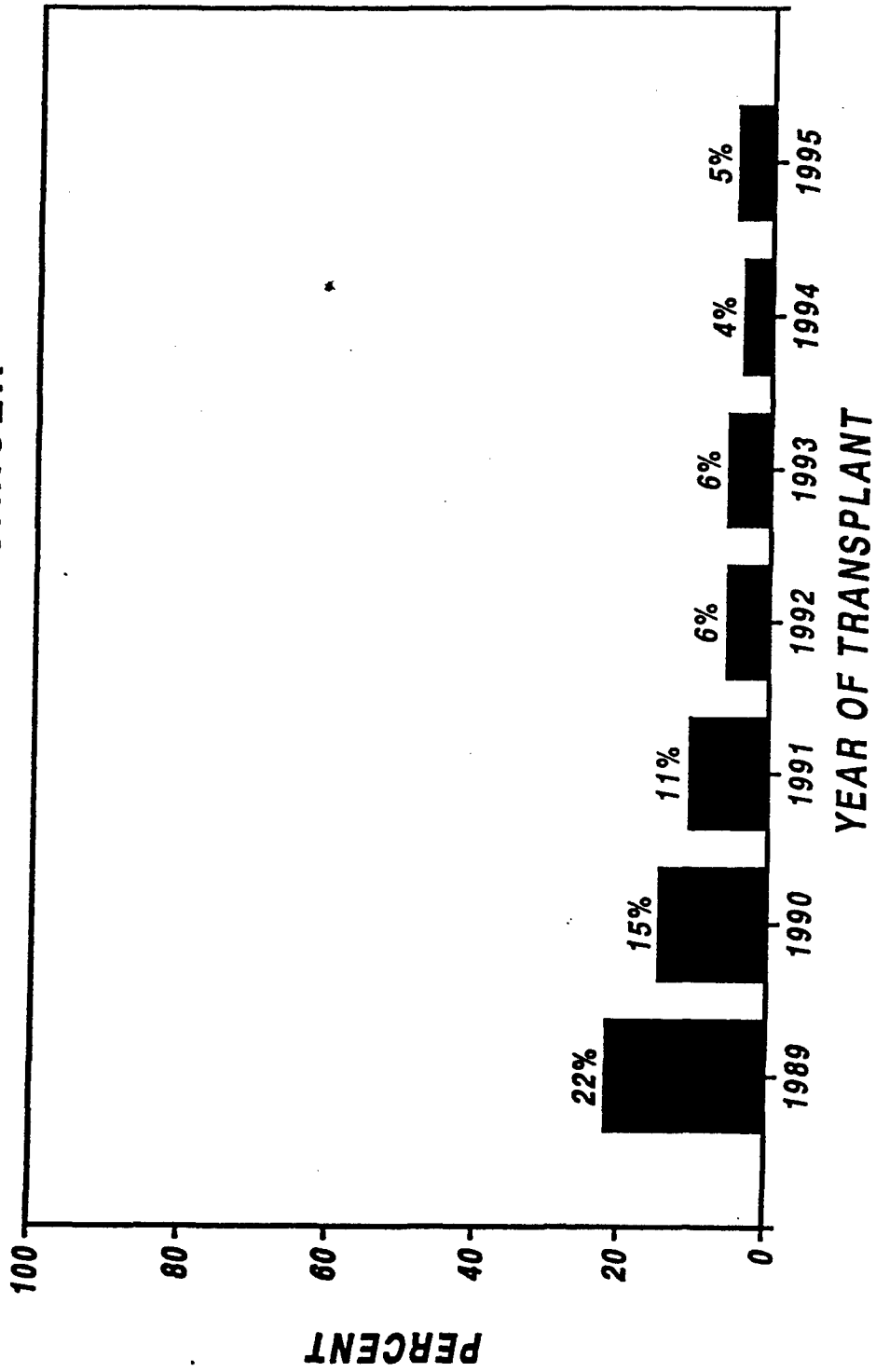
\*Average number of transplants done yearly in each 2-year period

# AUTOTRANSPLANTS FOR BREAST CANCER

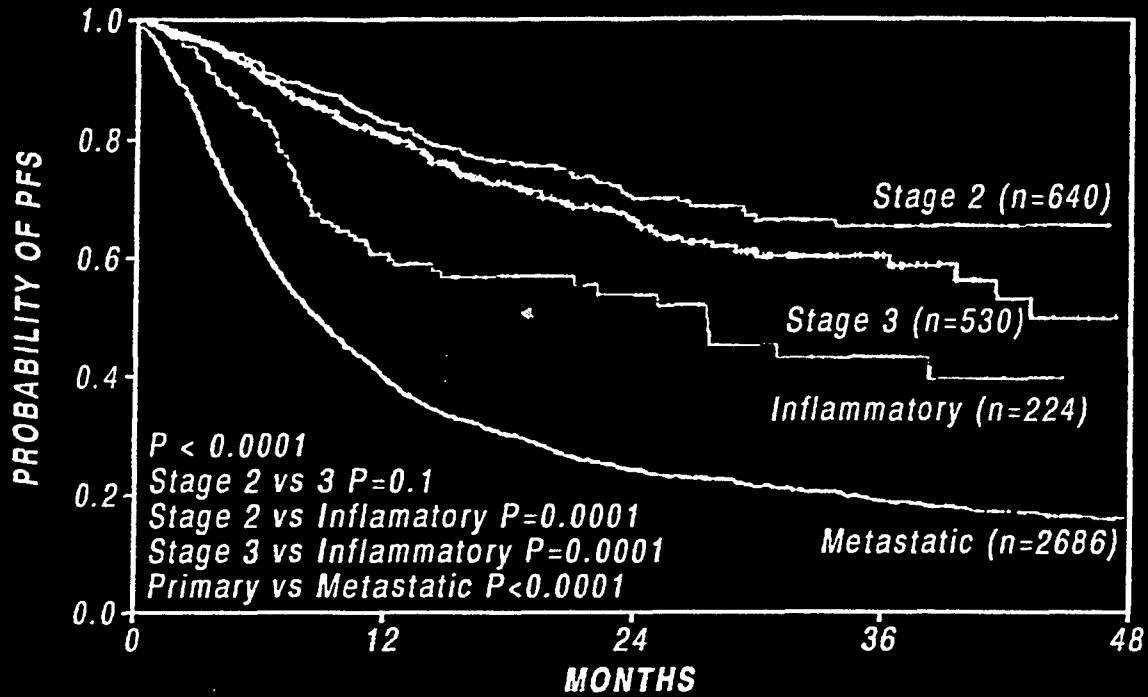
	<u>1989</u>	<u>1990</u>	<u>1991</u>	<u>1992</u>	<u>1993</u>	<u>1994</u>	<u>1995</u>
<b>N</b>	272	342	683	1069	1189	1513	818
<b>Disease Stage at TX</b>							
Local	7%	16%	23%	34%	31%	39%	49%
Metastatic	93%	83%	77%	65%	68%	50%	50%
Other	<1%	1%	<1%	1%	1%	1%	1%
<i>ft - already recorded on slide</i>							
<b>Graph Type</b>							
BM	81%	79%	58%	42%	30%	19%	10%
BM + PBSC	5%	7%	22%	33%	30%	25%	18%
PBSC	14%	14%	20%	25%	40%	56%	72%

Other = patients with locally persistent or recurrent disease post conventional therapy

# 100-DAY MORTALITY AFTER AUTOTRANSPLANTS FOR BREAST CANCER

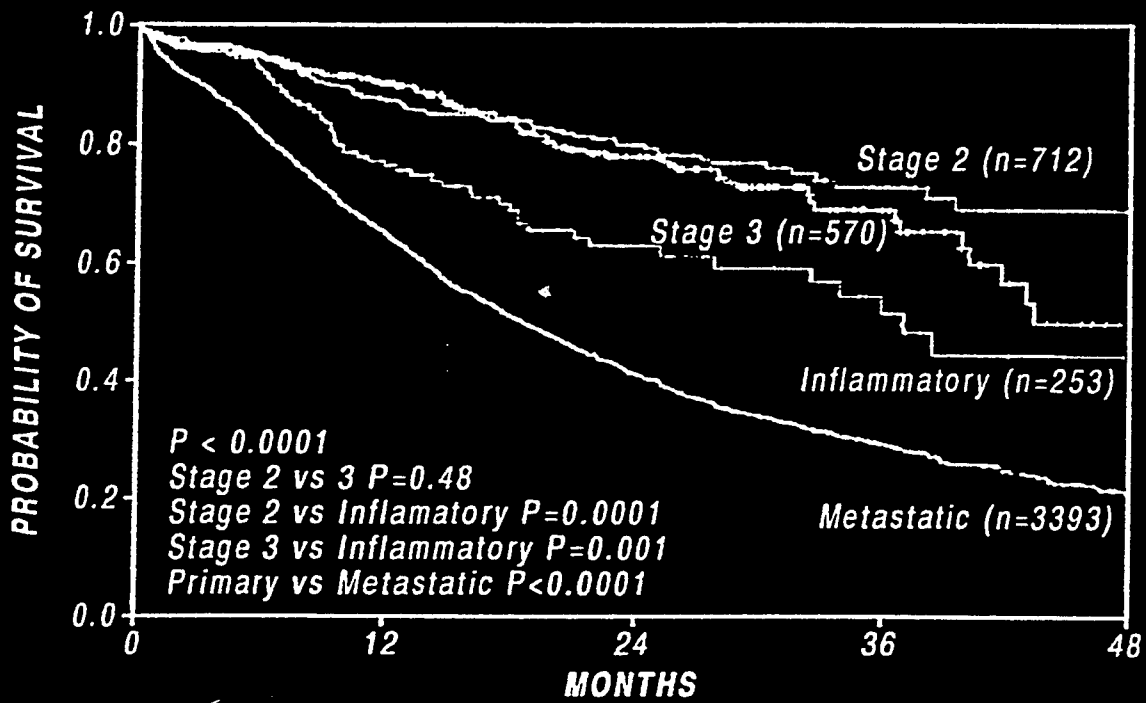


**PROGRESSION-FREE SURVIVAL AFTER AUTOTRANSPLANTS  
FOR PRIMARY (STAGE 2, 3 OR INFLAMMATORY)  
AND METASTATIC BREAST CANCER**



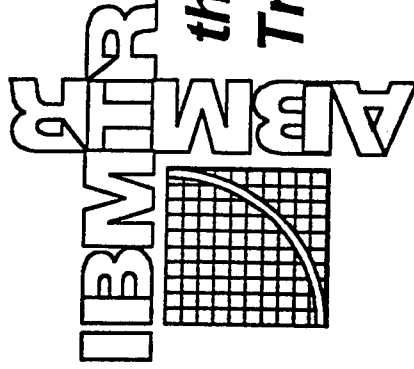
KBC96 6

**SURVIVAL AFTER AUTOTRANSPLANTS  
FOR PRIMARY (STAGE 2, 3 OR INFLAMMATORY)  
AND METASTATIC BREAST CANCER**



KBC96 7

# **PROGNOSTIC FACTORS IN AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER**



*A Report from*

*the Autologous Blood and Marrow  
Transplant Registry-North America*

# **OBJECTIVES**

- ***Determine outcome of autotransplants for metastatic breast cancer***
- ***Identify patient-, disease- and transplant-related factors associated with higher progression-free survival***



# **PATIENTS**

- *1,188 women receiving autotransplants for metastatic breast cancer from 1989-95*
- *Reported to the ABMTR by 63 institutions in North and South America*

# AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER - Patient and Disease Characteristics -

N: 1,188

Median age (range): 44 (18-70)y

ER status:	33%	Negative
	59%	Positive
	8%	Not Tested/borderline

Stage at diagnosis:	8%	Stage I
	32%	Stage II
	8%	Stage III
	33%	Not met, stage unknown
	19%	Metastatic

Type of initial surgery:	17%	Lumpectomy
	77%	Mastectomy
	6%	None

# **AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER**

## **- Prior Therapy -**

<b>Adjuvant chemotherapy:</b>	19% None
	24% CAF+ <u>o</u> ther
	31% CMF+ <u>o</u> ther
	7% Other
	19% Mets at diagnosis
<b>Radiation therapy pretransplant:</b>	52%
<b>Hormonal therapy pretransplant:</b>	51%
<b>Anthracycline pretransplant:</b>	83%
<b>Total anthracycline dose:</b>	240 (25-850) mg/m <sup>2</sup>
<b>Interval from dx to metastases:</b>	21 (<1-238)m
	19% Mets at diagnosis
	26% ≤ 18m
	55% > 18m
<b>Interval from met. to transplant:</b>	8 (<1-138)m



**AUTOTRANSPLANTS FOR  
METASTATIC BREAST CANCER**  
- Transplant Characteristics -

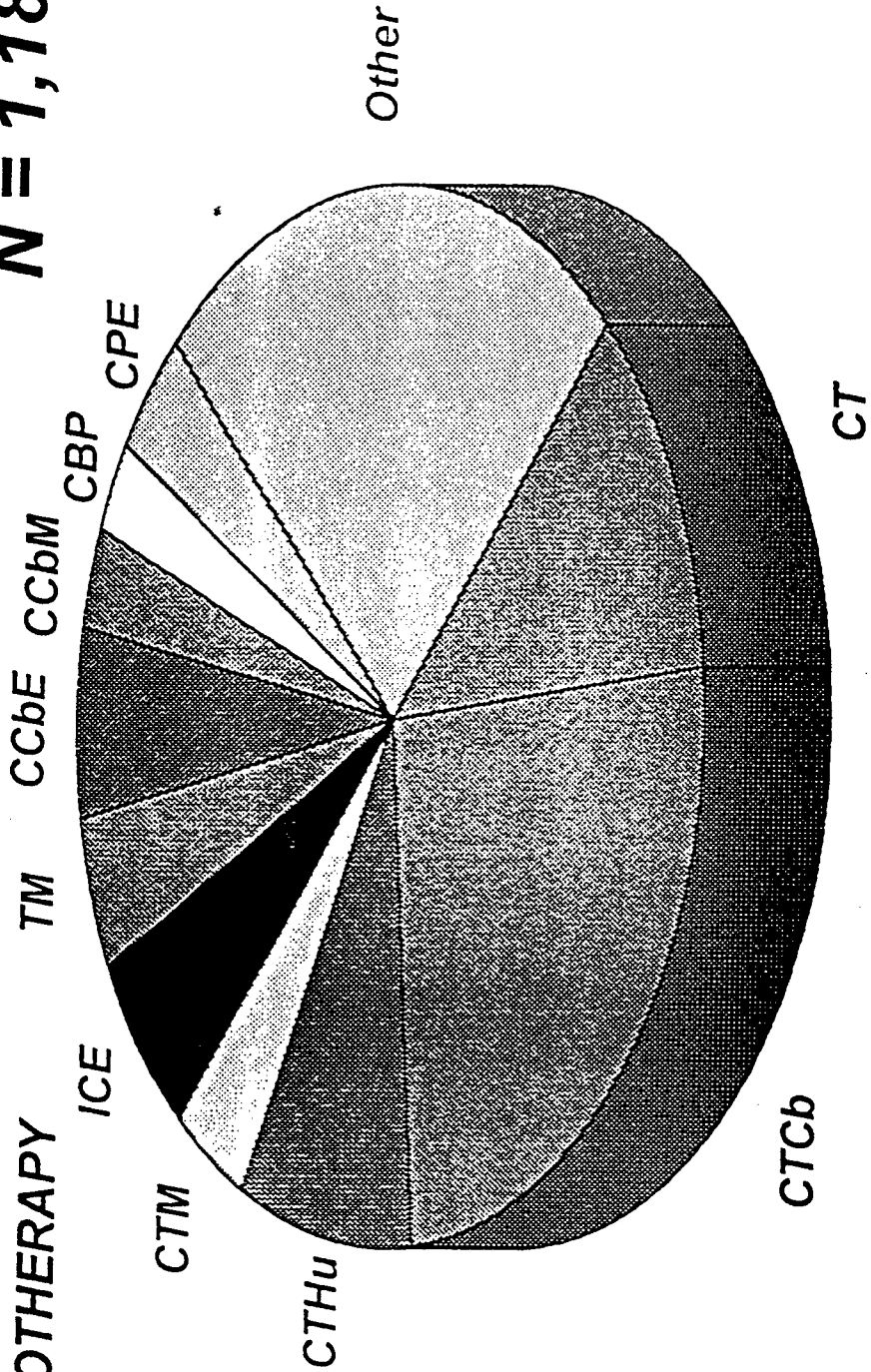
**Graft Source: 39% BM  
43% Blood  
18% BM + Blood**

**Growth factors  
posttransplant: 76%**

**Year of transplant: 17% 1989-90  
40% 1991-92  
43% 1993-95**

# AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER

HIGH-DOSE  
CHEMOTHERAPY **N = 1,188**



# MULTIVARIATE ANALYSIS I

- *Method: Cox proportional hazards regression*
- *Endpoint: Progression or death*

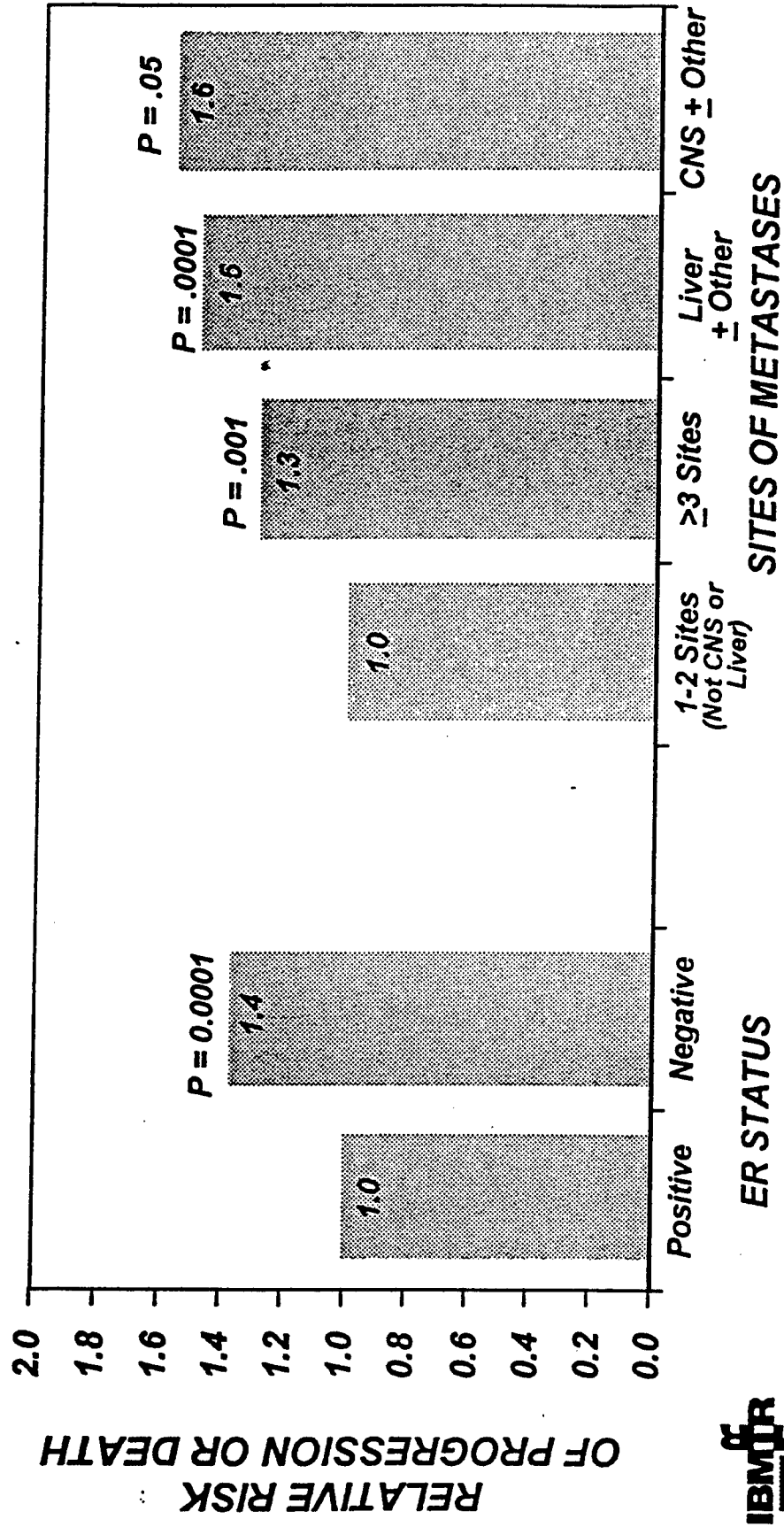
# MULTIVARIATE ANALYSIS II

## ■ Variables considered:

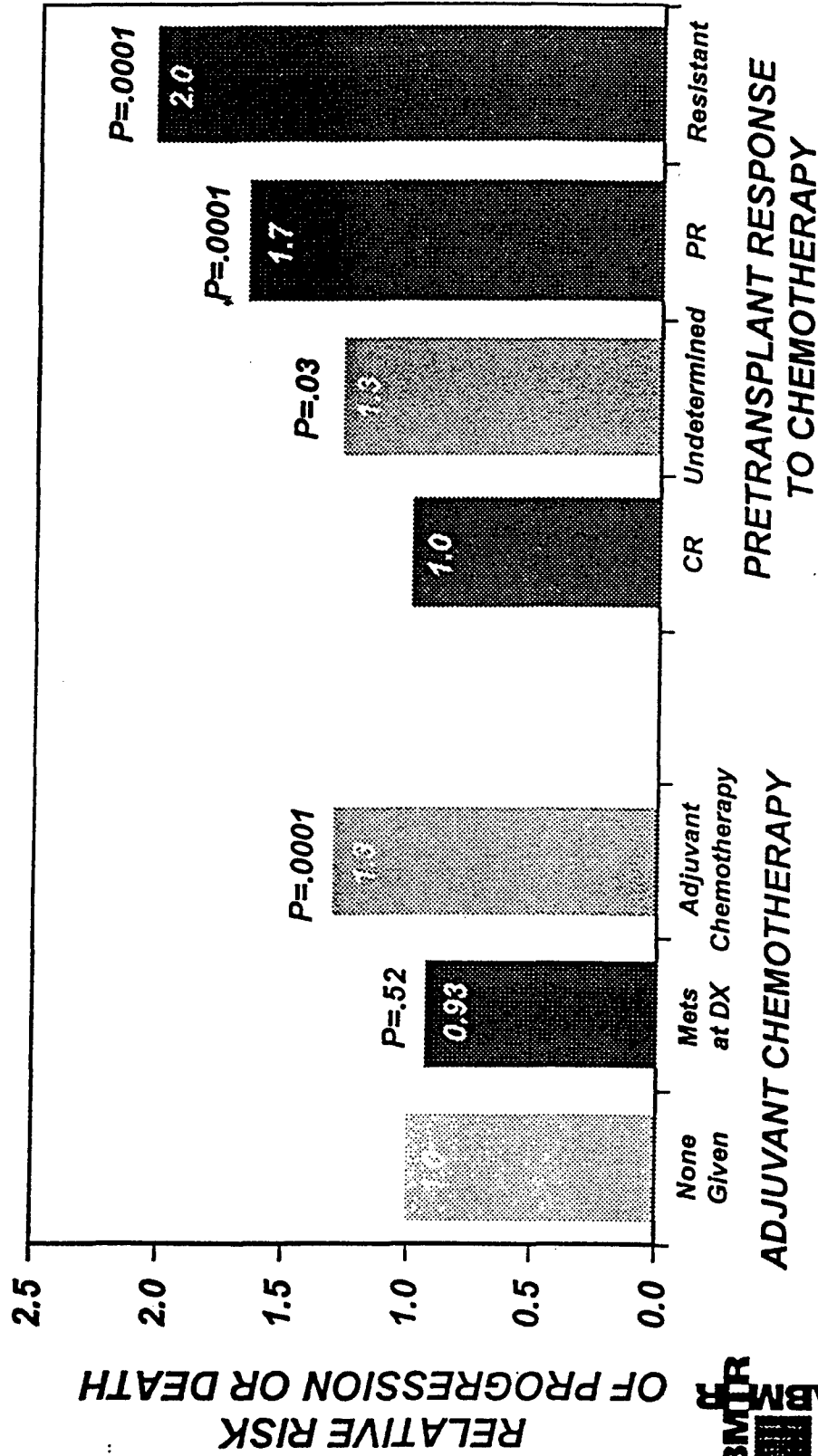
- Age
- ER status\*
- Stage at Dx
- Type of initial surgery
- Adjuvant chemotherapy\*
- Radiation therapy pretransplant
- Hormonal therapy pretransplant
- Anthracyclines pretransplant
- Interval from diagnosis to metastases
- Interval from metastases to transplant
- Sites of metastatic disease\*
- Response to chemotherapy\*
- Karnofsky Score pretransplant
- High-dose chemotherapy regimen
- Graft source
- Growth factors posttransplant
- Year of transplant



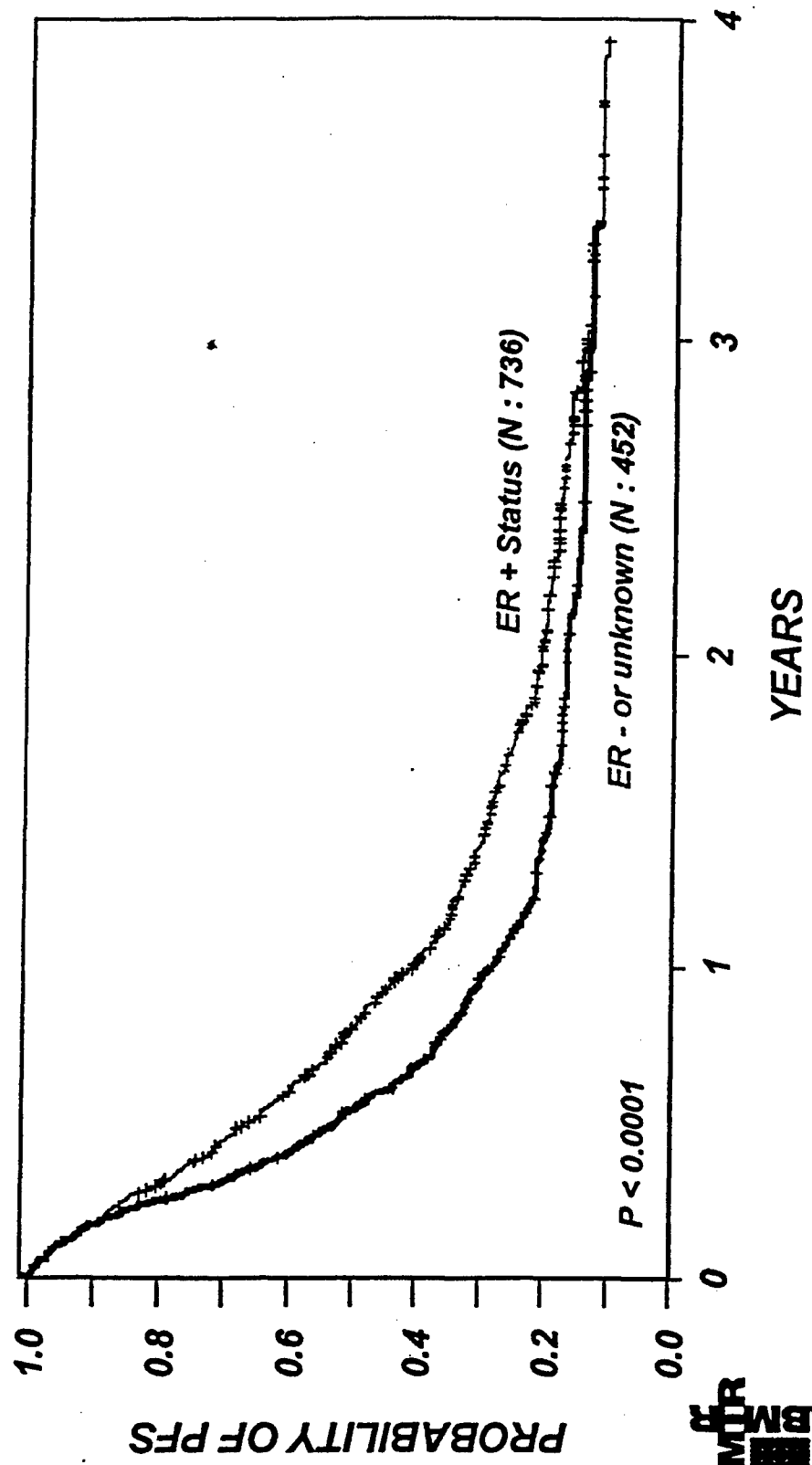
# AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER FACTORS ASSOCIATED WITH PFS



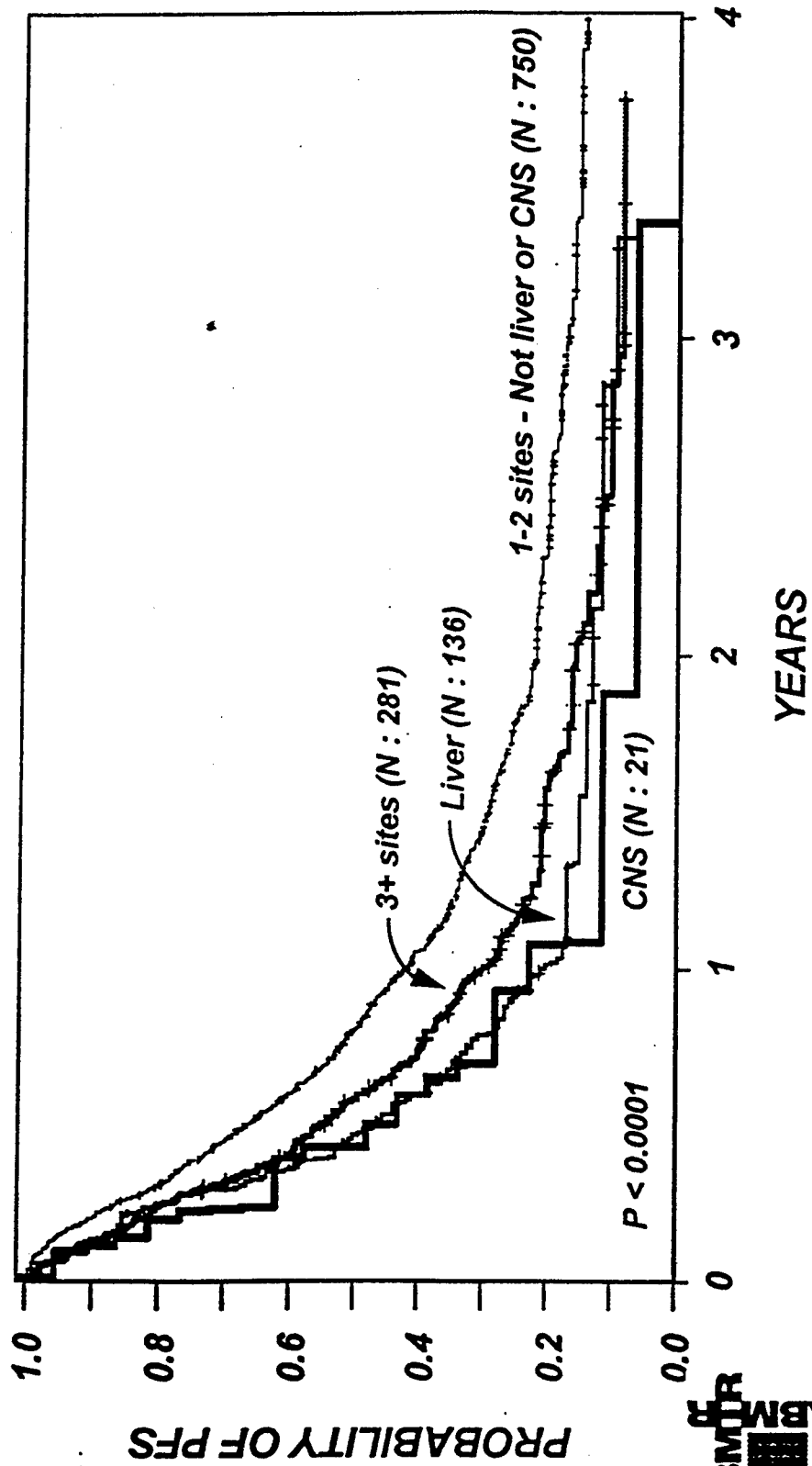
# AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER FACTORS ASSOCIATED WITH PFS



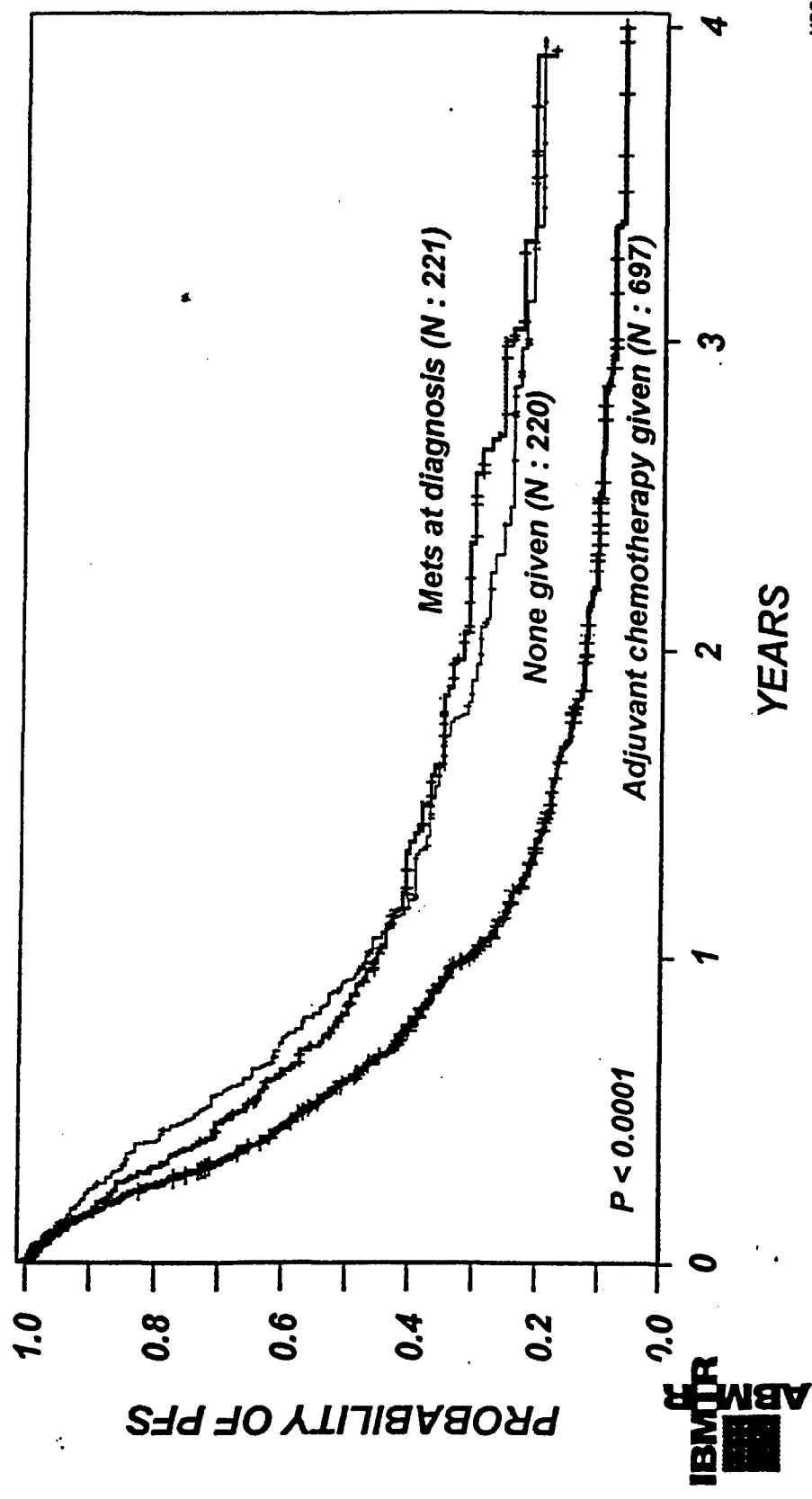
# PROBABILITY OF PROGRESSION-FREE SURVIVAL AFTER AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER BY ESTROGEN RECEPTOR STATUS



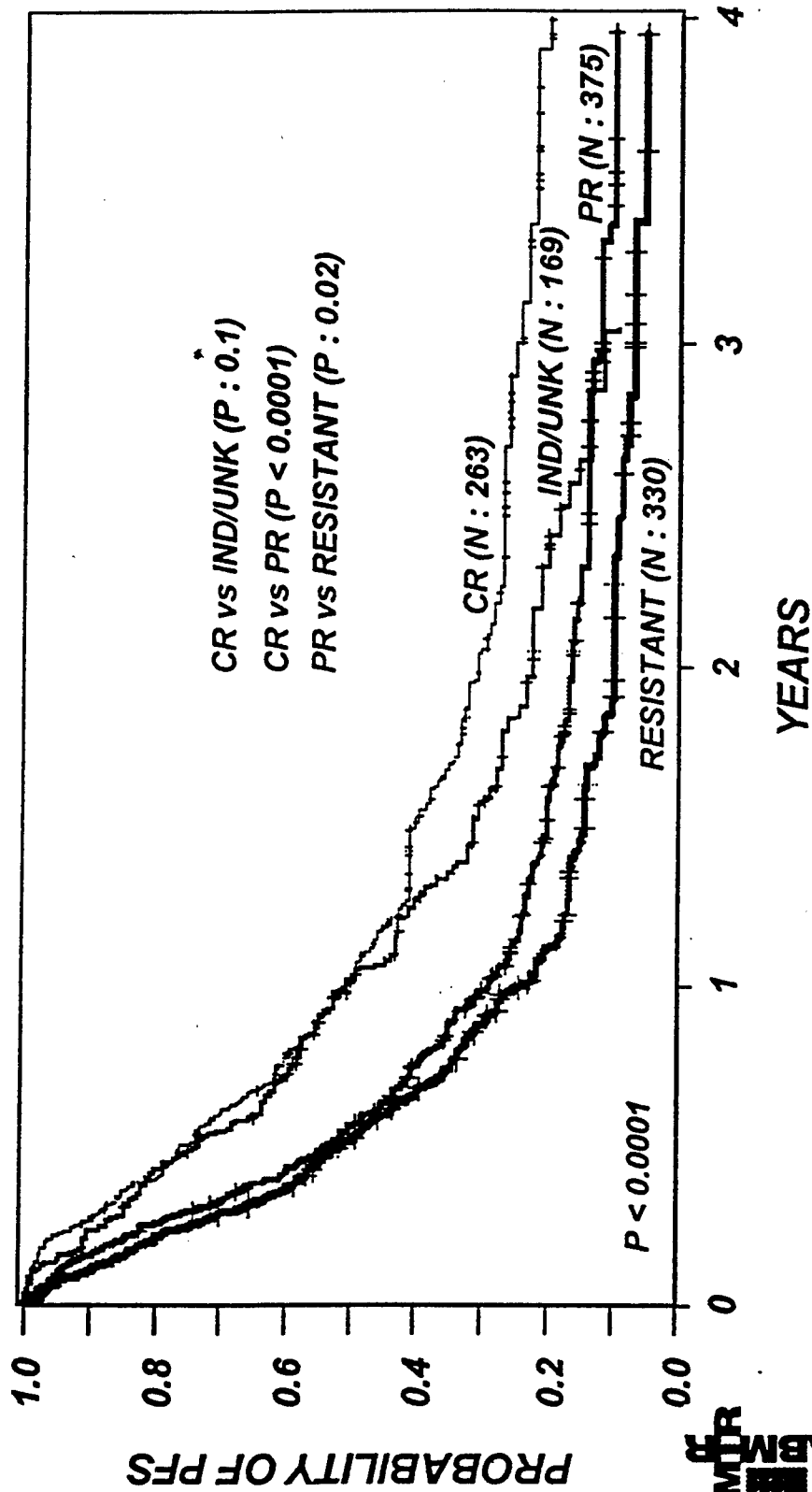
# PROBABILITY OF PROGRESSION-FREE SURVIVAL AFTER AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER BY SITES OF METASTATIC DISEASE PRETRANSPLANT



# PROBABILITY OF PROGRESSION-FREE SURVIVAL AFTER AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER BY ADJUVANT CHEMOTHERAPY



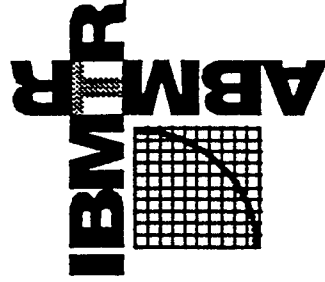
# PROBABILITY OF PROGRESSION-FREE SURVIVAL AFTER AUTOTRANSPLANTS FOR METASTATIC BREAST CANCER BY PRETRANSPLANT CHEMOTHERAPY SENSITIVITY



# CONCLUSIONS

- ***Higher progression-free survival:***
  - ***No prior adjuvant chemotherapy***
  - ***ER-positive disease***
  - ***No liver or CNS metastases***
  - ***Metastases limited to 1-2 sites***
  - ***CR prior to transplant***
- ***No difference in progression-free survival among most commonly used high-dose chemotherapy regimens***

**AUTOTRANSPLANTS FOR  
ACUTE HIGH RISK  
PRIMARY BREAST CANCER**



*A Preliminary Analysis from*

*Autologous Blood and Marrow  
Transplant Registry-North America*



# PATIENTS

- *466 women receiving autotransplants for Stage II (n = 206), Stage III (n = 191) or inflammatory (n = 69) breast cancer*
- *Autotransplant done 1989-1995 in 52 centers reporting data to the ABMTR*

**AUTOTRANSPLANTS FOR  
HIGH-RISK PRIMARY BREAST CANCER  
Patient Characteristics 1**

**N: 466**

**Median age (range): 43 (24-66) y**

**Performance Score <90: 5%**

**ER status: 33% Negative**

**60% Positive**

**7% Not tested/borderline**

**Number of axillary nodes: 20 (0-40)**

**4% ≤9**

**96% >9**

**Size of primary tumor: 16% <2 cm**

**45% 2-4 cm**

**39% >4 cm**

**AUTOTRANSPLANTS FOR  
HIGH-RISK PRIMARY BREAST CANCER**  
**Prior Treatment**

**Surgery pretransplant:** 11% Lumpectomy  
85% Mastectomy  
4% None

**Adjuvant chemotherapy:** 65% CAF/FAC  
27% Other adriamycin  
8% Other

**Radiation therapy pretransplant:** 15%

**Hormonal therapy pretransplant:** 13%

**Interval diagnosis to transplant:** 7 (3-18) m

**AUTOTRANSPLANTS FOR  
METASTATIC BREAST CANCER**  
*Transplant Characteristics*

**Graft source: 46% BM  
27% PBSC  
27% BM & PBSC**

**Growth factors posttransplant: 93%**

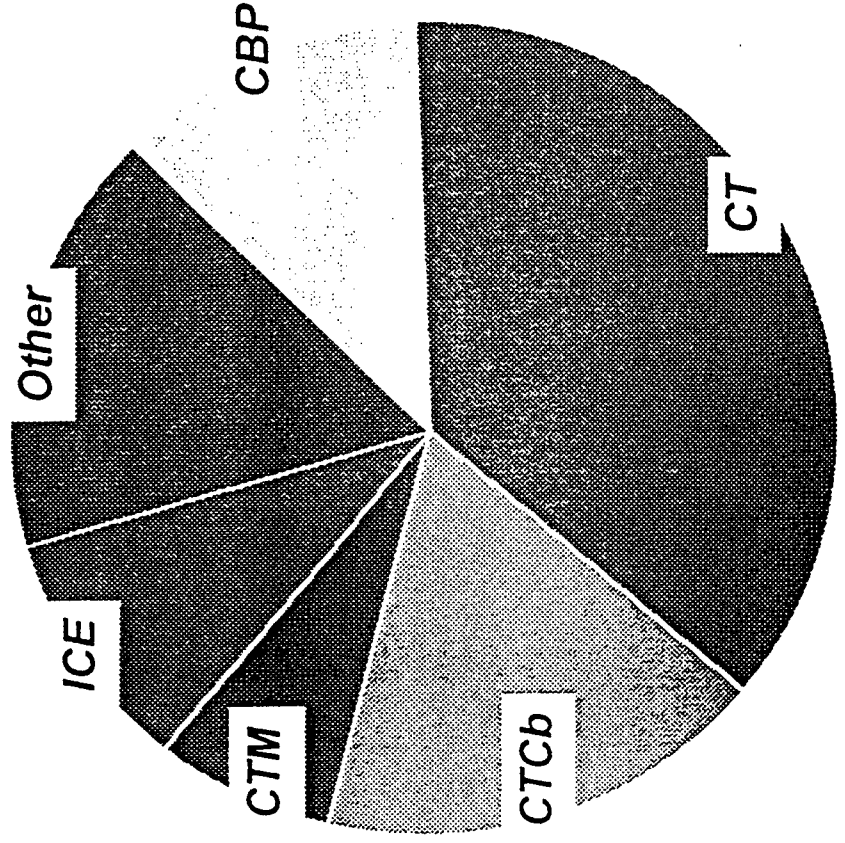
**Radiation posttransplant: 60%**

**Hormone therapy posttransplant: 43%**

**Year of transplant: 5% 1989-90  
35% 1991-92  
61% 1992-95**

# AUTOTRANSPLANTS FOR HIGH-RISK PRIMARY BREAST CANCER

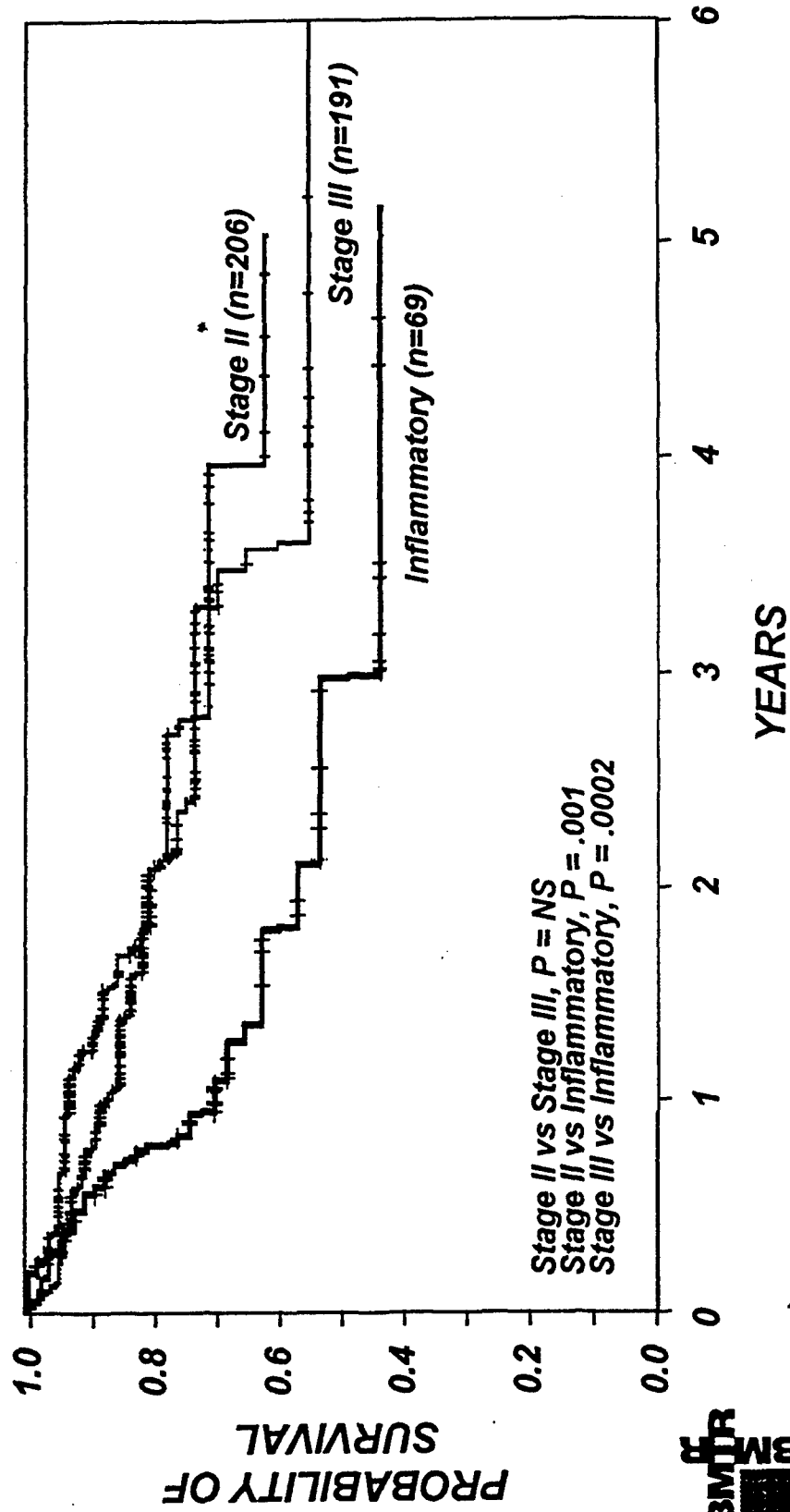
N = 466



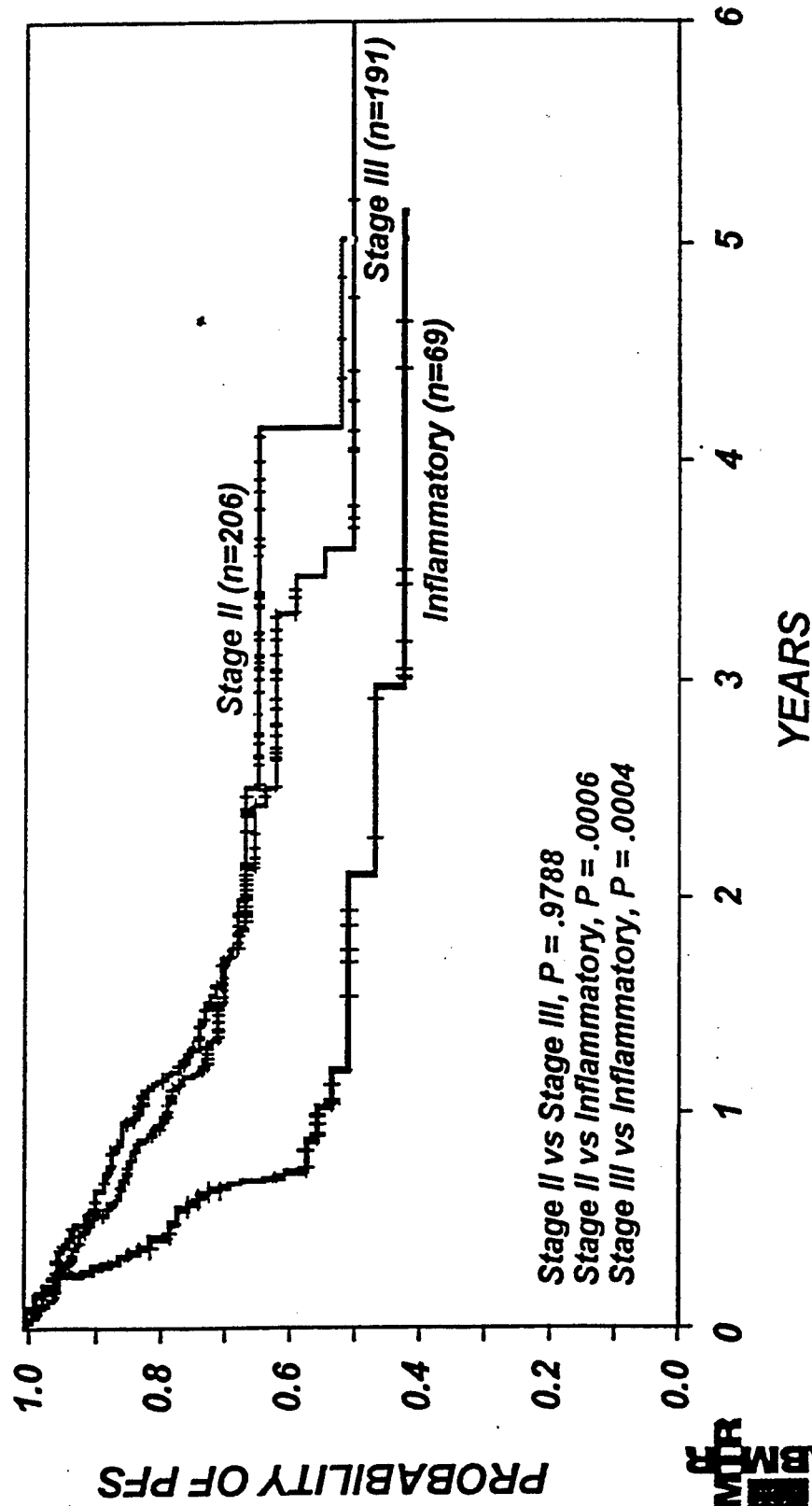
HIGH-DOSE  
CHEMOTHERAPY



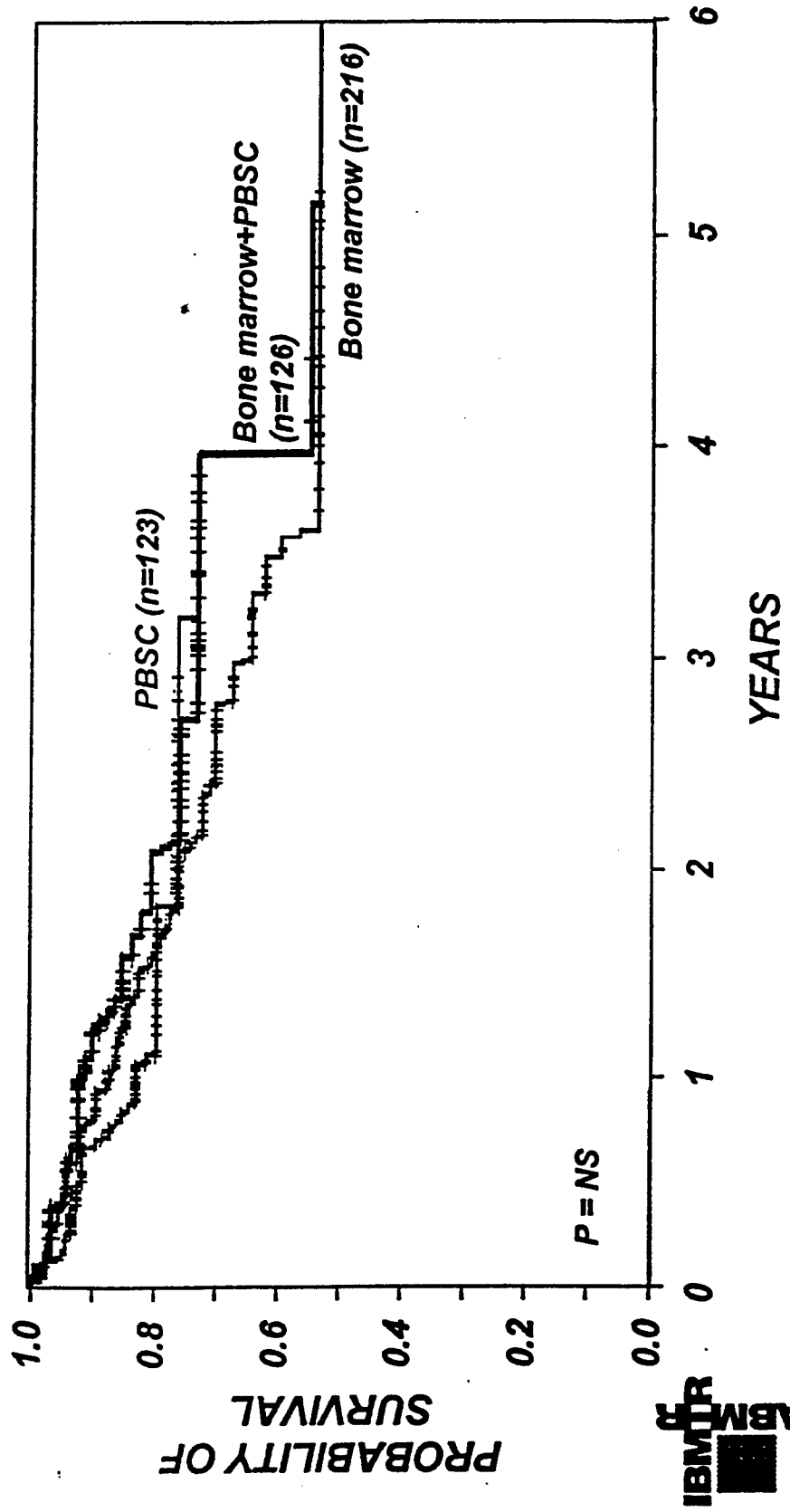
**PROBABILITY OF SURVIVAL  
AFTER AUTOTRANSPLANT FOR  
HIGH-RISK PRIMARY BREAST CANCER  
1989-1995**



# PROBABILITY OF PFS AFTER AUTOTRANSPLANT FOR HIGH-RISK PRIMARY BREAST CANCER 1989-1995

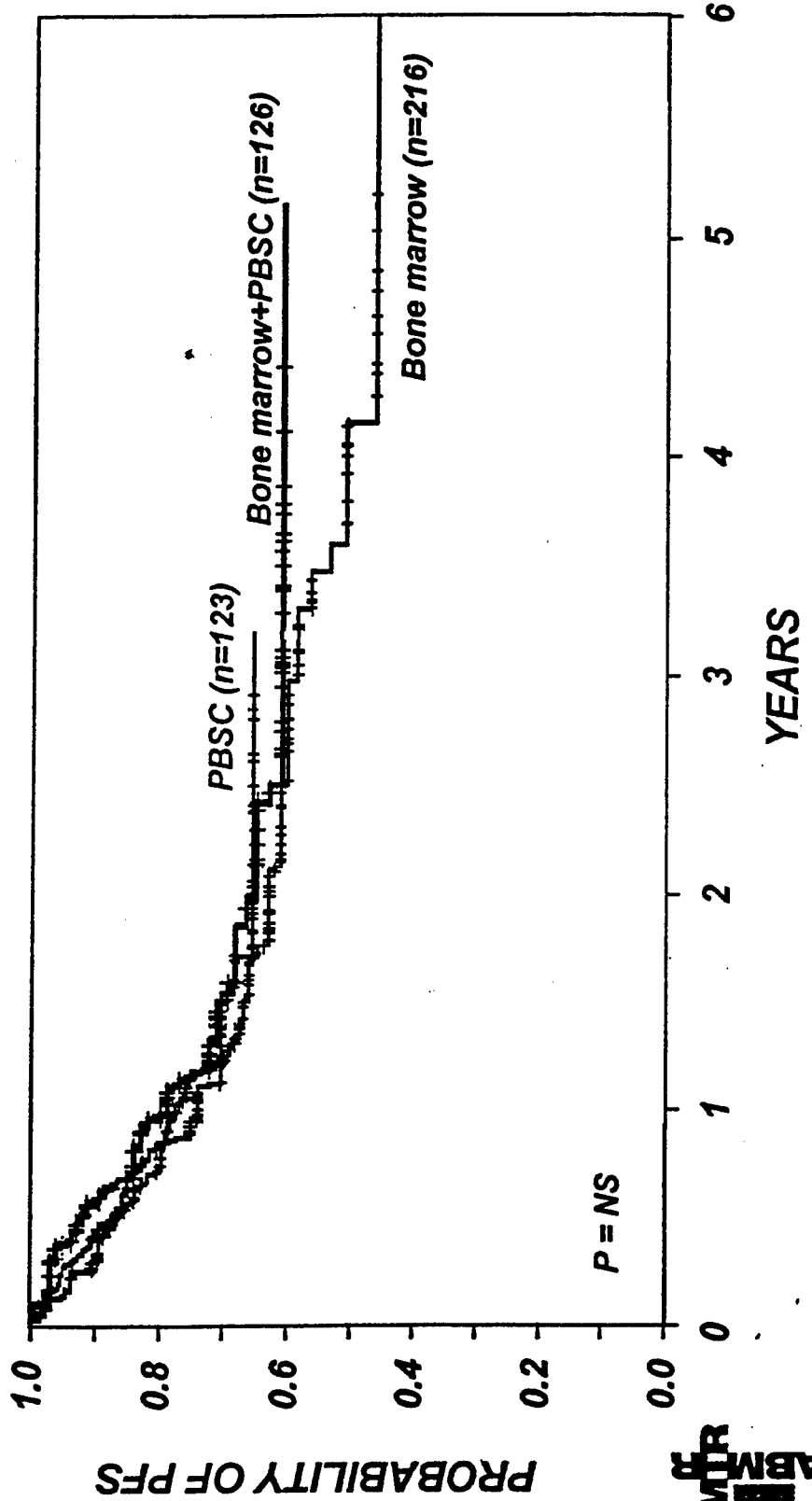


# PROBABILITY OF SURVIVAL AFTER AUTOTRANSPLANT FOR HIGH-RISK PRIMARY BREAST CANCER, BY GRAFT TYPE

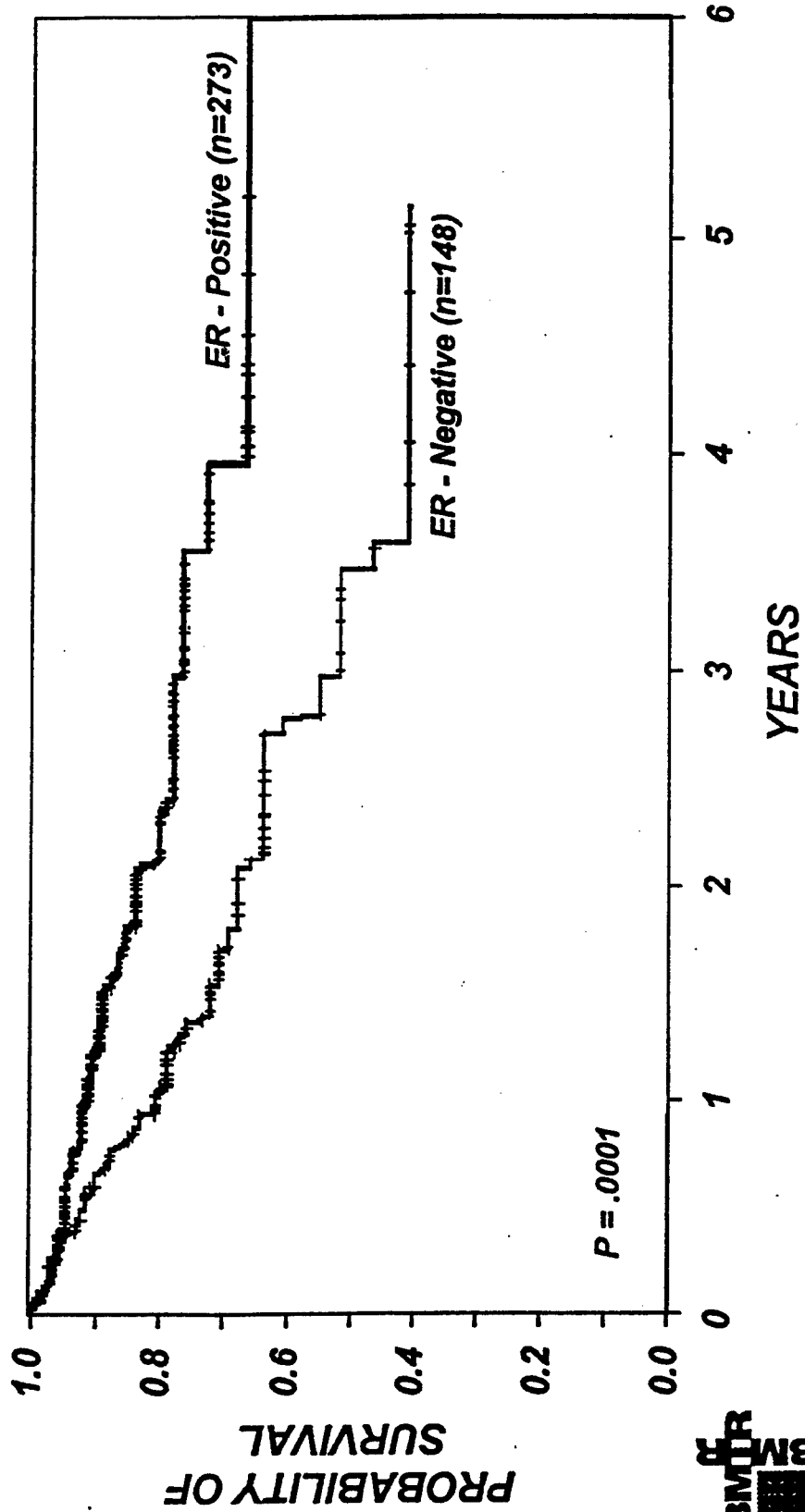




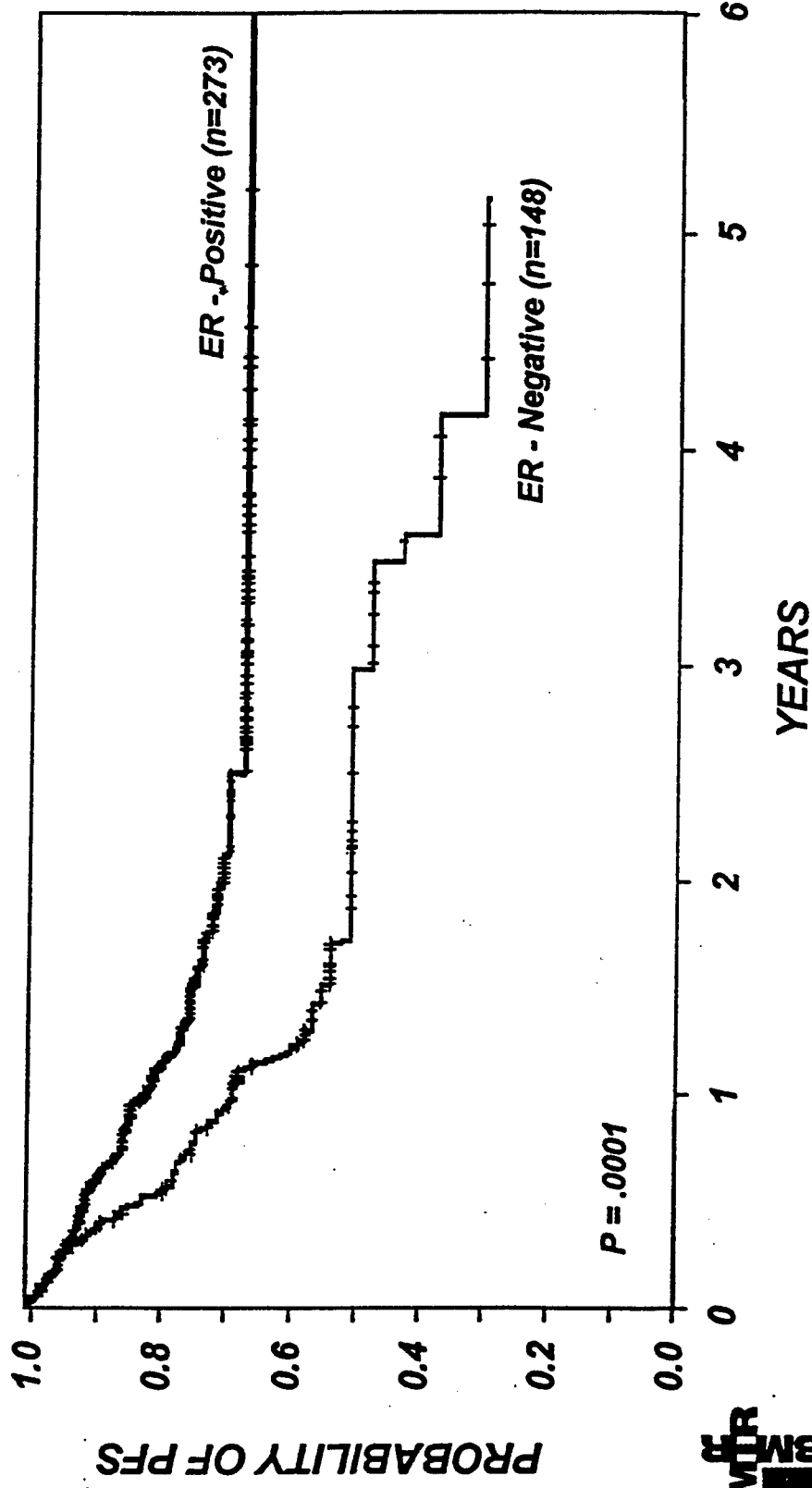
# PROBABILITY OF PFS AFTER AUTOTRANSPLANT FOR HIGH-RISK PRIMARY BREAST CANCER BY GRAFT TYPE



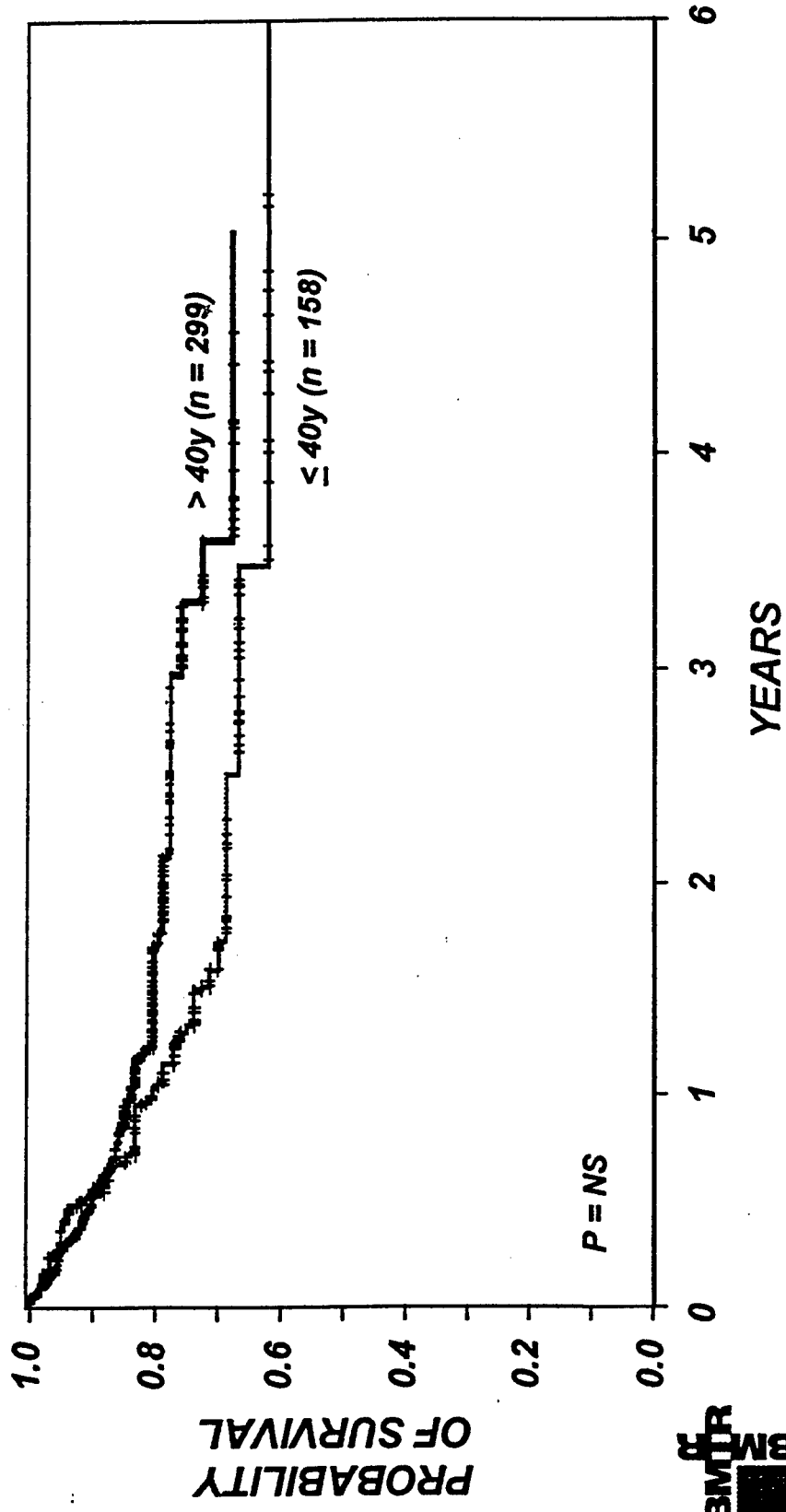
# PROBABILITY OF SURVIVAL AFTER AUTOTRANSPLANT FOR HIGH-RISK PRIMARY BREAST CANCER, 1989-1995



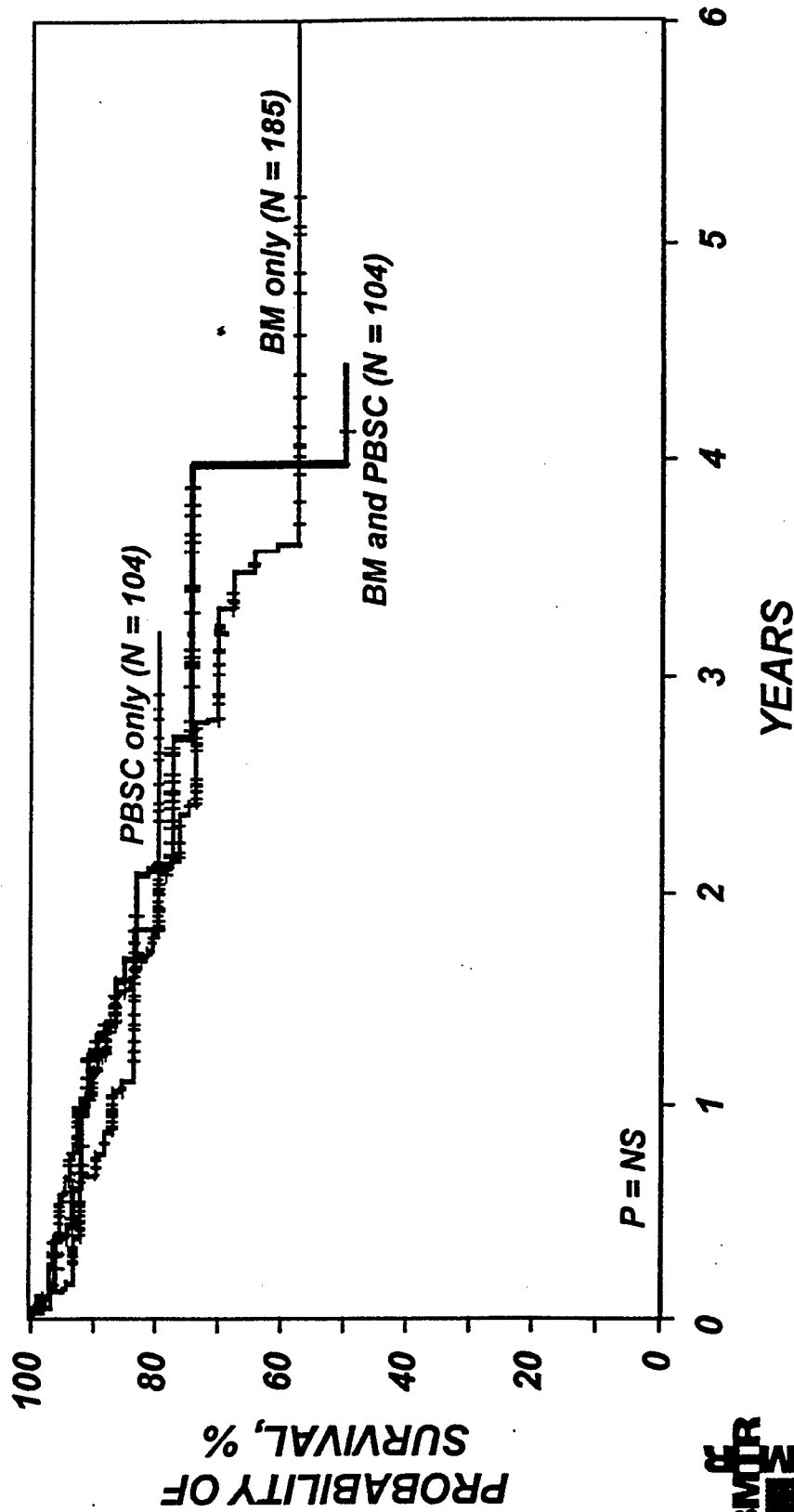
# PROBABILITY OF PFS AFTER AUTOTRANSPLANT FOR HIGH-RISK PRIMARY BREAST CANCER 1989-1995



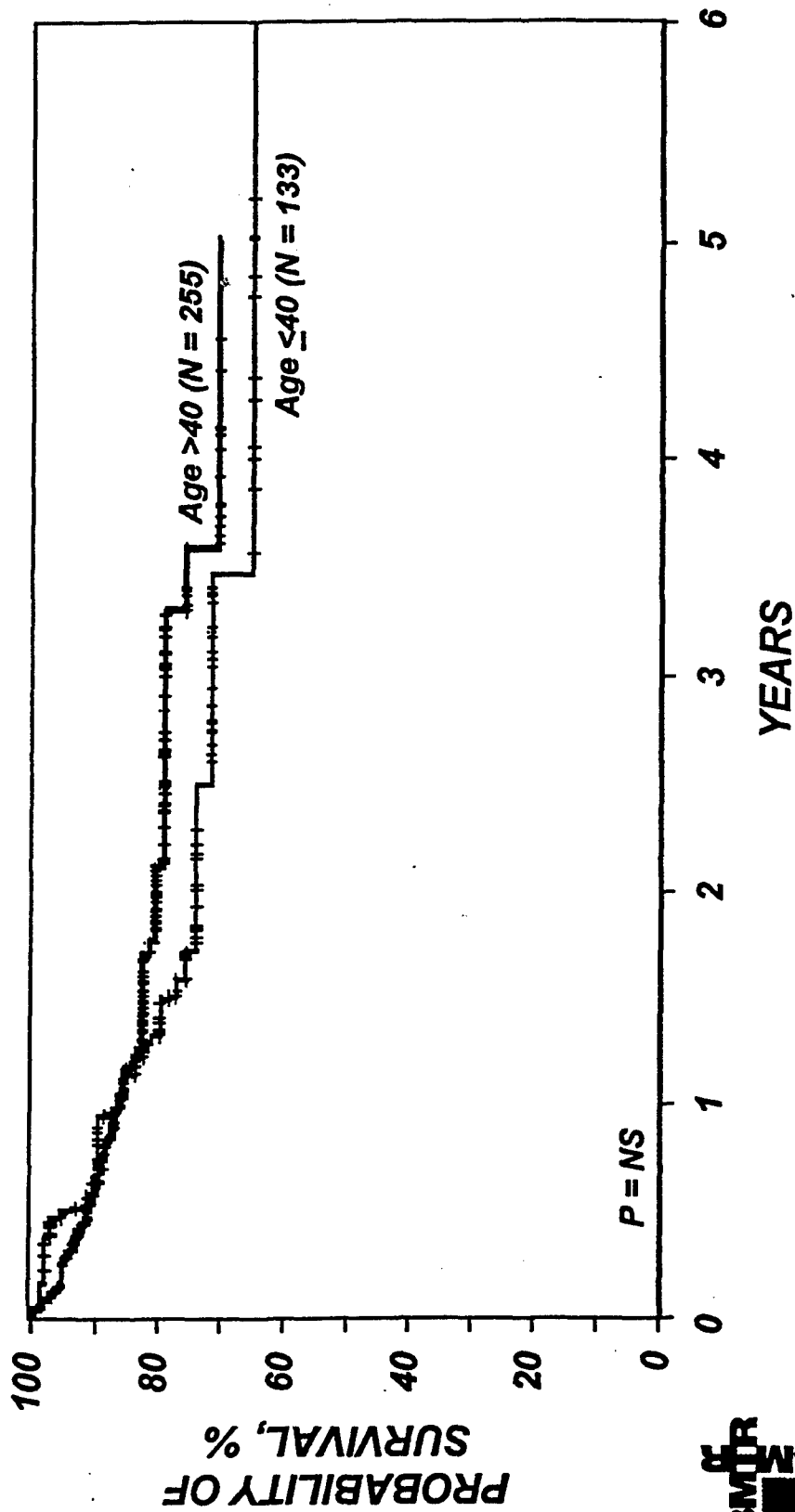
# PROBABILITY OF SURVIVAL AFTER AUTOTRANSPLANT FOR HIGH-RISK PRIMARY BREAST CANCER BY AGE AT TRANSPLANT



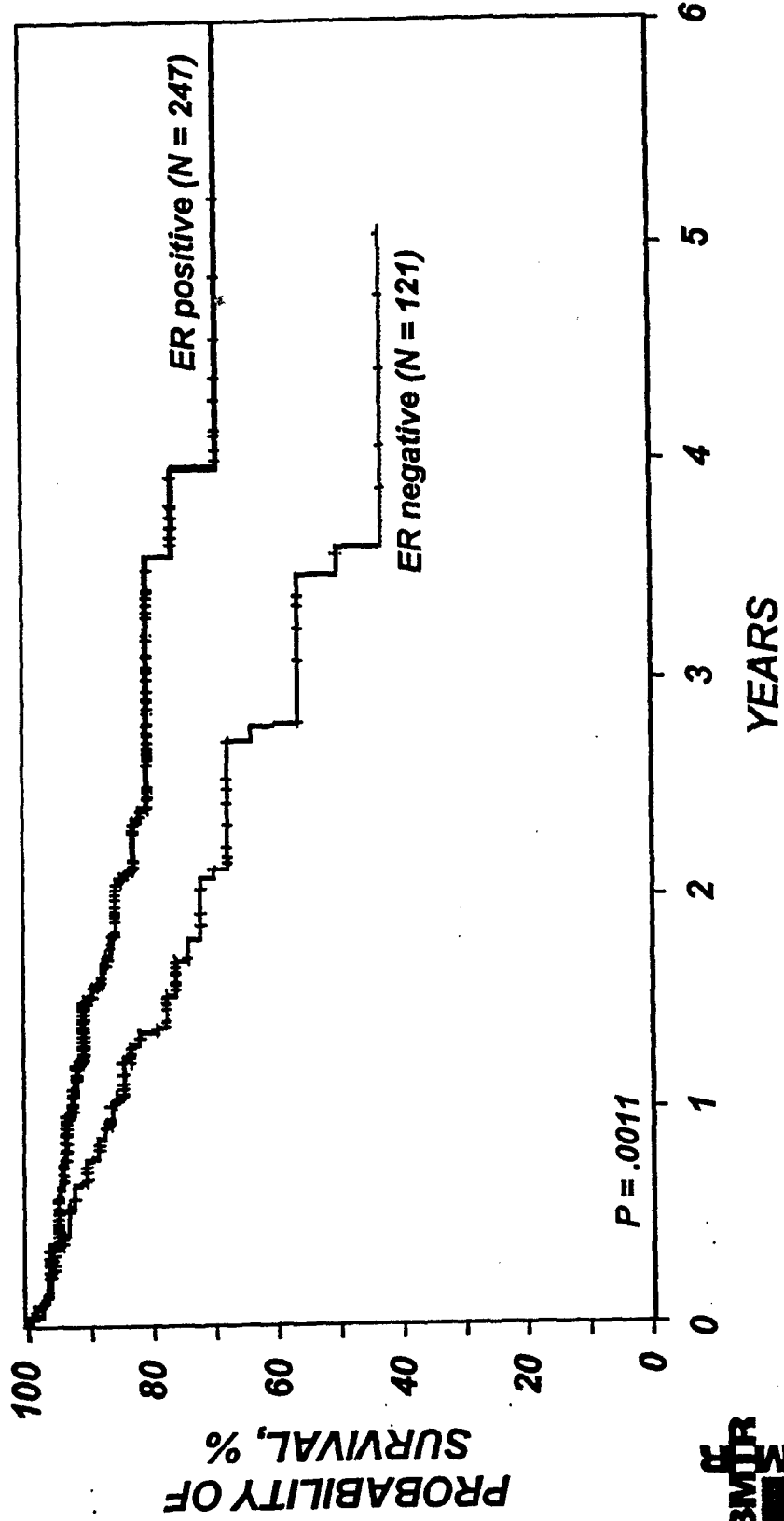
# PROBABILITY OF SURVIVAL AFTER AUTOTRANSPLANTS FOR STAGE II / III BREAST CANCER BY GRAFT TYPE, 1989-1995



# PROBABILITY OF SURVIVAL AFTER AUTOTRANSPLANTS FOR STAGE II / III BREAST CANCER BY AGE AT TRANSPLANT



# PROBABILITY OF SURVIVAL AFTER AUTOTRANSPLANTS FOR STAGE II / III BREAST CANCER BY ESTROGEN RECEPTOR STATUS, 1989-1995



# QUESTIONS

*Does high-dose chemotherapy cure breast cancer?*

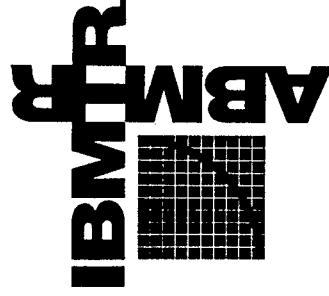
*Does high-dose chemotherapy prolong survival?*

*Can efficacy be improved by altering drugs, doses and/or schedules?*

*Are there late effects of high-dose chemotherapy?*



# **AUTOTRANSPLANTS IN MEN WITH BREAST CANCER**



*A Report from*

---

*the Autologous Blood & Marrow  
Transplant Registry*

# **MALE BREAST CANCER**

- **<1% of all breast cancers**
- **Annual Incidence: <1 in 100,000 men**
- **More advanced stage at presentation**
- **Median Age: 5-10 yrs greater than women**
- **80-90% estrogen and progesterone receptor positive**

# **MALE BREAST CANCER**

## **- Outcomes -**

- **Same as for women when matched for histopathology, receptor state and disease stage**
  - **Willsher et al. Ann J Surg, 1997**
  - **Cutuli et al. Eur J Cancer, 1995**
  - **Donegan & Redlich. Surg Clin N Amer, 1996**
  - **Borgen et al, Ann Surg Oncol, 1997**
  
- **Poorer outcome**
  - **Joshi et al. Cancer, 1996**

# **MALE BREAST CANCER**

## **- Therapy -**

- **Surgery**
- **Radiation**
- **Chemotherapy**
- **Hormone therapy**
- **What is the role of autotransplant?**

## **MALE BREAST CANCER - Autotransplants -**

- **13 of 3,254 autotransplants for breast cancer reported to the ABMTR**
- **January, 1989 to January, 1996**
- **Treated at 11 centers**
- **10 autotransplants as adjuvant therapy**
- **3 autotransplants for Stage 4 disease**

# AUTOTRANSPLANTS IN MEN WITH BREAST CANCER

## - Patient and Disease Characteristics (I) -

<b>Number</b>	<b>13</b>
<b>Age, median (range) y</b>	<b>50 (32-60) y</b>
<b>KPS pretransplant</b>	
<b>&gt;90%</b>	<b>12 (92%)</b>
<b>80%</b>	<b>1 (8%)</b>
<b>Stage</b>	
<b>II</b>	<b>6 (46%)</b>
<b>III</b>	<b>3 (23%)</b>
<b>III inflammatory</b>	<b>1 (8%)</b>
<b>IV</b>	<b>3(23%)</b>

**AUTOTRANSPLANTS IN MEN WITH BREAST CANCER**  
**- Patient and Disease Characteristics (II) -**

<b>Estrogen receptor positive</b>	<b>12/12 (100%)</b>	<b>1 not tested</b>
<b>Progesterone receptor positive</b>	<b>11/12 (92%)</b>	<b>1 not tested</b>
<b>Number of positive axillary nodes, median (range)</b>	<b>14 (0-21)</b>	<b>6 Stage II pts <math>\geq</math>10+ nodes</b>
<b>Mastectomy pretransplant</b>	<b>12/13 (92%)</b>	
<b>Interval from Dx <math>\rightarrow</math> BMT, median (range)</b>	<b>6 (4-9) m</b>	<b>12, 31, 32m</b>
	<b>10 adj pts</b>	<b>3 met pts</b>

# AUTOTRANSPLANTS IN MEN WITH BREAST CANCER

## - Transplant Characteristics -

<b>N</b>	<b>13</b>
<b>Graft source</b>	
<b>Bone marrow</b>	<b>3 (23%)</b>
<b>PBSC</b>	<b>8 (62%)</b>
<b>Bone marrow + PBSC</b>	<b>2 (15%)</b>
<b>Conditioning regimen</b>	
<b>Cyclophosphamide + Thiotepa + Carboplatin</b>	<b>5 (38%)</b>
<b>Alkylator based regimen</b>	<b>8 (62%)</b>



# **AUTOTRANSPLANTS IN MEN WITH BREAST CANCER**

## **- Outcomes (I) -**

***Time to ANC >1,000 cells /  $\mu$ l, median (range) 12 (8-22) d***

***Time to platelets >25,000 /  $\mu$ l, median (range) 14 (6-20) d***

***Non-myeloid grade 4 toxicity 0***

***Myelodysplastic syndrome 0***

***Primary chest wall radiation, adj pts 9***

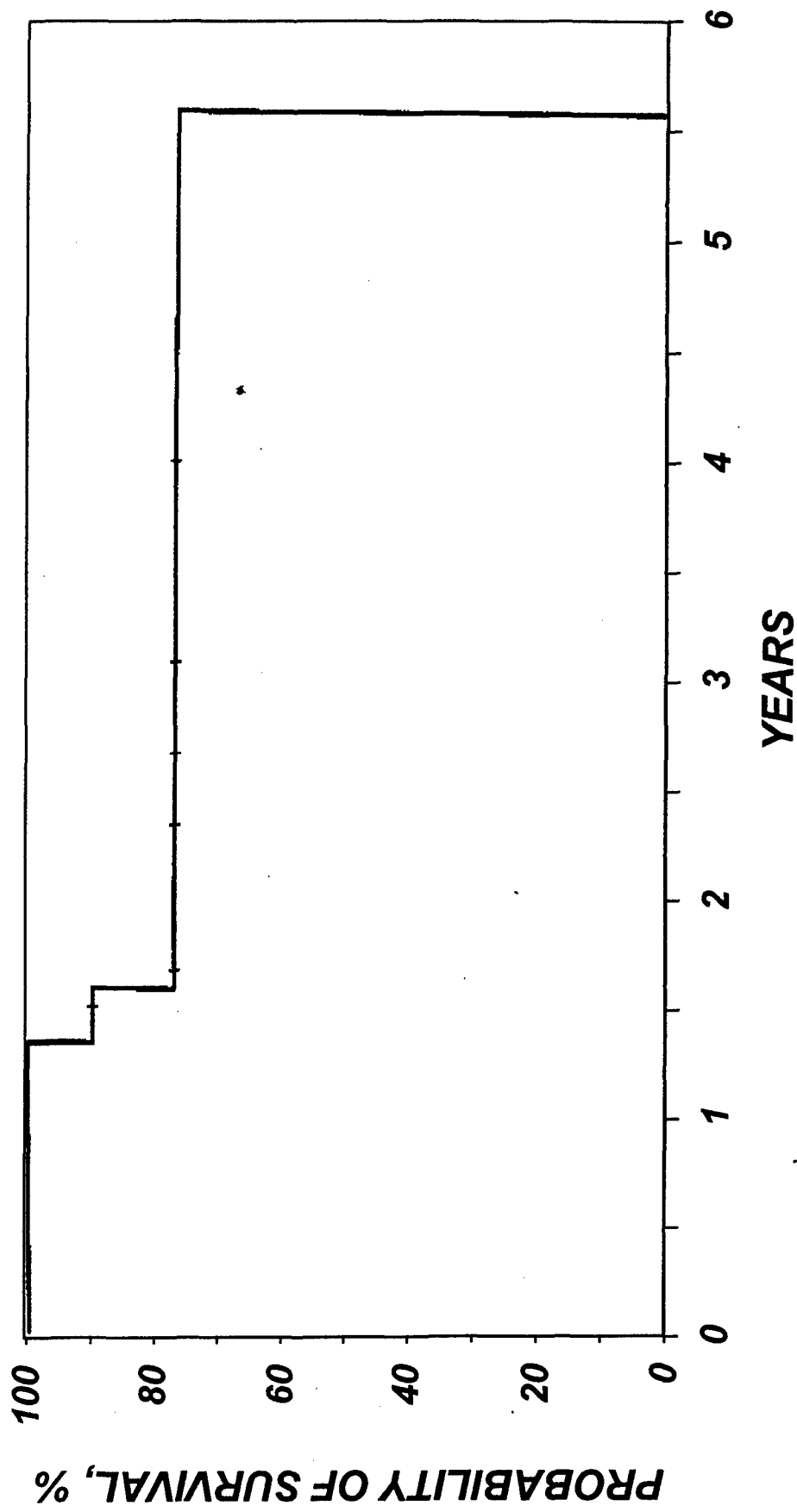
***Hormonal therapy post BMT, adj pts 6***

# **AUTOTRANSPLANTS IN MEN WITH BREAST CANCER**

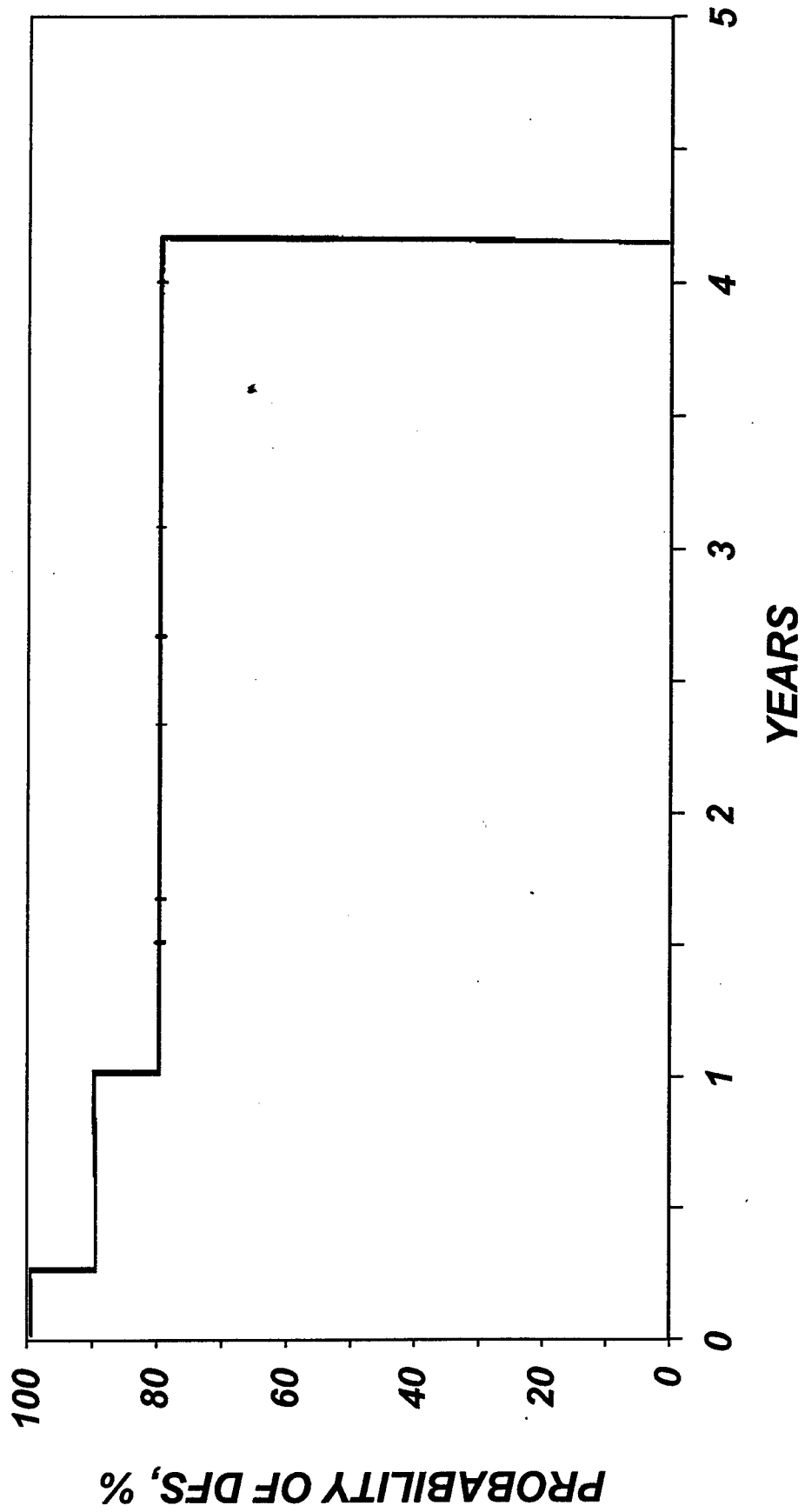
## **- Outcomes (II) -**

	<b>Disease-free Survival, median, range</b>	<b>Disease-free</b>	<b>Relapses, time after BMT</b>	<b>Death, time after BMT</b>
<b>Adjuvant patients</b>	<b>23 (6-50) m</b>	<b>7/10 (70%)</b>	<b>3, 5, 50m</b>	<b>16, 19, 67m</b>
<b>Metastatic patients</b>	<b>Not applicable</b>	<b>0/3 (0%)</b>	<b>5, 7, 16m</b> <b>2 CR, 1 SD</b>	<b>12, 13m</b> <b>1 alive @ 27m</b>

# PROBABILITY OF SURVIVAL AFTER AUTOLOGOUS TRANSPLANTS IN MALES WITH HIGH-RISK PRIMARY BREAST CANCER



**PROBABILITY OF DFS AFTER  
AUTOLOGOUS TRANSPLANTS IN MALES WITH  
HIGH-RISK PRIMARY BREAST CANCER**



## **CONCLUSIONS (I)**

- *The outcome of men with breast cancer receiving autotransplants appears comparable to women treated with identical therapy for similar stage disease*
- *Patients treated with autotransplant for high risk,  $\geq 10$  node positive disease or Stage III disease appear to do well with this therapy*

## **CONCLUSIONS (II)**

- *Few metastatic disease patients' disease have been treated with autotransplant*
- *No patients developed non-myeloid grade 4 toxicity or myelodysplasia*
- *Most patients received additional therapy consisting of radiation or hormone treatment*

## **CONCLUSIONS (III)**

- *Indications for high-dose therapy that develop in trials in women should be applicable in men*
- *Reporting of cases to the ABMTR is encouraged*
- *Should male breast cancer patients be included in large randomized studies for women with breast cancer?*

# **INVESTIGATORS**

- **DD Hurd, MD**
- **PA Rowlings, MD, MS**
- **SC Murphy, MS**
- **KS Antman, MD**
- **JO Armitage, MD**
- **D Cirenza, MD**
- **M Crump, MD, FRCPC**
- **J Doroshower, MD**
- **CO Freytes, MD**
- **RP Gale, MD, PhD**
- **LA Kalman, MD**
- **HM Lazarus**
- **WP Vaughn**
- **BB Weinberger, DO, MPH**
- **MC Wiemann, MD**
- **MM Horowitz, MD, MS**



## MAYER VENTURES

---

CLARENCE MAYER (713) 736-8636

FACSIMILE (713) 286-2980

 ASS: JILL NEEDHAM (713) 735-8526  
 INTERNET E-MAIL needhamj@ammg-law.com

 5647 SAN ANTONIO  
 SUITE 1700  
 HOUSTON, TEXAS 77057

 STARCHEM, LTD.  
 POTOMAC GROUP HOME CORPORATION  
 MAYER CATTLE COMPANY, LTD.  
 MAYER FARMS  
 HOLIDAY LODGE, L.P.  
 JACINTO CITY, L.P.  
 LYNN LODGE, L.P.  
 RETAMA MANOR, L.P.  
 SOUTHFIELD, L.P.  
 SPRING BRANCH, L.P.  
 VILLAGE, L.P.

December 16, 1998

Via Facsimile: 414/456-6530

Dr. Mary Horowitz  
 IBMTR/ABMTR  
 Medical College of Wisconsin  
 8701 Watertown Plank Rd.  
 Milwaukee, Wisconsin 53226

Dear Dr. Horowitz:

As you are aware, my wife Dede has recurrent breast cancer in the bone marrow. After Dede's recurrence of breast cancer, we met with the top high dose chemotherapy doctors in the country, as well as the top breast oncologist. We were always given anecdotal information, but there was no hard data from which an analytical decision could be made.

I offered to fund a program between three of the major hospitals to create a common database for high dose treatment of breast cancer. At first, all three hospitals agreed, but in the end, there was no follow-through or real commitment, and the proposal was not implemented.

The emphasis among the best doctors and hospitals is to develop a cure or better treatment than currently exist. Our problem has been to try to find the best available known treatment. There is a lack of hard data on outcome for breast cancer patients with specific characteristics of illness. Your national database for high dose chemotherapy has been the best source of information to evaluate the risk and benefits of high dose versus conventional dose therapy. Your information has been extremely beneficial to my wife in helping her make her decision for treatment.

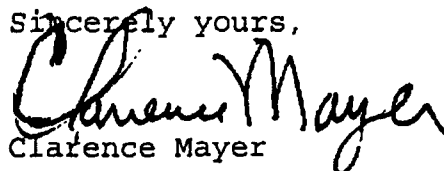
I believe that in all areas of treatment, a database should exist which allows patients and physicians access to data which shows outcome for patients who have certain characteristics of illness.

Dr. Mary Horowitz  
December 16, 1998

Page 2

I believe your program sets the standard that should be available for treatment of all serious illness. We very much appreciate your help, guidance and support.

Sincerely yours,

  
Clarence Mayer

CM/jn

cc: Mrs. Dede Mayer  
Ms. Sylvia Mayer Baker  
Ms. Laura Mayer

mayece:0225571:121698



DEPARTMENT OF THE ARMY  
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND  
504 SCOTT STREET  
FORT DETRICK, MARYLAND 21702-5012

REPLY TO  
ATTENTION OF:

MCMR-RMI-S (70-1y)

28 Jan 00

MEMORANDUM FOR Administrator, Defense Technical Information  
Center, ATTN: DTIC-OCA, 8725 John J. Kingman  
Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical report written for Grant DAMD17-95-1-5002. Request the limited distribution statement for Accession Document Number ADB247840 be changed to "Approved for public release; distribution unlimited." This report should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Virginia Miller at DSN 343-7327 or by email at virginia.miller@det.amedd.army.mil.

FOR THE COMMANDER:

PHYLLIS M. RINEHART  
Deputy Chief of Staff for  
Information Management