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14. ABSTRACT This program is intended to establish the infrastructure to provide state-of-the art targeted radiation therapy to military personnel and veterans with cancer. The research aspect of this project is intended to demonstrate whether 1) targeted radiation therapy with real time localization and tracking will allow use of a smaller planning treatment volume margin with a significant decrease in rectal and bladder volume treated and whether the use of such targeted therapy can occur within standard treatment times and thus feasible for routine clinical use, 2) the use of Vac-Lok® immobilization devices are necessary when patients are treated using the Calypso system, 3) Beacon® Transponder is of benefit in pelvic radiation therapy following prostatectomy, 4) the precision and accuracy of radiation therapy using breath-hold technique for left-sided breast cancer patients treated with adjuvant radiation therapy, with the benefit of confirmatory tracking via the Calypso® 4D Localization System will help to spare toxicity to the heart, 5) a military medical center department, with essentially fixed costs and without financial incentive to treat patients with multiple fractions, will manage patients differently than a typical civilian practice and whether this difference changed the outcome for palliative patients, 6) use of the Calypso system, and other advanced radiation therapy equipment, can improve treatment techniques and outcomes in malignancies arising in other parts of the body.					
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Table of Contents

	<u>Page</u>
Introduction.....	1
Body.....	2-10
Problem Areas.....	11
Key Personnel Updates.....	11
Key Research Accomplishments.....	11-12
Reportable Outcomes.....	12
Conclusion.....	12-13
References.....	13
Appendices.....	14

Targeted Radiation Therapy for Cancer Initiative Annual Report

Introduction:

The full potential of radiation therapy has not been realized due to the inability to locate and track the tumor target continuously during the delivery of the radiation dose. Without the ability to accurately locate the tumor target at the time of dose delivery, more of the patient's healthy tissue is exposed to radiation, which may result in acute or chronic complications. The research studies and activities described in this report will improve the techniques of modern radiation therapy and directly benefit the Department of Defense by: providing improved, state-of-the-art prostate cancer treatments to active-duty military personnel and veterans; continuing to investigate reduction of the number of daily radiation treatments required for each patient thereby reducing the cost of care and increasing treatment capacity within the military delivery system; enabling research to establish standards of care for targeted radiation therapy; establishing a DOD center of excellence in targeted radiation therapy and accelerating the development of the targeted radiation therapy platform to treat additional cancers that significantly affect service personnel, their families, and veterans, such as breast cancer and metastatic cancer. The Calypso® 4D Localization System is a FDA Class II device, utilized to track both inter-fraction and intra-fraction tumor movement in patients receiving radiation therapy for various malignancies.

Body: Task Completion

Task 1. *Establishment of centers for targeted radiation therapy at MAMC and VAPSHCS with installation of the Calypso® 4D Localization System.*

Installation of the Calypso® 4D Localization System occurred at MAMC. The radiation team continues to receive training and technical support of the system from Calypso as needed.

The installation and training of the Calypso System also occurred at VAPSHCS. No study patients were ever treated at the site. The system was de-installed and moved to MAMC to be used in the newly renovated second vault with the new linear accelerator.

Task 2. *Treatment for prostate cancer with state-of-the art technology to allow real-time localization and continuous tracking of the tumor target.*

A total of 25 non-study prostate cancer patients who did not otherwise qualify for a protocol were treated with the Calypso system at MAMC. Non-protocol patients have allowed the providers to gain further proficiency with the Calypso unit. Six of these patients were treated in the prone position. The experience and knowledge gained in this alternative positioning technique allowed for patients who were not anatomically compatible with the Calypso system in the supine position to be able to receive treatment with this state-of-the-art localizing/tracking device. The Reduced Margins protocol was amended to allow for prone positioning and we treated 3 study patients in this position with results comparable to supine.

MAMC has now been routinely using the approved FDA surface transponders off protocol to monitor breathing motion during our standard breath-hold technique for treating left-sided breast cancer, which allows sparing of the heart. We have treated 54 patients using these approved external beacons. The Calypso system provides a previously unavailable level of additional positional monitoring for these patients and we have gained considerable expertise with this technique. We presented three separate poster presentations at two professional meetings in September 2014 as well as an oral presentation at Madigan Research Day on 4/24/15. See Task 8 for further details on this protocol.

Task 3. *Feasibility study with reduced planning treatment volume (PTV) margins and intensity modulated radiation therapy (IMRT) using targeted radiation therapy.*

Thirty-five subjects were consented and thirty-one enrolled in the study with reduced PTV margins at MAMC. Twenty-one of these subjects completed the trial including all follow-up visits. All subjects have finished treatment, nine are in the follow-up phase,

one patient died while in the follow-up phase from lung cancer which was unrelated to study, four were screen failures that never started treatment.

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1. Change of Research Monitor from LTC Jonathan Davison, MC to MAJ Andrew Mosier, MC. 2. Brooke Army Medical Center (BAMC) was removed as a participating site. 3. Continuing review was approved by the MAMC IRB from 16 July 2015 through 15 July 2016. The site forwarded this approval to HRPO. This study was closed to enrollment May 31, 2015 to allow for 12 months of follow-up to assess for toxicity prior to grant closure.

We have now given four presentations at a national conference and two here at Madigan, supported by the data collected from this trial. Our most recent research was presented at the 2015 Genitourinary Cancers Symposium in Orlando, FL 26 February 2015 as well as at Madigan Research Day on 4/24/15. We continue to analyze data endpoints as the remaining subjects complete the follow-up phase.

Databases have been created for the raw data gained from the Expanded Prostate Cancer Index Composite (EPIC) and International Prostate Symptom Score (IPSS) questionnaires as well as for Toxicity Sheet surveys which are completed during specified pre-treatment, treatment, and follow-up visits through month 24. To date, 1,184 surveys have been recorded which contained 16,717 individual pieces of raw data. The fractions logs which have also been compiled in a digital database contain almost 15,000 additional pieces of raw data.

As examples of information that can be gleaned from this data:

For patients on this study, mean planning treatment volume was decreased by close to half (47.8%) with reduced margins. This reduced the mean dose to the external and internal anal sphincter, and rectum by 62.7%, 51%, and 18.5% respectively (a total of 33.5Gy less to these areas).

Reduced planning treatment volume margins result in minimized doses of radiation to healthy tissue which in turn lessens the chance of side effects. With our study we found that 83.9% of patients experienced acute side effects and 51.6% experienced late side effects. In general, side effects were mild. Only one patient (3.2%) experienced a grade 3 acute genitourinary side effect (urinary retention requiring TURP) and there were no grade 3 or 4 gastrointestinal side effects. Likewise, only a small percentage of patients (9.68%) experienced late grade 2 GU and GI side effects.

The completed EPIC questionnaires have also shown that patients tolerated definitive radiation therapy with reduced PTV margins for prostate cancer very well. Baseline EPIC bowel, urinary, and sexual function scores averaged 94%, 89%, and 48% respectively. At the end of treatment, average EPIC scores reflected patients' recorded acute toxicity with bowel function at 83%, urinary function at 75%, and sexual function at 41%. By four months post treatment, EPIC scores showed average bowel and urinary functions had returned to within the range of baseline with 91% and 87% respectively.

EPIC sexual function scores showed the greatest lasting side effects 4 months post treatment remaining at 41%.

As part of the fraction logs, daily treatment times were also recorded and analyzed. The mean total daily treatment time was less than 10 minutes with individual mean times ranging from 7.1-15.3 minutes. 95.81% of all treatments were completed within 20 minutes which is considered the standard treatment time. Of the less than 5% that took more than 20 minutes (50 fractions), 64% were within 25 minutes and all but nine individual fractions (82%) were within 30 minutes. 21 of the 31 study patients experienced at least one day where total daily time exceeded 20 minutes. Of these, only nine patients had more than two days where total daily time went longer than the standard. Final analysis of all data is pending completion of the study.

We are currently working on an abstract discussing predictive factors for rectal toxicity for presentation at the 2016 ASTRO/ASCO/SUO symposium in San Francisco, CA. Our ultimate goal is to publish our final report in a renowned radiation oncology journal.

VAPSHCS received full regulatory approval for this protocol, but never consented any subjects. This site is closed.

In an effort to boost enrollment, we collaborated with Brooke Army Medical Center and added them as a site on this protocol, however due to lack of enrollment BAMC was removed as a participating site. The statistical significance of the data was not affected by this setback as MAMC exceeded expected enrollment

Task 4. *Become an RTOG member to better serve as a center of excellence.*

The Radiation Therapy Oncology Group is a recognized leader in working to increase survival and improve the quality of life for cancer patients. We completed our task of becoming a RTOG member and were excited to open our first RTOG study as an affiliate member. Subsequently, we were informed that our parent site was acquired by a different group and felt they did not have the capability to maintain the oversight needed to act as our parent since they are located in CA. However, since Madigan falls under the cooperative group, SWOG (southwestern oncology group), we are able to participate in certain RTOG studies that are encompassed with SWOG.

We had originally planned to participate in RTOG 0938, but this trial has reached its accrual goal. We requested an amendment to the SOW to include RTOG 0924 under this task and it was recently approved. This is an equally important study for higher-risk prostate cancer patients. Participation in this national study will help us to continue to establish Madigan as a "center of excellence" in targeted radiation therapy. Also, an added benefit with this trial is that it will not compete with our reduced PTV margins study (like 0938 would have).

Androgen Deprivation Therapy and High Dose Radiotherapy With or Without Whole-Pelvic Radiotherapy in Unfavorable Intermediate or Favorable High Risk Prostate Cancer: A Phase III Randomized Trial (RTOG 0924)

This study will help to answer important questions with regard to necessary length of hormone therapy and the radiation target required for high-risk patients being treated with modern techniques. This study is currently approved and open to enrollment. We expect to accrue our first patients to this study within the next quarter.

Task 5. *A Randomized Study Comparing External Pelvic Immobilization to Limited Immobilization for the Treatment of Prostate Cancer with IMRT Using Real-Time, State-of-the-Art Motion Tracking with the Calypso® 4D Localization System.*

Thirteen subjects have been enrolled in the immobilization study at MAMC. A total of sixteen signed consent; three were screen failures and never started treatment. Ten of these subjects have completed the study from consent to the one year follow-up and three are in the follow-up phase. Enrollment was closed June 30, 2015 to allow for the one year follow-up period.

We submitted an abstract to a professional conference, but were not chosen to present due to our limited data at the time. Although no additional analysis was done on this study this fiscal year, we updated the existing fraction log database to include all protocol patients and plan to continue analyzing compiled data and anticipate submitting another abstract in the future.

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1. Change of Research Monitor from LTC Jonathan Davison, MC to MAJ Andrew Mosier, MC. The continuing review package was submitted to MAMC IRB and is scheduled to be reviewed on 25 August 2015. The current review approval period is from 27 August 2014 through 26 August 2015.

VAPSHCS received partial regulatory approval. No subjects were ever consented. This site is now closed.

This study has proven to be difficult to enroll since most patients who are intermediate to high-risk choose to have a prostatectomy. Our original goal of 20 subjects did not seem feasible based on our patient population. Our enrollment of 13 participants should allow us to gather enough data to support hypothesis-generating research.

Task 6. *Post-prostatectomy Daily Target Guided Radiotherapy Using Real-Time, State-of-the-Art Motion Tracking with the Calypso® 4D Localization System: A Feasibility Study.*

Twenty subjects were enrolled in the post-prostatectomy study at MAMC. A total of twenty-five signed consent; five were screen failures and never started treatment. Seventeen of these subjects have completed the entire study, 1 is in the follow-up phase, 1 is still on treatment, and one was withdrawn during treatment due to an inability to accurately localize him to Calypso due to an anatomical shift that was occurring when using his calypso beacons.

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1. Change of Research Monitor from LTC Jonathan Davison, MC to MAJ Andrew Mosier, MC. 2. The current review approval period is from 22 October 2014 through 21 October 2015.

We have presented a total of three poster presentations at national conferences as well as an oral presentation at Madigan's Research Day based on our work from this protocol.

Enrollment was closed May 31, 2015 to allow for the one year follow-up period prior to conclusion of grant.

The data gathered from this process is helping us to determine how much we can safely reduce the PTV margins for a follow-on reduced PTV margins study. The localization data captured from this protocol and from any future follow-on reduced PTV margins protocol will eventually be analyzed in aggregate to provide the best possible data on localizing the prostatic fossa using Calypso beacons.

Over the past 12 months we have continued to build our largest database for all the raw data gathered from fraction logs, calypso records, and all measurements taken from cone-beam CT scans. In total, there are 169,804 individual pieces of raw data in this database so far. The vast majority of this information (79%) comes from measurements and calculations based directly off of CBCT images. The location of the anterior rectal wall, the plane of symphysis pubis, and the posterior bladder wall on five equally spaced axial CBCT slices (interior, inferior-mid, middle, superior-mid, and superior) are recorded. In addition to this, the distances between each of these structures is calculated, the obturator internus muscles are measured on the middle slice, and the 3-dimensional location of the apex, Lbase, and Rbase beacons are recorded. All CBCT measurements are done before and after auto-fusing each CBCT scan with the treatment planning scan.

Daily changes in bowel and bladder position which is often affected by excessive gas in the rectum, the fullness of the bladder, etc. appears to be responsible for a large amount of the random motion that has been tracked in beacon location. The average shifts from the beacon to CBCT-localized isocenter were 2.1mm, 2.0mm, 0.35mm, and 0.05° in the vertical, longitudinal, lateral, and rotational planes respectively. We are currently studying the clinical significance of all of the recorded intra-fraction and inter-fraction movement.

VAPSHCS received partial regulatory approval. No subjects were ever consented. This site closed.

The study met expected enrollment of 20 subjects.

Task 6a. Reduced PTV Margins Post-prostatectomy Daily Target Guided Radiotherapy Using Real-Time, State-of-the-Art Motion Tracking with the Calypso® 4D Localization System: A Feasibility

The quantitative analysis of the cone-beam CT scan data collected from the original protocol outlined in Task 6 will determine how much of the PTV margins can safely be reduced. To date, we have determined that using Calypso beacons for localization will allow us to safely spare approximately 1 cm of normal bladder, which is included in the clinical target volume (CTV) when treatments are localized with other techniques.

Our analysis to date of the CBCT data collected in Task 6 demonstrates that most patients would be appropriately treated with significantly decreased circumferential margins; however, a few patients are outliers who require more margin. It has been demonstrated by other groups that these outliers can be identified by analysis of target volume coverage during the first five treatments, followed by margin adaptation based on this analysis. Therefore, this protocol will also include an adaptive radiation therapy component, by which each patient's first five fractions of radiation therapy will be analyzed for a pattern of excessive target volume motion, and margin adjustments will then be made to the patient's radiation treatment plan if necessary.

A protocol manuscript has been initiated and we hope to have it completed once we finish our analysis of the original post-prostatectomy clinical trial which has met the enrollment goal of 20 patients, with the 20th patient finishing treatment in September 2015.

Task 7. *Central Dose Escalated Palliative Conformal Radiation Therapy*

This study will include two phases and has the potential to dramatically alter the efficiency and efficacy of palliative radiation therapy. The primary goal of this study is to develop and validate a set of dosing guidelines that will allow widespread use of advanced technology radiation therapy techniques, such as IMRT and VMAT, in treating palliative patients. The main obstacle to overcome in reaching this goal is to establish practice patterns that allow simplified, though still safe, use of this technology in order to decrease the expense associated with these treatments. The first phase of this study will involve a retrospective portion where we review the patients treated palliatively here at MAMC in the past, and by using their CT scan data compare dose that would be delivered to the target volume and nearby structures with a conformal "central-boost" plan vs. a conventional palliative plan. The second phase of this study will prospectively

evaluate the feasibility of this strategy with specific quality of life outcome measurements.

So far under this study we have evaluated all palliative patients treated between June 2006 – December 2007 and those treated from January 2013 – June 2014. A significant increase in average dose per fraction with a mean increase of 175cGy in the latter group was found. A 26% increase in the number of single fraction treatments and use of IMRT, VMAT, and Arc plans was also found. On the other hand, both the mean total dose per site and the mean number of fractions decreased; the mean total dose per site dropped by 676cGy. These changes represent the implementation of modern techniques when deemed necessary and beneficial to patients, in a setting less constrained by insurance billing practices. In addition, the increase in single fraction treatments represents a more cost effective use of palliative radiation which follows consensus guidelines supported by randomized evidence.

We are actively tracking and recording additional information for further work on this study including tracking any and all related side effects patients experienced. Treatments have also been broken down for billing purposes and we are in the process of determining more in depth financial ramifications of these treatments on a national scale which will allow us to better analyze how the special financial circumstances surrounding a military facility may impact patient care.

We recently gave an oral presentation based on this research at the 54th Annual Conference of the Particle Therapy Co-Operative Group (PTCOG), held in Conjunction with the 2nd Annual PTCOG-NA Conference from May 21st to 23rd, 2015 in San Diego, California. Although we were not chosen to present at the annual ASTRO conference 2015, we were selected to also present this data at the 101st Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA).

We are currently working on a paper to be submitted for publication to the International Journal of Particle Therapy.

Task 8. *A Retrospective Study of Breast and Chest Wall Positioning During Whole Breast Radiation Therapy for Left-Sided Breast Cancer Using Breath-Hold Technique Supplemented by Motion Tracking with the Calypso® 4D Localization System.*

This study examines the precision and accuracy of radiation therapy using breath-hold technique for left-sided breast cancer patients treated with adjuvant radiation therapy, with the benefit of confirmatory tracking via the Calypso® 4D Localization System.

We have concluded thus far that this technique demonstrates accuracy and precision that is well within the traditional 1 cm margin of error, allowing a potential decrease in planning margins.

As with all other projects, we have created a digital database containing all raw data for this retrospective study. This database contains approximately 97,000 pieces of raw data representing numerous measurements taken from calypso reports and calculations based on these measurements. From this data we have been able to show that using the deep inspiration breath hold technique in conjunction with external beacon tracking significantly reduced mean heart (MH) and left anterior descending coronary artery (LAD) dose compared to free breathing plans. This technique decreased MH dose by 55.7% and LAD dose dropped by 69.8% which equates to approximately 14.24 ± 5.8 Gy spared in these areas.

The coaching from technicians based on real-time Calypso tracings which helped patients to have reproducible breath holds allowed for the beam-on times of treatment to occur in a very precise window in comparison to the breath hold as a whole. As a result, in each dimension, chest wall excursion during breath hold was significantly greater than chest wall excursion during beam-on time. Average chest wall excursion was decreased by 56% laterally, 66% longitudinally, and by 69% vertically. Treatment was paused in 23% of fraction to adjust for suboptimal breath hold or chest wall position, while this added a small amount to the treatment time it was ideal for patients as it ensured that treatment was limited to the most stable portion of the deep inspirational breath hold plateau, significantly reducing intra-fraction motion.

We included 15 patients on our retrospective protocol. Three poster presentations based on our work were presented at 2 different national conferences in September 2014. MAJ Kathpal's contributions during her residency rotations with us on this project were instrumental to its overall success. We also gave an oral presentation at Madigan Research Day on 4/24/15. We are currently working on a paper for submission to the journal of Practical Radiation Oncology (PRO).

Task 9: *Establish a center of excellence for targeted radiation therapy. The intent of this task is to create a facility specialized in all modalities of targeted radiation therapy such as cone beam CT, on board kilovoltage orthogonal imaging, and the Calypso® 4D Localization System*

The staff at MAMC has treated approximately 160 patients with the Calypso® 4D Localization System and continue to develop expertise as a center of excellence in targeted radiation therapy. This grant continues to facilitate continuing medical education for the staff at MAMC on image guided radiotherapy. Additional education materials and visits from other DOD providers will be coordinated in upcoming years of the project.

Active duty Army Radiation Oncologist resident, Madeera Kathpal completed her fifth and final rotation at MAMC in September 2014. The resident learned advanced techniques of tumor targeting with the Calypso system and assisted in evaluating data and writing scientific papers under the guidance of the MAMC physicians. MAJ Kathpal worked on many projects under the guidance of MAMC physicians, including analyzing

data from the post-prostatectomy trial and then writing/presenting 3 abstracts based on the findings at 2 national conferences and at Madigan's Research Day. She also contributed in developing our retrospective breast protocol as well as writing abstracts and papers based on our data analysis (as explained in the task above 2). MAJ Kathpal presented this data in 3 separate poster presentations at 2 different national meetings. Dr. Kathpal is now an attending radiation oncologist at the Fort Belvoir military treatment facility in Virginia. We hope to collaborate with her in the future as she is very interested in initiating research in targeted radiation therapy at her new facility.

Our team of researchers continues to grow. In addition to MAJ Kathpal, we have had a MAMC Radiology resident, and two medical students on research rotations as well as a pre-medical student assist in evaluating, preparing and writing abstracts based on the data gathered in our Reduced PTV Margins and Immobilization protocols. Our most recent Radiation Oncology Resident, Chris Premo, completed a one month rotation at our site earlier this year. We had one Madigan transitional intern and another undergraduate Geneva Foundation volunteer contribute to our research efforts this summer. Two research assistants have been provided employment supported by this research grant. Their work on this project has been fundamental in collecting data for our current and future research.

We have hosted six educational conferences/visiting professorships in the area of urology and radiation oncology since the inception of this grant. We have committed to making these events an annual occurrence. We believe these educational events promote our site as a "center of excellence in target radiation therapy" and encourage physicians in the community to seek our expertise. Our most recent event was held on 24 July 2015. Dr. Daniel Lin, a professor of medicine and Chief of Urologic Oncology at the University of Washington's Department of Urology discussed, 'Novel Aspects of Neoadjuvant Treatment and New Paradigms in High Risk Prostate Cancer'. The targeted audiences for this symposium were urologists, urology residents, radiation oncologists and ancillary staff. We had a very good turnout resulting in engaging discussion. We look forward to hosting the 7th annual symposium next year.

We continue to collect information regarding problems/challenges encountered with Calypso as a "Lessons Learned Log" which identifies the problems encountered with possible causes and the techniques used to solve the problem. The physicist at our site gave an oral presentation about the Calypso System at a professional physics conference in October 2013. She incorporated some of our "lessons learned" information in her speech.

We have also been using the Calypso System with surface transponders while treating lung cancer patients with SBRT (stereotactic body radiation therapy). SBRT is a type of radiation therapy in which a few very high doses of radiation are delivered to small, well-defined tumors. The goal is to deliver a radiation dose that is high enough to kill the cancer while minimizing exposure to surrounding healthy organs. We have successfully treated 9 patients thus far using the Calypso System to track breathing motion. We are very excited to be incorporating this technique with SBRT and believe it supports our overarching goal in establishing a center of excellence for targeted radiation therapy.

Task 10: *Present findings of feasibility studies at professional conference.*

We have presented a total of 10 poster presentations and 1 oral presentation at 5 prominent medical symposiums based on the continued findings of our research. Also mentioned prior in this report, we have given 3 oral presentations and 1 poster presentation at Madigan research day. Our next presentation based on our palliative research will be presented in the fall of 2015 at Radiological Society of North America (RSNA) annual conference.

Problem Areas:

As previously reported, it was unanimously decided to discontinue efforts at VAPSHCS based on several factors which included: radiation therapy staffing issues at the VA, the slow pace of the VA IRB system, and most fundamentally the practice pattern of the Seattle VA which focuses on brachytherapy as treatment for prostate cancer. It seemed unlikely that patient accrual would substantially contribute to our research. The SOW was updated to remove the VA.

BAMC did not enroll any participants on The Reduced PTV Margins study. As stated previously, BAMC has decided to close the study at their site due to this lack of enrollment. They are now officially closed. Fortunately this was not a setback to the study as MAMC exceeded expected enrollment.

Our RTOG affiliate membership was discontinued as stated in task 4. Since our parent site was acquired by a different group they felt they did not have the capability to maintain the oversight needed to act as our parent since they are located in CA. However, since Madigan falls under the cooperative group, SWOG (Southwestern Oncology Group), we are able to participate in RTOG studies that are encompassed with SWOG.

Key Personnel Updates:

- None

Key Research Accomplishments:

- Enrolled 31 on the Reduced PTV Margins protocol
- Enrolled 13 subjects on the Immobilization protocol

- Enrolled 20 subjects on the Post-prostatectomy protocol
- Treated 84 non-study patients with Calypso (including prostate, breast and lung).
- Analyzed data on 15 patients enrolled in the retrospective breast cancer study.
- Developed a database of volumetric and dosimetric anatomical data correlated with patient quality of life outcomes for patients treated on the reduced PTV margins study.
- Developed a database of anatomical data describing quantitatively the morphology of the prostatic fossa measured on over 500 treatment-matched CT scans in post-prostatectomy patients receiving radiation therapy.
- Continued development of Madigan as a center of excellence in Targeted Radiation therapy, including continued success of our annual multidisciplinary educational conference/visiting professorship.
- Developed technical expertise in using Calypso surface beacons to track breathing motion in left-sided breast cancer, allowing sparing of the heart.
- Presented our research findings orally and in poster form at national conferences and Madigan Research Day.

Reportable Outcomes:

Over the course of this fiscal year we completed a manuscript for publication based on our *Retrospective Study of Breast and Chest Wall Positioning During Whole Breast Radiation Therapy for Left-Sided Breast Cancer Using Breath-Hold Technique Supplemented by Motion Tracking with the Calypso® 4D Localization System* (Task 8). This paper will be submitted to the Journal of Practical Radiation Oncology.

Our other primary focus over the last year has been on the *Central Dose Escalated Palliative Conformal Radiation Therapy* study (Task 7). In addition to creating a digital database, we have started the initial analysis of the data. While we are still actively tracking and recording additional information for further work on this study including tracking any and all related side effects patients experienced as well as financial ramifications of treatment, we gave an oral presentation based on the initial analysis of this research at the 54th Annual Conference of the Particle Therapy Co-Operative Group (PTCOG), held in Conjunction with the 2nd Annual PTCOG-NA Conference from May 21st to 23rd, 2015 in San Diego, California. We were also selected to present this data at the 101st Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA) during the week of November 29th, 2015.

Through our analysis of the above mentioned palliative study, we found notable changes which represented the implementation of modern techniques when deemed necessary and beneficial to

patient. In addition, the increase in single fraction treatments represents a more cost effective use of palliative radiation which follows consensus guidelines supported by randomized evidence. This study has also shown that it may be possible to improve patient care through phenomena related to disruptive innovation if we develop simplified planning and quality assurance methods for lower-dose palliative proton therapy with treatment fit into patient flow gaps at proton therapy centers. This same theory predicts that offering this treatment at prices low enough to maximize its use could lead to increased efficacy of proton therapy along previously undervalued axes, with eventual recoupment of initial investment.

For additional details on this and other presentations, please see the appendix section of this report for all abstracts presented/scheduled to be presented to date as well as a complete listing of all presentations to date for ease of reference.

Conclusion: The “Targeted Radiation Therapy for Cancer Initiative” has provided a framework for developing Madigan Radiation Oncology into a center of excellence for targeted radiation therapy. Now we see our research momentum increasing, particularly as our prospective studies mature.

Our currently underway analysis of our new database of post-prostatectomy anatomical information in over 500 treatment fractions will allow an unprecedented look at the inter- and intra- fraction changes in morphology of the prostatic fossa. Our planned participation in SWOG encompassed protocols will allow us to contribute our expertise with Calypso localization to national research. The continued accrual to our reduced PTV margins protocol, and participation of BAMC in this protocol, will lead to important quality of life outcomes publications in prostate cancer.

The research and education opportunities afforded by this progress have not gone unnoticed. On one of our abstract submission we had the opportunity to collaborate with the Madigan Radiology Department; a collaboration which we hope will expand. We also were able to include members of the pathology department in our visiting professorships, included a substantial number of primary care providers in our visiting professorship this year and the year prior as well as medical oncologists, and hope to continue to develop research collaboration with these groups in the upcoming year. We continue to work closely with Madigan Urologists to refine techniques and management strategies for our entire cohort of prostate cancer patients.

As discussed in this report, we are moving toward exciting new areas of research, including use of Calypso beacons to track breathing motion in breast cancer and lung-cancer patients and using targeted radiation therapy modalities to improve our decades-old methods for treating metastatic lesions in the palliative setting. In addition to these areas of investigation we also envision in the distant future developing expertise with Calypso beacons implanted in the lung and other sites.

This is an exciting era for targeted radiation therapy. With the help of the Congressionally Directed Medical Research Program we plan to treat our patients – military servicemen and women and their families – with lifesaving technology at the forefront of our field for years to come.

References: N/A

Appendices: See attached abstracts

APPENDIX I

Abstract: Dose to the muscles of fecal continence during radiation therapy for prostate cancer. *

**Waggoner A, Brown M, Tinnel B, Halligan J, Brand T, Brooks J, Ninneman S, Hughs G, Macdonald D. (2-4 February 2012). Dose to the muscles of fecal continence during radiation therapy for prostate cancer. Poster presented at the ASCO/ASTRO/SUO 2012 Genitourinary Cancers Symposium, San Francisco, CA.*

INTRODUCTION AND OBJECTIVE: Radiation therapy for prostate cancer can lead to loss of fecal continence; our understanding of the dose-volume relationships of this late toxicity continues to develop. The external anal sphincter (EAS), internal anal sphincter (IAS), the puborectalis (PRM), the pubococcygeus (PCM), and the iliococcygeus (ICM) muscles all contribute to fecal continence. We developed a reproducible method for contouring these muscles and in this preliminary study evaluate whether decreased planning target volume (PTV) margins lead to potentially clinically significant decreases in dose to these muscles during definitive radiation therapy for prostate cancer.

METHODS: Muscles involved in fecal continence were contoured for 10 consecutive patients on a prospective study of reduced PTV margins for treating low-to-intermediate risk prostate cancer with intensity modulated radiation therapy (IMRT) using an electromagnetic localization system. IMRT plans to a prescribed dose of 7740 cGy were developed using 10mm PTV margins (5mm posteriorly), and compared with actual treatment IMRT plans using 3mm circumferential PTV margins. Decreases in dose were evaluated for statistical significance using an unpaired t-test.

RESULTS: Reducing PTV margins decreased the mean PTV volume from 176.2 ml to 91.9 ml. Mean doses to the EAS, IAS, and rectum (REC) decreased significantly; from 11.0 Gy to 4.1 Gy ($p=0.005$), from 30.5 Gy to 15.0 Gy ($p = 0.004$), and from 43.7 Gy to 35.6 Gy ($p=0.006$) respectively. Decrease in the mean dose to the PRM was nearly statistically significant, 48.7 Gy to 34.6 Gy ($p = 0.055$). Decreases in mean doses to the PCM and ICM were not statistically significant; from 61.9 Gy to 55.2 Gy ($p = 0.107$), and from 40.7 Gy to 34.8 Gy ($p = 0.176$), respectively.

CONCLUSIONS: Using electromagnetic tracking to reduce PTV margins leads to a significant decrease in dose to the muscles of fecal continence, with mean dose decreases in a range that may be clinically significant.

APPENDIX II

Abstract: Anorectal Angle is Associated With Bowel Toxicity One Month Following Radiation Therapy for Prostate Cancer *

* Gossweiler M, Waggoner A, Huang R, Ninneman S, Hughs G, Wendt S, Brown M, Tinnel B, Macdonald D. (8-9 February 2013). Anorectal angle is associated with bowel toxicity one month following radiation therapy for prostate cancer. Poster presented at the ASTO/RSNA 2013 Cancer Imaging and Radiation Therapy Symposium, Orlando, FL.

* Gossweiler M, Waggoner A, Huang R, Ninneman S, Hughs G, Wendt S, Brown M, Tinnel B, Macdonald D. (2013, April). Anorectal angle is associated with bowel toxicity one month following radiation therapy for prostate cancer. Oral presentation given at Madigan Army Medical Center's Annual Research Day, Tacoma, WA.

PURPOSE/OBJECTIVES: Bowel toxicity following radiation therapy (XRT) for prostate cancer can cause a significant decrease in patient quality of life. Some of this toxicity - such as rectal bleeding - seems to relate directly to damage to the rectal wall, while other elements of bowel toxicity - such as urgency, frequency, or fecal leakage - may be related to anal canal geometry and musculature. The anorectal angle (ARA) and the volume of the puborectalis muscle (VPRM) - which assists in maintaining the anorectal angle - are two image-based measurements which are known to be related to the maintenance of fecal continence. Here we explore whether a large pre-treatment ARA or a small VPRM are associated with increased bowel toxicity following XRT.

MATERIALS/METHODS: We studied 10 consecutive patients with low-to-intermediate risk prostate cancer treated on a prospective study with definitive intensity-modulated radiation therapy (IMRT). All patients completed the EPIC quality of life questionnaire at the end of treatment, and at 1 and 4 months post-treatment. We used the patients' answers on the bowel section of these questionnaires to divide the patients into two groups: one with few side effects as reflected by a score within 10% of the most favorable score possible, and the other with more side effects as reflected by a lower score. The patients' VPRMs were measured by contouring on planning CT scans. The anorectal angle was measured on sagittal CT scan reconstructions as the angle between the line down the center of the long axis of the anal canal, and the line down the center of the long axis of the rectum immediately superior to the anal canal. Both the VPRM and the ARA measurements were then categorized as "small" or "large" using the mean as the dividing line. We used Fisher's exact test to evaluate for a significant association between ARA and bowel toxicity and between VPRM and bowel toxicity.

RESULTS: EPIC bowel toxicity scores varied from a low of 56.7 to a high of 100, with a mean of 83.8 and standard deviation of 14.76. VPRM varied from 6.45cc to 15.87cc (std. dev. 3.13), and was not associated with bowel toxicity ($p = 1.000$ at all time points). ARA varied between 93.5 and 121.8 deg (std. dev. 9.69), and was correlated with bowel toxicity one month following completion of therapy ($p = 0.048$), but not at the end of XRT ($p = 1.000$) or at 4 months post-treatment ($p = 0.524$).

CONCLUSIONS: These results are hypothesis-generating and based on a very small sample size. Further evaluation of the association of ARA with bowel toxicity following XRT for prostate cancer in a larger cohort is warranted. If there is an association between baseline ARA and bowel toxicity, measuring the ARA on a pre-treatment CT scan could allow more informed counseling of patients regarding the risks for bowel toxicity following XRT.

APPENDIX III

Abstract: The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy. *

* Kathpal M, Ninneman S, Huang R, Wendt S, Malmer C, Brand T, Halligan J, Brooks J, Brown M, Tinnel B, Macdonald D. (14-16 February 2013). The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy. Poster presented at the ASCO/ASTRO 2013 Genitourinary Cancers Symposium, Orlando, FL.

* Kathpal M, Ninneman S, Huang R, Wendt S, Malmer C, Brand T, Halligan J, Brooks J, Brown M, Tinnel B, Macdonald D. (2013, April). The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy. Oral presentation given at Madigan Army Medical Center’s Annual Research Day, Tacoma, WA.

BACKGROUND: We determined necessary PTV margins when beacons are used to localize the prostatic fossa in post-prostatectomy patients. We hypothesized beacon localization would allow for decreased PTV margins and increased normal tissue sparing.

METHODS: 10 patients requiring post-prostatectomy radiation were treated on this IRB-approved prospective study. Each patient had 3 beacons placed in the prostatic fossa. Daily radiation was localized by beacons and a cone-beam CT (CBCT) taken for analysis. By measuring differences between the treated clinical target volume (CTV) and relevant anatomy on 5 equally-spaced axial CT slices we calculated necessary PTV margins for each fraction. We then auto-fused each CBCT scan with the treatment planning scan, recorded the shifts incurred, and repeated our measurements, representing a hypothetical CBCT - localized treatment. We report a PTV margin for each technique that would cover the CTV during 90% of all 304 fractions analyzed. We also used intra-fraction motion data to produce a worst-case estimate of required PTV bladder margins.

RESULTS: The average shifts from the beacon to CBCT- localized isocenter were 2.9, 3.2, 1.0 mm and 0.58 degrees in the vertical, longitudinal, lateral, and rotational planes, respectively. Necessary PTV margins for beacon and CBCT localization are listed in Table 1.

CONCLUSIONS: Beacon localization “attaches” the CTV to the bladder, allowing a decrease in PTV margin or the amount of posterior bladder included in the CTV. This could lead to decreased rates of bladder toxicity.

Table 1: Necessary PTV margins based on 90th percentile of 304 fractions analyzed

Axial CT slice location and reference structure	Necessary PTV margins							
	Direction				Without intra-fraction motion		With intra-fraction motion	
	ANT	POST	LT	RT	BEACONS (mm)	CBCT (mm)	BEACONS (mm)	CBCT (mm)
INFERIOR								

Symphysis pubis	X				3	6		
Ant rectal wall		X			9	7		
INFERIOR-MID								
Symphysis pubis	X				3	6		
Ant rectal wall		X			7	5		
MIDDLE								
Symphysis pubis	X				3	6		
Ant rectal wall		X			5	3		
Left obt internus			X		4	4		
Right obt internus				X	5	3		
SUPERIOR-MID								
Post bladder wall	X				7	12	8	13
Ant rectal wall		X			7	2		
SUPERIOR								
Post bladder wall	X				8	15	8	15
Ant rectal wall		X			9	6		

APPENDIX IV

Abstract: Differences between beacon-localized and cone-beam CT (CBCT)-localized radiation therapy to the prostatic fossa.*

* Kathpal M, Brand T, Ninneman S, Hughs G, Katz L, Brown M, Halligan J, Brooks J, Macdonald D, Tinnel B. (22-25 September 2013). Differences between beacon-localized and cone-beam CT (CBCT)-localized radiation therapy to the prostatic fossa. Poster presented at the ASTRO 2013 Annual Conference, Atlanta, GA.

PURPOSE/OBJECTIVES: Either CBCT or electromagnetic beacon transponders can localize the prostatic fossa for adjuvant or salvage radiation therapy. We hypothesize that beacons localize this isocenter differently than CBCT. We sought to test this hypothesis, and to evaluate if the beacon-localized isocenter more closely aligns the clinical target volume (CTV) with daily changes in rectum and bladder position such that planning target volume (PTV) margins may be reduced.

MATERIALS/METHODS: 12 patients requiring post-prostatectomy radiation were treated on this IRB-approved prospective study. Each patient had 3 beacons placed in the prostatic fossa; one to the right of the vesico-urethral anastomosis and two others in the location of the left and right prostate pedicles adjacent to the removed seminal vesicles. Daily radiation was localized by beacons and a CBCT was taken for analysis. By measuring differences between the CTV and relevant anatomy on 5 equally-spaced axial CT slices we calculated necessary PTV margins for each fraction. We then auto-fused each CBCT scan with the treatment planning scan, recorded the shifts incurred, and repeated our measurements, representing a hypothetical CBCT -localized treatment. We report a PTV margin for each technique that would cover the CTV during 95% of all 379 fractions analyzed. We also used intra-fraction motion data (considering anterior motion to coincide with anterior movement of the posterior bladder wall) to produce a worst-case estimate of required anterior PTV margins.

RESULTS: When shifting from the beacon-localized isocenter to the CBCT-localized isocenter, the mean vertical patient shift for all 379 fractions was 1.3 mm ant (SD 2.9 mm, range 5 mm post to 10 mm ant). The mean longitudinal shift was 2.2 mm sup (SD 3.1 mm, range 7 mm inf to 12 mm sup). The mean lateral shift was 0.3 mm to the left (SD 1.5, range 13 mm left to 4 mm right). For beacon-localized treatment, maximum necessary PTV margins were 10 mm ant, 12 mm post, and 6 mm lat. Incorporating measured intra-fraction motion, the anterior margin would be increased to 11 mm. For CBCT-localized treatment, maximum necessary PTV margins were 18 mm ant, 8 mm post, and 6 mm lateral. Inclusion of intra-fraction motion did not change the necessary anterior margin for CBCT-localized treatment. Intra-fraction motion exceeded tracking limits of 5 mm (corrected with treatment pause or reposition) in 13% of fractions.

CONCLUSIONS: In our cohort, beacon localization placed the isocenter (on average) anterior and superior to the CBCT isocenter, with significant variation over the entire group. The beacon-localized isocenter accounts for some changes in bladder position, thus allowing a decreased anterior PTV margin, or decreased amount of the posterior bladder included in the CTV.

APPENDIX V

Abstract: Inter-fraction displacement of electromagnetic beacons in patients receiving post-prostatectomy radiation therapy. *

* Kathpal M, Brand T, Ninneman S, Hughs G, Smith A, Brooks J, Halligan J, Malmer C, Tinnel B, Macdonald D. (22-25 September 2013). Inter-fraction displacement of electromagnetic beacons in patients receiving post-prostatectomy radiation therapy. Poster presented at the ASTRO 2013 Annual Conference, Atlanta, GA.

PURPOSE/OBJECTIVES: Optimally using beacon transponders during radiation therapy to the prostatic fossa requires understanding daily variations in the spatial relationships of the three beacons with each other and surrounding target areas. In a beacon-localized post-prostatectomy radiation therapy cohort we sought to understand variation in beacon geometry and location by tracking each beacon's daily position within the coordinate system of the planning CT.

MATERIALS/METHODS: 12 patients on an IRB-approved prospective study had treatments localized by beacon transponders, and a daily cone-beam CT (CBCT) taken for position verification. Each CBCT was retrospectively auto-matched to the treatment planning CT using a reproducible algorithm. We recorded the location of each beacon within the auto-matched CBCT coordinate system, making the assumption that this accurately reflected the planning CT coordinate system. We then quantified inter-fraction beacon displacement over a total of 379 fractions. We also measured daily differences between each beacon's planned and actual distance from each other beacon in each axis.

RESULTS: Mean inter-fraction beacon displacements in mm (with standard deviation (SD) in mm) are displayed in Table 1. Mean daily differences from plan in distance between beacons were all less than 1 mm in each axis, but SD varied significantly. In the lateral axis, these differences for all beacons had a SD of 2.0 – 2.4 mm. For the R base and L base beacons these differences in all axes had a SD of 1.9 – 2.0 mm. In contrast, the difference from plan in distance between either base beacon and the apex beacon in the sup/inf or ant/post axis had a SD of 3.1 – 3.4 mm.

CONCLUSIONS: On average beacons moved 0.2 – 2.0 mm superior and anterior from the planned location during radiation therapy, but this was overshadowed by a large SD representing significant random motion. The difference from plan in the distance between each base beacon and the apex beacon also varied significantly in the sup/inf and ant/post axes. These beacon displacements likely reflect daily changes in bowel and bladder position - we are currently studying their clinical significance.

Table 1: Mean inter-fraction beacon motion in mm with SD.

Beacon	Sup/Inf Axis	Ant/Post Axis	Left/Right Axis
Apex	1.3 sup SD 2.6	0.8 ant SD 2.6	0.1 left SD 1.3
L Base	1.9 sup SD 3.9	1.0 ant SD 3.8	0.4 right SD 1.5
R Base	2.0 sup SD 4.0	0.2 ant SD 4.1	0.0 left SD 1.9

APPENDIX VI

Abstract: Reduced Planning Target Volume (PTV) Margins With Real-Time Electromagnetic Tracking During Definitive Radiation Therapy For Prostate Cancer.*

* Sun K, Brand T, Hughs G, Halligan J, Tinnel B, Macdonald D. (26 October 2014). Reduced planning target volume (PTV) margins with real-time electromagnetic tracking during definitive radiation therapy for prostate cancer. Poster presented at the Western Section American Urology Association, Maui, HI.

PURPOSE: Definitive radiation therapy for prostate cancer may lead to gastrointestinal (GI) and genitourinary (GU) toxicities. Real-time electromagnetic tracking of the prostate minimizes intra-fraction prostate motion and allows decreased PTV margins, which should decrease the dose administered to the bowel and bladder near the prostate. We evaluated the feasibility and clinical outcome of this strategy, and report preliminary results here.

MATERIALS AND METHODS: 24 patients with low-to-intermediate risk prostate cancer were treated on a prospective study with definitive intensity-modulated radiation therapy (IMRT) using an electromagnetic localization system. 3mm PTV margins were used, with 2mm electromagnetic tracking limits. Timing metrics were recorded for each treatment. Patients completed the EPIC quality of life questionnaire prior to treatment, at the last treatment, and at regular follow-up intervals. During clinical follow-up at the same time points, toxicity scores were assigned by a radiation oncologist using the NCI Common Toxicity Criteria.

RESULTS: The median follow-up period was 24 months (range, 3-59 months), during which no patient experienced biochemical failure (Phoenix definition). Mean total daily treatment time was 10.0 minutes (range 7.1 to 15.3 minutes). 79% of patients experienced acute side effects and 54% experienced late side effects – but, in general, side effects were mild. 1 patient (4%) experienced an acute grade 3 GU side effect (urinary retention requiring TURP) and there were no acute grade 3 GI side effects. 13% of patients experienced late grade 2 GU side effects and 13% late grade 2 GI side effects, with no late grade 3 or 4 side effects reported. Mean EPIC scores for bowel, urinary, and sexual function areas at three time points are presented in Table 1 below.

Table 1: Mean EPIC Scores (% of best possible score)

	Bowel	Urinary	Sexual Function
Baseline	93.0 ± 6.9	89.3 ± 10.7	49.7 ± 28.8
Final XRT	79.5 ± 15.1	72.9 ± 19.2	37.3 ± 29.3
4 Months Post Treatment	88.4 ± 32.4	86.4 ± 16.2	35.0 ± 13.9

CONCLUSIONS: Definitive radiation therapy for prostate cancer with reduced PTV margins was clinically feasible and very well tolerated. Serial EPIC scores demonstrate mild changes in bowel, urinary and sexual function areas. This data will be useful in counseling patients regarding treatment options for low-to-intermediate risk prostate cancer.

APPENDIX VII

Abstract: Margins for Deep Inspiration Breath Hold (DIBH) With Electromagnetic Confirmation of Chest Wall Position for Adjuvant Therapy of Left Breast Cancer*

* Kathpal M, Tinnel B, Malmer C, Ninneman S, Wendt S, Hughs G, Gossweiler M, Valentich D, Sillings J, Macdonald D. (15 September 2014). Margins for deep inspiration breath hold (DIBH) with electromagnetic surface transponder confirmation of chest wall position for adjuvant therapy of left breast cancer. Poster presented at The American Society for Radiation Oncology (ASTRO) Annual Conference, San Francisco, CA.

PURPOSE/OBJECTIVES: While DIBH is often used for radiation of left breast cancers to reduce heart dose, the combination of DIBH and electromagnetic surface transponders is new. We examined the accuracy of this combination in terms of systematic and random error to develop a theoretical necessary margin for such treatment using the technique of van Herk et al. initially derived for prostate cancer patients.

MATERIALS/METHODS: This IRB-approved study included 15 patients planned and treated with DIBH with electromagnetic surface transponders used to confirm chest wall (CW) position. After set-up and shifts, confirmatory port films were taken just prior to treatment daily. Surface transponders were used to track the position of the CW during port film and treatment. We retrospectively compared port films to planning DRRs using a reproducible auto-match technique to determine interfraction error in 3 dimensions. We then used transponder tracking reports to compare the CW position during treatment to that at the time of port film. By combining the port-film and tracking report analyses we determined positioning error for the "worst case" (using the largest error recorded for each axis on each day), and for the "most likely case" (using the error from the CW position at which the majority of the treatment was delivered each day). We then used the method of Van Herk et al., including a 2D margin formula (margin = $2.15\Sigma + 0.7\sigma$), to calculate estimates of systematic and random error and margins along each axis for the "most likely" and "worst-case" situations.

RESULTS: For both "most likely" and "worst case" situations, mean, systematic and random error, and necessary margin for 95% coverage of 90% of patients according to 2D parameters described by Van Herk, et al. are displayed in Table 1.

CONCLUSIONS: Necessary margins for breast cancer treatment with DIBH and surface transponder tracking include a 9 mm longitudinal margin, 5 mm vertical margin, and 4 mm lateral margin. Margins required for the "worst case" did not differ significantly. Margins were predominantly determined by interfraction error.

Table 1: Errors and necessary margins ("most likely case"/"worst case")

	Lateral (LR) (mm)	Longitudinal (SI) (mm)	Vertical (AP) (mm)	
Mean error (M)	0.5 /	2.1 /	-0.5 /	
Systematic error (Σ)	1.2 /	2.7 /	1.4 /	
Random error(σ)	2.0 /	3.2 /	2.0 /	
Necessary margin ($2.15\Sigma + 0.7\sigma$)	4.0 /	8.1 /	4.4 /	

APPENDIX VIII

Abstract: Deep Inspiration Breath Hold (DIBH) With Electromagnetic Surface Transponder Confirmation of Chest Wall Position for Adjuvant Therapy of Left-Sided Breast Cancer.*

* Kathpal M, Tinnel B, Malmer C, Ninneman S, Wendt S, Hughs G, Gossweiler M, Valentich D, Buff S, Macdonald S. (15 September 2014). Deep inspiration breath hold (DIBH) with electromagnetic surface transponder confirmation of chest wall position for adjuvant therapy of left-sided breast cancer. Poster presented at The American Society for Radiation Oncology (ASTRO) Annual Conference, San Francisco, CA.

PURPOSE/OBJECTIVES: While DIBH is often used for radiation of left breast cancers to reduce heart dose, the combination of DIBH and electromagnetic surface transponders is new. We examined intra-fraction motion and dose reduction to the heart with this technique.

MATERIALS/METHODS: 15 patients were included in this IRB-approved study. Patients were planned and treated using DIBH. We also obtained treatment-position free-breathing (FB) CT scans and fused them to DIBH scans based on breast position to compare mean heart (MH) and left anterior descending coronary artery (LAD) dose with either technique. We used daily port films to verify treatment position. Surface transponders were used to track the position of the chest wall (CW) during port film and treatment. We retrospectively used transponder tracking reports to compare CW position during treatment to that at the time of port film and to determine total CW motion in each axis during beam-on time and each total breath hold period (a surrogate for potential CW position during an unmonitored breath-hold). A paired t-test was used to compare heart dose with and without DIBH and CW excursion during beam-on and total breath hold time.

RESULTS: DIBH significantly reduced MH and LAD dose versus FB plans (MH 1.26 ± 0.51 Gy v 2.84 ± 1.55 Gy, $p \leq 0.001$), (LAD 5.49 ± 4.02 Gy v 18.15 ± 8.78 Gy, $p \leq 0.001$). Mean CW positional difference from port film $\pm 2SD$ and CW excursion $\pm 1SD$ during breath hold and beam-on time are reported in Table 1. In each dimension, CW excursion during breath hold was significantly greater than CW position during beam-on time with $p \leq 0.001$. Treatment was paused in 23% of fractions to adjust for suboptimal breath hold or CW position.

CONCLUSIONS: Electromagnetic confirmation of CW position is technically feasible, allowed verification of breath-hold reproducibility to within 3.2 mm in 95% of fractions, and allows therapists to constrain beam-on time to the most reproducible and stable portion of each breath hold leading to a significant reduction in intrafraction motion during DIBH. With our technique DIBH during irradiation of left-breast cancer patients reduced the mean heart and LAD dose by at least 50%.

Table 1:

	Lateral (LR) (mm)	Longitudinal (SI) (mm)	Vertical (AP) (mm)
Difference in CW position between port film and treatment $\pm 2SD$	0.1 ± 2.5	0.1 ± 3.1	0.1 ± 2.3
CW excursion during breath hold	2.5 ± 2.3	5.0 ± 4.0	4.2 ± 2.8
CW excursion during beam-on	1.1 ± 1.2	1.7 ± 1.4	1.3 ± 0.9

APPENDIX IX

Abstract: Deep Inspiration Breath Hold (DIBH) With Electromagnetic Surface Transponder Confirmation of Chest Wall (CW) Position During Radiation for Left Breast Cancer.*

* Kathpal M, Sun K, Malmer C, Ninneman S, Wendt S, Hughs G, Macdonald D, Tinnel B. (4 September 2014). Deep inspiration breath hold (DIBH) with electromagnetic transponder confirmation of chest wall position for radiation therapy of left breast cancer. Poster presented at The American Society of Clinical Oncology/Breast Cancer Symposium, San Francisco, CA.

* Kathpal M, Tinnel B, Malmer C, Ninneman S, Wendt S, Hughs G, Gossweiler M, Valentich D, Buff S, Macdonald S. (2015, April). Deep inspiration breath hold (DIBH) with electromagnetic surface transponder confirmation of chest wall position for adjuvant therapy of left breast cancer. Oral presentation given at Madigan Army Medical Center's Annual Research Day, Tacoma, WA.

BACKGROUND: DIBH during radiation of left breast cancers reduces heart dose, potentially reducing late cardiac ischemic events, but requires a treatment CW position significantly different from a free-breathing (FB) position. We sought to improve the accuracy of radiation therapy during DIBH by using electromagnetic surface transponders to track the position of the CW during treatment. We examined the benefit of this technique in reducing dose to the heart and consistently reproducing the DIBH position. We also evaluated the difference between FB and DIBH CW position and compared CW movement within the plateau of each DIBH to within beam-on time.

METHODS: 15 patients participated in this IRB-approved study. Patients were planned and treated using DIBH. We fused treatment-position FB CT scans to DIBH scans to compare mean heart (MH) and left anterior descending coronary artery (LAD) dose. We used surface transponder tracking reports to determine CW motion at the time of daily port films, during FB, the plateau of each DIBH, and beam-on time. We summed anterior and superior motion using the Pythagorean Theorem and report our results in this combined axis. Paired t-test was used to compare heart dose with vs. without DIBH and CW motion during plateau DIBH vs. beam-on.

RESULTS: DIBH significantly reduced MH and LAD dose vs. FB plans (MH 1.26 ± 0.51 Gy v 2.84 ± 1.55 Gy, $p < 0.01$), (LAD 5.49 ± 4.02 Gy v 18.15 ± 8.78 Gy, $p < 0.01$). DIBH CW position was a mean of 13.9 ± 5.3 mm anterior and superior to FB position. The mean difference in CW position at the time of daily port film vs. beam-on was -1.0 ± 2.5 mm. Plateau DIBH CW motion was 2.8 ± 2.3 mm, significantly increased from CW motion during beam-on (1.1 ± 1.2 mm, $p < 0.01$). Treatment was paused in 23% of fractions to adjust for suboptimal breath hold or CW position.

CONCLUSIONS: DIBH reduced the MH and LAD dose by at least 50%. Real-time tracking with electromagnetic transponders allowed us to limit treatment to the most stable portion of the DIBH plateau, significantly reducing intra-fraction motion. Electromagnetic confirmation of CW position allowed verification of breath-hold reproducibility.

Appendix X

Abstract: Prostate Cancer Radiation Therapy with Reduced Planning Target Volume (PTV) Margins. *

* Sun K, Kathpal M, Tinnel B, Brand T, Ninneman S, Hughs G, Halligan J, Brown M, Brooks J, Macdonald D. (26 February 2015). Prostate cancer radiation therapy with reduced planning target volume (PTV) margins. Poster presented at the 2015 Genitourinary Cancers Symposium, Orlando, FL.

* Sun K, Kathpal M, Tinnel B, Brand T, Ninneman S, Hughs G, Halligan J, Brown M, Brooks J, Macdonald D. (2015, April). Prostate cancer radiation therapy with reduced planning target volume (PTV) margins. Poster presented at Madigan Army Medical Center’s Annual Research Day, Tacoma, WA.

BACKGROUND: Electromagnetic tracking of the prostate during definitive radiation therapy for prostate cancer allows decreased PTV margins which may reduce dose to nearby tissues. Sandler, et al. reported a reduction in patient-reported acute morbidity with this strategy. We conducted a similar prospective study and compare our results with Sandler’s Assessing Impact of Margin Reduction (AIM) study and with a group treated with radiation therapy without reduced PTV margins from the Sanda, et al. PROST-QA cohort.²

METHODS: 25 patients with low-to-intermediate risk prostate cancer were treated on an IRB-approved prospective study with definitive intensity-modulated radiation therapy with 3 mm circumferential PTV margins and daily electromagnetic localization. An EPIC quality of life questionnaire was completed prior to treatment and at the last treatment. Using data from the referenced publications, we performed a two-tailed t-test to compare EPIC scores from our cohort with the AIM and PROST-QA cohorts treated with external beam radiation therapy alone.

RESULTS: Table 1 lists mean pre- and post-treatment EPIC scores and the differences between them.

Table 1: Mean EPIC Score Comparison.

EPIC Domain/Study (n)	Mean (SD)		Mean Difference (95% CI)	P-value in relation to this study
	Pretreatment	Post-treatment		
Bowel/Rectal				
This study (25)	95 (7)	83 (17)	12 (5, 19)	
AIM (41)	92 (19)	90 (18)	2 (-5, 9)	0.07
Prost-QA (148)	94 (11)	79 (21)	16 (13, 19)	0.32
Urinary Irritation				
This study (25)	90 (10)	69 (22)	21 (12, 29)	
AIM (38)	85 (18)	81 (23)	4 (-2, 10)	0.002
Prost-QA (148)	87(14)	70 (21)	17 (13, 20)	0.36
Urinary Incontinence				
This study (25)	90 (18)	86 (22)	4 (-2, 9)	
AIM (43)	93 (13)	86 (21)	7 (1, 12)	0.47
Prost-QA (138)	93 (13)	85 (21)	8 (5, 11)	0.28
Sexual				
This study (25)	58 (35)	42 (34)	17 (6, 28)	0.28
AIM (43)	51 (32)	51 (27)	0 (-9, 9)	0.02
Prost-QA (133)	64 (28)	52 (30)	12 (9, 15)	

CONCLUSIONS: Our patients fared similarly to the PROST-QA cohort, but had a significantly greater mean decrement in the urinary irritation and sexual domains, and a trend toward a greater mean decrement in the bowel/rectal domain, in comparison to the AIM cohort.

Appendix XI

Abstract: Disruptive Innovation in Proton Therapy. *

* Macdonald D, Ninneman S, Tinnel B. (27 February 2015). *Disruptive innovation in proton therapy*. Oral presentation given at the 54th Annual Conference of the Particle Therapy Co-Operative Group (PTCOG), San Diego, CA.

BACKGROUND: The theory of disruptive innovation has been used to describe the process by which large incumbent businesses are overtaken by businesses which initially produce a simpler, cheaper, and inferior product, but gain a foothold with less-demanding customers and are then propelled along a unique improvement trajectory. We examined whether applying proton therapy in the palliative setting could provide opportunities for improvement in patient care through phenomena related to disruptive innovation.

METHODS: We contrasted low-to-moderate dose palliative proton therapy with definitive high-dose proton therapy in relation to hallmarks of disruptive innovation as described by Christensen¹:

Hallmark 1 - a situation in which there is a limit in the ability to absorb new technology

Hallmark 2 - a population of customers for whom the technology has outpaced their ability to use it

Hallmark 3 - the opportunity for a simpler product to be introduced to a larger, less-demanding customer base followed by a rapid improvement cycle.

RESULTS: We found good correlation between palliative proton therapy and the above listed elements of disruptive innovation including (Hallmark 1) logistic, economic, and clinical research hurdles which limit the widespread use of proton therapy as currently delivered. (Hallmark 2) High dose proton therapy is viewed as useful mainly for either improving high dose conformality or reducing low dose spillage, overshooting the needs of palliative patients in both these areas. (Hallmark 3) There is an opportunity for lower-dose palliative proton therapy to succeed with simplified dosimetry and delivery techniques particularly applicable to spot-scanning proton therapy systems, with short palliative treatment courses fit into otherwise unused treatment slots, decreasing the true cost of such treatment. Finally, and most importantly (also Hallmark 3), palliative proton therapy would allow for a rapid improvement cycle secondary to a short clinical trial completion time and important research opportunities suited to this population such as proton RBE modulation, spatial fractionation, and immunomodulatory effects.

CONCLUSIONS: It may be possible to improve patient care through phenomena related to disruptive innovation if we develop simplified planning and quality assurance methods for lower-dose palliative proton therapy with treatment fit into patient flow gaps at proton therapy centers. Disruptive innovation theory predicts that offering this treatment at prices low enough to maximize its use could lead to increased efficacy of proton therapy along previously undervalued axes, with eventual recoument of initial investment.

REFERENCES: 1) Christensen, Clayton M. (2014): *Disruptive Innovation*. In: Soegaard, Mads and Dam, Rikke Friis (eds.). "The Encyclopedia of Human-Computer Interaction, 2nd Ed.". Aarhus, Denmark: The Interaction Design Foundation. Available online at https://www.interaction-design.org/encyclopedia/disruptive_innovation.html

Appendix XII

Abstract: Change in Practice Patterns and Increasing Use of Modern Technology for Palliative Treatments at a Military Hospital. *

** Premo C, Tinnel B, Collins M, Ninneman S, Kathpal M, Buff S, Ahrmendi J, Stanke A, Valentich D, Macdonald D. (29 November – 4 December 2015). Change in practice patterns and increasing use of modern technology for palliative treatments at a military hospital. Poster to be presented at the 101st Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA), Chicago, IL.*

PURPOSE/OBJECTIVES: A wide range of doses, fractionation schemes, and techniques can be employed for palliative treatments. Randomized trials and recent ASTRO guidelines support the use of single fraction or hypo-fractionated regimens, particularly for painful bone metastasis. With comparable efficacy, regimens of 1-5 fractions are more cost effective and convenient for patients and caregivers. The choice of total dose, fractions, and technique may be influenced by financial factors including insurance coverage. In military hospitals these decisions are determined on a case by case basis with different financial considerations than those faced in non-military institutions. Herein we examine the change in practice patterns for palliative treatment over the course of 8 years at a military hospital.

MATERIALS/METHODS: Patients treated with palliative intent from June 2006 – December 2007 and from January 2013 - June 2014 were retrospectively reviewed in this IRB-approved study. This included 80 and 69 patients, respectively. Total dose, dose per fraction, number of fractions, number of sites treated, technique, and number of single fraction treatments were compared between the two groups, using a paired t-test for continuous variables and 95% confidence intervals (95% CI) for categorical variables. We excluded whole brain treatments and non-solid tumor treatments which led to the inclusion of 100 and 129 treated sites, respectively.

RESULTS: Between 2006-2007 (group 1) and 2013-2014 (group 2), there was a significant increase in the average dose per fraction, with mean dose of 328 cGy for group 1 vs 504 cGy for group 2 (mean difference 175 cGy, $p < 0.0001$). The mean total dose per site and mean number of fractions decreased over time. The mean total dose/site was 2858 cGy in group 1 and 2182 cGy in group 2 ($p < 0.0001$). There was a large difference in the use of single fraction treatments between the two groups as well, 8% in group 1 (95% CI 4% to 15%) and 34% in group 2 (95% CI 26% to 43%). The use of IMRT/VMAT/Arc increased from 0% in group 1 (95% CI 0% to 4%) to 21% in group 2 (95% CI 15% to 29%). The mean number of sites treated per patient was not significantly different (2.3 and 2.6 in groups 1 and 2, respectively, $p = 0.3$).

CONCLUSIONS: We found a significant increase in the use of shorter palliative treatments, higher doses per fraction, single fraction treatments, and use of advanced technologies over the time range studied. These changes represent the implementation of modern techniques when deemed necessary and beneficial to patients, in a setting less constrained by insurance billing practices. In addition, the increase in single fraction treatments represents a more cost effective use of palliative radiation which follows consensus guidelines supported by randomized evidence.

Appendix XIII

Complete listing of all presentations for ease of reference

1. Waggoner A, Brown M, Tinnel B, Halligan J, Brand T, Brooks J, Ninneman S, Hughs G, Macdonald D. (2-4 February 2012). Dose to the muscles of fecal continence during radiation therapy for prostate cancer. Poster presented at the ASCO/ASTRO/SUO 2012 Genitourinary Cancers Symposium, San Francisco, CA.
2. Gossweiler M, Waggoner A, Huang R, Ninneman S, Hughs G, Wendt S, Brown M, Tinnel B, Macdonald D. (8-9 February 2013). Anorectal angle is associated with bowel toxicity one month following radiation therapy for prostate cancer. Poster presented at the ASTO/RSNA 2013 Cancer Imaging and Radiation Therapy Symposium, Orlando, FL.
3. Gossweiler M, Waggoner A, Huang R, Ninneman S, Hughs G, Wendt S, Brown M, Tinnel B, Macdonald D. (2013, April). Anorectal angle is associated with bowel toxicity one month following radiation therapy for prostate cancer. Oral presentation given at Madigan Army Medical Center's Annual Research Day, Tacoma, WA.
4. Kathpal M, Ninneman S, Huang R, Wendt S, Malmer C, Brand T, Halligan J, Brooks J, Brown M, Tinnel B, Macdonald D. (14-16 February 2013). The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy. Poster presented at the ASCO/ASTRO 2013 Genitourinary Cancers Symposium, Orlando, FL.
5. Kathpal M, Ninneman S, Huang R, Wendt S, Malmer C, Brand T, Halligan J, Brooks J, Brown M, Tinnel B, Macdonald D. (2013, April). The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy. Oral presentation given at Madigan Army Medical Center's Annual Research Day, Tacoma, WA.
6. Kathpal M, Brand T, Ninneman S, Hughs G, Katz L, Brown M, Halligan J, Brooks J, Macdonald D, Tinnel B. (22-25 September 2013). Differences between beacon-localized and cone-beam CT (CBCT)-localized radiation therapy to the prostatic fossa. Poster presented at the ASTRO 2013 Annual Conference, Atlanta, GA.
7. Kathpal M, Brand T, Ninneman S, Hughs G, Smith A, Brooks J, Halligan J, Malmer C, Tinnel B, Macdonald D. (22-25 September 2013). Inter-fraction displacement of electromagnetic beacons in patients receiving post-prostatectomy radiation therapy. Poster presented at the ASTRO 2013 Annual Conference, Atlanta, GA.
8. Sun K, Brand T, Hughs G, Halligan J, Tinnel B, Macdonald D. (26 October 2014). Reduced planning target volume (PTV) margins with real-time electromagnetic tracking during definitive radiation therapy for prostate cancer. Poster presented at the Western Section American Urology Association, Maui, HI.

9. Kathpal M, Tinnel B, Malmer C, Ninneman S, Wendt S, Hughs G, Gossweiler M, Valentich D, Sillings J, Macdonald D. (15 September 2014). Margins for deep inspiration breath hold (DIBH) with electromagnetic surface transponder confirmation of chest wall position for adjuvant therapy of left breast cancer. Poster presented at The American Society for Radiation Oncology (ASTRO) Annual Conference, San Francisco, CA.
10. Kathpal M, Tinnel B, Malmer C, Ninneman S, Wendt S, Hughs G, Gossweiler M, Valentich D, Sillings J, Macdonald D. (15 September 2014). Margins for deep inspiration breath hold (DIBH) with electromagnetic surface transponder confirmation of chest wall position for adjuvant therapy of left-sided breast cancer. Poster presented at The American Society for Radiation Oncology (ASTRO) Annual Conference, San Francisco, CA.
11. Kathpal M, Sun K, Malmer C, Ninneman S, Wendt S, Hughs G, Macdonald D, Tinnel B. (4 September 2014). Deep inspiration breath hold (DIBH) with electromagnetic transponder confirmation of chest wall position for radiation therapy of left breast cancer. Poster presented at The American Society of Clinical Oncology/Breast Cancer Symposium, San Francisco, CA.
12. Kathpal M, Tinnel B, Malmer C, Ninneman S, Wendt S, Hughs G, Gossweiler M, Valentich D, Buff S, Macdonald S. (2015, April). Deep inspiration breath hold (DIBH) with electromagnetic surface transponder confirmation of chest wall position for adjuvant therapy of left breast cancer. Oral presentation given at Madigan Army Medical Center's Annual Research Day, Tacoma, WA.
13. Sun K, Kathpal M, Tinnel B, Brand T, Ninneman S, Hughs G, Halligan J, Brown M, Brooks J, Macdonald D. (26 February 2015). Prostate cancer radiation therapy with reduced planning target volume (PTV) margins. Poster presented at the 2015 Genitourinary Cancers Symposium, Orlando, FL.
14. Sun K, Kathpal M, Tinnel B, Brand T, Ninneman S, Hughs G, Halligan J, Brown M, Brooks J, Macdonald D. (2015, April). Prostate cancer radiation therapy with reduced planning target volume (PTV) margins. Poster presented at Madigan Army Medical Center's Annual Research Day, Tacoma, WA.
15. Macdonald D, Ninneman S, Tinnel B. (27 February 2015). Disruptive innovation in proton therapy. Oral presentation given at the 54th Annual Conference of the Particle Therapy Co-Operative Group (PTCOG), San Diego, CA.
16. Premo C, Tinnel B, Collins M, Ninneman S, Kathpal M, Buff S, Ahrmendi J, Stanke A, Valentich D, Macdonald D. (29 November – 4 December 2015). Change in practice patterns and increasing use of modern technology for palliative treatments at a military hospital. Poster to be presented at the 101st Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA), Chicago, IL.