AD_____

COOPERATIVE AGREEMENT NO: DAMD17-94-V-4012

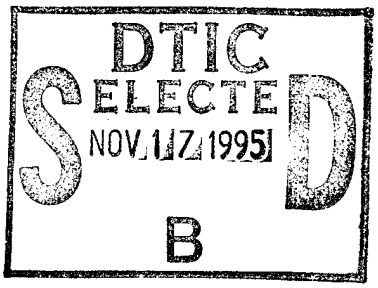
TITLE: PET-FDG Imaging in Metastatic Breast Cancer Treated With High Dose Chemotherapy and Stem Cell Support

PRINCIPAL INVESTIGATOR(S): Doctor Abass Alavi

CONTRACTING ORGANIZATION: University of Pennsylvania
Philadelphia, Pennsylvania 19104-3246

REPORT DATE: September 1995

TYPE OF REPORT: Annual



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

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 1995	Annual 1 Sep 94 - 31 Aug 95

4. TITLE AND SUBTITLE
PET-FDG Imaging in Metastatic Breast Cancer Treated with High Dose Chemotherapy and Stem Cell Support

5. FUNDING NUMBERS
DAMD17-94-V-4012

6. AUTHOR(S)
Dr. Abass Alavi

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Pennsylvania
Philadelphia, Pennsylvania 19104-3246

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
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

The study is designed to assess the effectiveness of PET-FDG imaging in patients with metastatic breast cancer who are being treated with high dose chemotherapy and stem cell rescue. This study was to include a homogeneous group of patients entered on two studies (PBT-1 and Protocol UPCC #1192) for the treatment of breast cancer with high dose chemotherapy. We have amended our study by adding protocol UPCC #3195 as an additional source of patient accrual. The chemotherapy protocol #3195 is identical to the chemotherapy regimen used in PBT-1, but with peripheral stem cell rescue. Until now, 5 patients have had their initial PET study before high dose chemotherapy. Two of these patients have normal or nearly normal studies, one patient has questionable right hilar uptake, one patient has diffuse bone marrow and splenic activity attributed to reactive bone marrow, but with active metastases in the dorsal spine. One patient has uptake in her right breast. These preliminary data indicate that PET can potentially predict therapeutic failures, although a larger sample and the follow-up studies will be necessary for confirmation.

14. SUBJECT TERMS
Positron emission tomography; breast cancer; fluoro-2-deoxy-2-glucose; bone marrow transplantation.

15. NUMBER OF PAGES
10

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

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

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

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

____ 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.

Accession For	
NTIS GRA&I	☑
DTIC TAB	☐
Unannounced	☐
Justification	
By	
Distribution/	
Availability Codes	
Dist	Avail and/or Special
A-1	

[signature] 9/22/95
PI - Signature Date

TABLE OF CONTENTS

INTRODUCTION

Positron emission tomography (PET) was introduced as a research modality to investigate physiological and biochemical alterations in the brain and heart [Reivich, 1985]. Many radiopharmaceuticals have been introduced for the study of various organs, but ^{18}F-fluoro-2-deoxy-2-glucose (FDG) is generally considered the most useful radiopharmaceutical for the diagnosis of various tumors. The extreme avidity of tumors for glucose explains the high uptake of FDG in tumor tissue, and thus the interest in using this compound to differentiate malignant from benign lesions.

There are now several reports of studies of patients with breast cancer, suggesting that the PET-FDG technique is effective in diagnosing and following patients with primary and metastatic breast tumors[Minn & Soini, 1989; Wahl, 1991; Tse, 1992a, 1992b; Niewig, 1993; Hoh, 1993; Adler, 1993]. A recent retrospective study on the efficacy of PET in detecting axillary lymph node involvement has suggested potential cost savings of up $161,000,000 on total health care charges in the United States by reducing the number of axillary dissections for breast cancer. Almost 74,000 women (75% patients) with primary breast tumors could potentially be spared axillary dissection based on the sensitivity and specificity of PET-FDG imaging to detect lymph node involvement [ICP, 1994].

Some groups have now reported on the use of PET to evaluate tumor response to therapy. Wahl et al, [1993] described the use of PET-FDG for monitoring the treatment response of primary breast cancer. Eleven patients with large primary cancers were studied before chemohormonotherapy and at four times after initiating treatment (at days 8, 21, 42 and 63). The quantitative PET scans showed a rapid decrease in tumor glucose metabolism in all eight patients whose cancers responded clinically, but no change in the 3 nonresponding patients. Qualitative (visual) analysis gave the same result. The metabolic change preceded clinical evidence of response (mammographic change), and in some patients the mammogram was difficult to interpret due to dense breast tissue. Thus, the PET-FDG appeared to be an early and accurate predictor of breast cancer response. Huovinen et al [1993], using ^{11}C-Methionine, reported changes in uptake in soft tissue lesions of eight patients treated with chemotherapy, hormone therapy or radiation. The PET responses correlated with clinical responses; uptake increased in those who showed progressive disease, and decreased in patients with stable or improving lesions. Jansson et al [1995] studied sixteen patients with locally advanced and metastatic breast cancers receiving chemotherapy. They noted a decrease in uptake (^{11}C-Methionine or FDG) compared to pretreatment scans in eight of twelve responders after the first course of therapy (scans were performed at 6 - 13 days after treatment.). Scans done after a third chemotherapy course showed a decrease in all clinical responders. These responses were noted in breast, axillary nodes, pleura and liver.

The purpose of our study is to evaluate the effectiveness of PET-FDG in patients with metastatic breast cancer who are also being treated with high dose chemotherapy and stem cell rescue. The hypothesis of the study are as follow:

1) Active tumor sites shown by anatomical imaging methods will be associated with high levels of metabolic activity while inactive sites will be reflected by low levels of FDG uptake.
2) Reduction in tumor metabolic activity of tumors will be an early predictor of response to high dose chemotherapy.
3) Patients with no abnormal FDG uptake prior to high dose chemotherapy will live longer than patients with tumor that are metabolically active.

The use of PET in this setting is potentially cost-saving considering the high costs of stem cell rescue. Non responders do not need to undergo further chemotherapy with consequent suffering and high costs, when palliation is more appropriate. On the other hand, the ability to predict the

response to chemotherapy in responders might enable the physician to modulate the treatment for each patient.

The original design of the study included a homogeneous group of patients entered on two University of Pennsylvania studies for the treatment of breast cancer with high dose chemotherapy. These two studies were PBT-1 and Protocol UPCC #1192. The Bone Marrow Transplant Team has recently activated Protocol UPCC #3195, "Phase II Study of High Dose Sequential Chemotherapy with Melphalan and Cyclophosphamide, Thiotepa and Carboplatin and Cyclophosohamide and G-CSF Augmented Peripheral Stem Cell Support for Women with Metastatic Breast Cancer". This will be the replacement protocol for UPCC #1192. Therefore, we have amended our study by adding Protocol #3195, without modification to the basic study design. The approval process for the protocol modification has resulted in delays in recruiting patients for the PET-FDG study. However, with the increased number of patients available from the new chemotherapy protocol, we do not expect any difficulty in recruiting the planned number of patients (40) in the remaining time period.

BODY

Materials and Methods

Patient Selection:

Patients selected for entry in this study are mainly women accepted for one of the two high dose chemotherapy protocols utilizing autologous stem cell support at the University of Pennsylvania, PBT-1 ("Phase III Randomized Comparison of Maintenance Chemotherapy With Cyclophosphamide, Methotrexate and 5-FU Versus High Dose Chemotherapy With Cyclophosphamide, Thiotepa and Carboplatin and Autologous Bone Marrow Support For Women With Metastatic Breast Cancer Who Are Responding To Conventional Induction Chemotherapy") and Protocol UPCC#3195 ("Phase II Pilot Study Of High Dose Chemotherapy With Cyclophosphamide, Thiotepa, Carboplatin and G-CSF Augmented Peripheral Stem Cell Support For Women With Metastatic Breast Cancer").

Chemotherapy Studies:

PBT-1: The purpose of this study is to compare the time to treatment failure, overall survival and toxicity in patients with metastatic breast cancer who are treated with conventional chemotherapy alone or conventional dose chemotherapy followed by high dose chemotherapy and autologous bone marrow rescue. Patients are entered in this trial prior to receiving any chemotherapy for metastatic disease. They will then receive Cytoxan, Adriamycin and 5-FU. At the end of 4 - 6 cycles of treatment for metastatic disease, the patients will be reevaluated. Those in a partial response or in a complete response will then be randomized either to continue the same chemotherapy (or change from Adriamycin to Methotrexate after a total dose of Adriamycin has been given) until rlapse or to receive high dose therapy and autologous bone marrow treatment with no further therapy after the transplant. The high dose regimen consists of 4 days of Cyclophosphamide (1500 mg/m^2), Thiotepa (125 mg/m^2) and Carboplatin (200 mg/m^2).

UPCC #3195: This study is an University of Pennsylvania Cancer Center single institutional trial is designed for patients with metastatic disease or inflammatory breast cancer. Those patients with no evaluable disease or a documented complete or partial response to standard chemotherapy are treated with high dose sequential chemotherapy and peripheral stem cell rescue. The entry criteria are almost identical to those of the previous protocol, UPCC #1192. Patients receive high dose Cyclophosphamide followed by G-CSF to stimulate stem cell production. This is followed by apheresis to harvest stem cells. When blood count recovery has occured, high dose Melphalan is

administered to the patient followed by infusion of one-third of the collected stem cells. Twenty-one days later, the patient is treated with high dose chemotherapy regimen consisting of Cyclophosphamide (1500 mg/m^2), Thiotepa (125 mg/m^2) and Carboplatin (200 mg/m^2), each drug being given daily for four days. This is followed by peripheral stem cell reinfusion.

PET Camera:

The PENN PET 240H camera, manufactured by UGM, has been used extensively over the last 5 years for FDG and ^{15}O-water brain studies, FDG whole-body cancer studies, and FDG/^{13}N-ammonia cardiac studies. This scanner is based on NaI(Tl) position-sensitive detectors, which leads to high spatial resolution, 5.5 mm (FWHM) in the transverse and axial directions, and fine spatial sampling, 2 mm in both the transverse and axial directions [Karp 1990, Karp 1993]. The fine axial sampling, in particular, is a unique advantage of the system, leading to a maximum of 64 slices, which helps us achieve accurate quantitation and reduce the partial volume effect in PET [Karp 1991]. To achieve the maximum sensitivity, the scanner operates as a full-time 3D system, without septa.

Whole body scanning technique:

The whole-body scanning is carried out according to the ongoing protocol in our laboratory. Currently, 114 μCi/kg is injected intravenously in the patient. Forty minutes later, the patient is positioned supine in the scanner, feet first, with her arms extended and folded behind the neck. The scanner is then moved by successive 6 cm steps to image the desired areas. This position allows imaging the entire supraclavicular and axillary lymph node sites. A post-emission transmission scan is then obtained. The scanning area includes the entire chest and supraclavicular regions.

Qualitative interpretation:

Until now, the images are read by an experienced observer on whole body images, without attenuation or scatter correction. The reader is blinded to clinical and other radiological information.

Quantitation

Quantitative analysis will be carried out on attenuation and scatter corrected images by assigning regions of interest (ROI) over the area(s) of abnormal uptake visually determined. One quantitative measure of the uptake of a given isotope in a tumor is the standardized uptake value (SUV) which is defined as:

SUV = (uptake activity/gram of tissue)/(injected activity/gram of patient weight).

In malignant tumors, SUV > 2, sometimes reaching as high as 9-10, whereas in normal tissue SUV ≈ 1. Two types of measurements will be made with this analysis. One will consist of drawing a ROI which will include the entire area of abnormal uptake from which an average SUV for the abnormality will be calculated. The other will consist of sampling the most active portion of the lesion to determine the maximum activity concentration in the tumor. While the former will be used to measure the overall tumor activity, the latter will be considered for grading the tumor.

Results:

Five patients have until now completed their initial PET study. The change in the chemotherapy protocol has introduced delays in the initiation of the PET studies, but with the increased number of

patients from the UPCC #3195 protocol, we expect no difficulty in obtaining the required number of patients.

Since these patients are currently under protocol, we are accumulating data concerning clinical evaluation, biochemical tests, and correlative imaging methods. These will be analyzed when all PET studies will have been completed.

We are also currently implementing alternative reconstruction algorithms (maximum-aposteriori algorithm) to improve the image quality of whole-body studies and reduce artifacts produced by non uniform distribution of activity, especially in the thorax and the pelvis [Mumcuoglu, 1994; Yan 1991]. This may considerably improve lesion detectability. With the iterative algorithm, we will study the effect of smoothing (via constraints) and the use of ordered subsets [Meikle, 1995a], together with reducing the number of iterations, so that the overall reconstruction time will be practical from a clinical imaging point of view. We will be able to apply these techniques to the PET scan raw data obtained for patients entered in the protocol. This may considerably improve qualitative image interpretation by reducing streak artifacts, especially when combined with attenuation correction methods [Meikle, 1995b].

Qualitative interpretation:

Until now, 5 patients have had their initial PET studies when before entering their high dose chemotherapy protocol. Two of these patients have normal or near-normal PET studies. One patient has a questionable right hilar uptake, and one patient has diffuse bone marrow uptake, with definite metastases in the dorsal spine. The last patient has uptake in her left breast.

In order to be blinded to the clinical data, the comparison between the qualitative and quantitative PET interpretations with clinical and other radiological data will only be done at the end of the study. We are also studying normal variants from whole body PET studies performed in other research protocols unrelated to cancer applications. This will allow us to refine our quantitative and qualitative criteria for confirmation or exclusion of the presence of disease.

Conclusion:

We have initiated the study proposed in our application and have successfully accumulated enough preliminary data to proceed with our project. Our hypotheses and specific aims remain unaltered and we expect successful and effective implementation of the project. We believe the results of this study will be of considerable importance in the management of patients with breast cancer who are being considered for bone marrow transplation.

References:

Adler LP, Crowe JP, al-Kaisi NK, Sunshine JL. Evaluation of breast masses and axillary lymph nodes with [F-18] 2-deoxy-2-fluoro-D-glucose PET. *Radiology* 1993;187:743-750.

Crowe JP, Adler LP, Shenk RR, Sunshine J. Positron emission tomography and breast masses: comparison with clinical, mammographic, and pathological findings. *Ann Surg Oncol* 1994;1:132-140.

Diamandidas D, Kim E, Singletory S, Hortobagyi G. The role of positron emission tomography (PET) imaging with breast cancer - preliminary data. *Proc Amer Soc Clin Oncol* 1993;12:68 (Abstract).

Huovinen R, Leskinen-Kallio S, Nagren K, Lehikoinen P, Ruotsalainen U, Teras M. Carbon-11-methionine and PET in evaluation of treatment response of breast cancer. *Br J Cancer* 1993;67:787-791.

Ichiya Y, Kuwabara Y, et al. Assessment of Response to Cancer Therapy using ^{18}F-FDG and PET. *J Nucl Med,* 1991;34:73P.

ICP Breast Cancer Task Force. Clinical application and economic implications of PET in the assessment of axillary lymph node involvement in breast cancer: a retrospective study. Abstract from the 1994 Institute for Clinical PET Meeting. Publication No. CE-BREAST-94.001.

Jansson T, Westlin JE, Ahlstrom H, Lilja A, Langstrom B, Bergh J. Positron emission tomography studies in patients with locally advanced and/or metastatic breast cancer: a method for early therapy evaluation?? *J Clin Oncol* 1995;13:1470-1477.

Hawkins RA, Hoh C, Glaspy J, Rege S, Choi Y, Phelps ME. Positron emission tomography scanning in cancer. *Cancer Investig* 1994;12:74-87.

Hoh CK, Hawkins RA, Glaspy JA et al. Cancer detection with whole body PET using FDG. *J Comput Assis Tomog* 1993;17:582-589.

Meikle SR, Hutton BF, Bailey DL, Hooper PK, Fulham MJ. Accelerated EM Reconstruction in Total Body PET: Potential for Improving Tumour Detectability. *Phys Med Bio,* 1994(a);39:1689-1704.

Meikle SR, Bailey DL, Hooper PK, et al. Simultaneous emission and transmission measurements for attenuation correction in whole-body PET. *J Nucl Med* 1995; 36:1680-1688.

Minn H, Soini I. [18F]fluorodeoxyglucose scintigraphy in diagnosis and follow-up of treatment in advanced breast cancer. *Eur Nucl Med* 1989;15:61-66.

Mumcuoglu EU, Leahy R, Cherry SR, Zhou Z. Fast Gradient Based Methods for Bayesian Reconstruction of Transmission and Emission PET Images. *IEEE Trans Med Imag,* 1994;13:687-701.

Nieweg OE, Wong WH, Singletary SE, Hortobagyi GN, Kim EE. Positron emission tomography of glucose metabolism in breast cancer. Potential for tumor detection, staging, and evaluation of chemotherapy. *Ann NY Acad Sci* 1993;698:423-428.

Reivich M, Alavi A (eds). *Positron Emission Tomography*, Alan Liss Inc., 1985.

Tse NY, Hoh CK, Hawkins RA et al. The application of positron emission tomographic imaging with fluorodeoxyglucose to the evaluation of breast disease. *Ann Surg* 1992(a);216:27-34.

Tse NY, Hoh CK, Hawkins RA, et al. The UCLA experience of whole body positron emission tomography in human breast cancer. *Proc. Am. Soc. Clin. Oncol.* 1992(b);11:54 (Abstract).

Wahl RL, Cody RL, Hutchins GD, Mudgett EE. Primary and metastatic breast carcinoma: Initial evaluation with PET with the radioloabeled analogue 2-(^{18}F)-flurodeoxyglucose. *Radiology,* 1991;179:765-770.

Wahl RL, Helvie MA, Chang AE, Andersson I. Detection of breast cancer in women after augmentation mammoplasty using fluorine-18-fluorodeoxyglucose PET. *J Nucl Med* 1994;35:872-875.

Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. *J Clin Oncol* 1993;11:2101-2111.

Yan X, Leahy R. MAP Image Reconstruction Using Intensity and Line Processes for Emission Tomography Data. *Proc SPIE-1991,* 1991;1452:158-169.