Award Number: W81XWH-08-2-0174

TITLE: Targeted Radiation Therapy for Cancer Initiative

PRINCIPAL INVESTIGATOR: Dusten Macdonald, MD

CONTRACTING ORGANIZATION: Geneva Foundation
Tacoma, WA

REPORT DATE: September 2016

TYPE OF REPORT: Annual

PREPARED FOR: 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. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2016	Annual	04 Aug 2015 – 03 Aug 2016

4. TITLE AND SUBTITLE
Targeted Radiation Therapy for Cancer Initiative

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-08-2-0174

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Stephanie Ninneman, RN
Dusten Macdonald, MD
Stacie Wendt, BA

E-Mail: stacie.g.wendt.ctr@mail.mil

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Geneva Foundation
917 Pacific Avenue, Suite 600
Tacoma, WA 98402

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. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

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.

15. SUBJECT TERMS
Calypso, Prostate, Intensity Modulated Radiation Therapy (IMRT), Planning Target Volume (PTV), Beacon Transponders

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	51	

Table of Contents

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 Madigan Army Medical Center (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 VA Puget Sound Health Care System (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 36 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. Seven 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 three study patients in this position with results comparable to supine.

MAMC has now been routinely using the FDA-approved 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 88 off-protocol patients using these approved external beacons, 62 breast cancer patients, 22 Stereotactic Body Radiotherapy (SBRT) patients, and four non-SBRT lung cancer patients. The Calypso system provides a previously unavailable level of additional positional monitoring for these patients, and we have gained considerable expertise with this technique.

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-five of these subjects completed the trial including all follow-up visits through Month 24. All subjects have finished treatment, four are in the follow-up phase, and four were screen failures that never started treatment. Two patients

died while in the follow-up phase; one from lung cancer, which was unrelated to the study, and the second from comorbidities, which were also unrelated to the study. These two subjects completed study follow-up visits through Month 12 and Month 18, respectively. 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.

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 MAJ Andrew Mosier, MC to LTC Jonathan M. Davison, MC; 2. Collaborating Staff member, Stacie Wendt, was added to the protocol; and 3. Change of local site PI at MAMC from LTC Dusten Macdonald, MC to CPT Christopher Premo, MC. (Dr. Macdonald remains the overall PI of the grant and an associate investigator on all protocols.) Continuing review was approved by the MAMC IRB from 15 July 2016 through 14 July 2017. The site prepared the continuing review package for HRPO secondary level approval, and the package was submitted 9 August 2016, following the reporting period of this report.

We have now given five presentations at a national conference and two at Madigan supported by the data collected from this trial. Our most recent research was presented at the ACRO (American College of Radiation Oncology) Annual Meeting in Orlando, FL March 17-19, 2016. 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, 1,209 surveys have been recorded, which contained 20,605 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.

Through analysis of part of this data we have found that reduced margins decreased the mean planning treatment volume by close to half (47.8%), which spared an average of 33.5Gy to the external and internal anal sphincter and rectum.

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 physician-reported acute side effects, and 51.6% experienced physician-reported late side effects. In general, side effects were mild. Only one patient (3.2%) experienced a grade 3 acute genitourinary (GU) side effect (urinary retention requiring transurethral resection of the prostate, or TURP), and there were no grade 3 or 4 gastrointestinal (GI) 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. At the end of treatment, average EPIC scores reflected patients' recorded acute toxicity with bowel,

urinary, and sexual function scores having dropped by 11%, 14%, and 7% respectively. By four months post-treatment, EPIC scores showed average bowel and urinary functions had returned to within the range of baseline. EPIC sexual function scores showed the greatest lasting side effects four months post-treatment, as they remained 7% below baseline.

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. Twenty-one of the thirty-one 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.

In the course of our ongoing analysis, we analyzed the anorectal angle (ARA) of the 28 study patients who have completed at least 12 months of follow-up. The ARA was measured on the mid-sagittal slice of each patient's treatment planning CT scan at the angle formed by the intersection of the central axes of the lower rectum and the anal canal. The mean angle measured was 104°. Having divided the sample cohort by the mean into two groups, "large ARA" and "small ARA", we found no statistically significant difference between small and large ARA in baseline EPIC bowel scores nor in acute or chronic toxicity scores. Given this study data, there appears to be no association between larger ARA and increased bowel toxicity following radiation therapy for prostate cancer. This information adds depth to an earlier, exploratory study we performed to evaluate for an association between pre-treatment ARA and post-treatment bowel toxicity.

Final analysis of all data is currently underway. Our ultimate goal is to publish our final analysis 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 (BAMC) and added them as a site on this protocol. However, due to lack of enrollment, BAMC was removed as a participating site effective as of April 9, 2015. 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 (RTOG) is a recognized leader in working to increase survival and improve the quality of life for cancer patients. We completed our

task of becoming an RTOG member and were excited to open our first RTOG study as an affiliate member. Subsequently, we were informed that MAMC's 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 California. However, since MAMC falls under the cooperative group, Southwestern Oncology Group (SWOG), we are able to participate in certain RTOG studies that are encompassed within that group.

We had originally planned to participate in RTOG 0938, but this trial has reached its accrual goal. We requested an amendment to the Statement of Work (SOW) to include RTOG 0924 (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), which we have now opened through SWOG. This is an equally important study for higher-risk prostate cancer patients. 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. Participation in this national study will help us to continue to establish MAMC 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. We have not yet had the opportunity to enroll any patients for this study but anticipate the accrual of 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 16 signed consent; three were screen failures and never started treatment. All 13 subjects have completed the study from consent to the one year follow-up. 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. We continue to analyze 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 MAJ Andrew Mosier, MC to LTC Jonathan Davison, MC; 2. Collaborating Staff member, Stacie Wendt, was added to the protocol; and 3. Change of local site PI at MAMC from LTC Dusten Macdonald, MC to CPT Christopher Premo, MC. (Dr. Macdonald remains the overall PI of the grant and an associate investigator on all protocols.) The current MAMC IRB review approval period is from 25 August 2016 through 24 August 2017.

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

Enrollment for this study has proven to be difficult, 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 25 signed consent; five were screen failures and never started treatment, and one was withdrawn during treatment due to an inability to accurately localize with Calypso because of an anatomical shift that was occurring when using his Calypso beacons. Nineteen subjects have completed the entire study including all study interventions and follow-up visits.

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 MAJ Andrew Mosier, MC to LTC Jonathan Davison, MC; 2. Collaborating Staff member, Stacie Wendt, was added to the protocol; and 3. Change of local site PI at MAMC from LTC Dusten Macdonald, MC to CPT Christopher Premo, MC. (Dr. Macdonald remains the overall PI of the grant and an associate investigator on all protocols.)The current review approval period is from 21 October 2015 through 20 October 2016.

The last subject for this protocol started treatment at the end of July 2015 and is scheduled to complete the final one year post treatment follow-up in September of 2016.

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.

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 aggregately to provide the best possible data on localizing the prostatic fossa using Calypso beacons.

The database which has been created for this study is in large part built around measurements and calculations that are based directly off of daily subject cone beam computed tomography (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 (inferior, 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-dimentional 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 are often affected by gas or feces in the rectum, the fullness of the bladder, etc., appear to be responsible for a large amount of the random motion that has been tracked via beacon location. In our preliminary analysis, 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. This data will be fundamental in the development of the analysis for the upcoming manuscripts.

A radiation oncology resident from the Uniformed Service University of the Health Sciences, Charlton Smith, completed a rotation at MAMC throughout the month of March, 2016. During this time and under the guidance of MAMC physicians, he focused on drafting a preliminary manuscript based on this research to be submitted to a renowned radiation oncology journal.

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 CBCT 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 one centimeter 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.

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 Volumetric Modulated Arc Therapy (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 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 and December 2007, and those treated from January 2013 to 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.

Although new radiation therapy technologies are expensive, they open the door for increased use of multi-site palliation (MSP) in palliative patients. In modern practice, MSP provides cost benefits to patients when analyzed in terms of cost per treated site. In analyzing patients treated between January 2013 and June 2014, we found that the mean cost per site was significantly less in the MSP cohort compared to the cost of single site palliative (SSP) treatments. The mean cost per site for MSP and SSP was $2,220.09 and $4,552.68 respectively. We also found that when compared to SSP, MSP significantly decreased the daily treatment time per site by an average of three minutes and 40 seconds.

Over the past year we have had five abstracts accepted for presentation or publication based on the information gleaned from this study. Most recently, our abstract entitled "Use of Simultaneous Multi-site Radiation Therapy Palliation: Patterns of Care at a Military Hospital" was published by the American Society of Clinical Oncology (ASCO) for their 2016 Annual Meeting. We also presented "Change in Practice Patterns and Increasing Use of Modern Technology for Palliative treatments at a Military Hospital" at the 101st Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA), as well as the 2016 Madigan Research Day. In addition, an abstract

based on this data was presented at the 2016 Uniformed Services University of the Health Sciences Research Day. We look forward to a subsequent presentation at the American Society for Radiation Oncology (ASTRO) 2016 Annual Meeting this Fall.

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 one centimeter 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 (CW) 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 found that electromagnetic confirmation of CW position allows for verification of breath-hold reproducibility to within 3.1 millimeters in 95% of fractions. We determined that the CW is not necessarily stable during deep inspiration breath-hold, but that the use of electromagnetic confirmation of CW position is technically feasible and allows for

potential improvement in accurate delivery of adjuvant radiation therapy for left breast cancer.

We included 15 patients on our retrospective protocol. Three poster presentations based on our work were presented at two 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. Our manuscript entitled "Deep Inspiration Breath Hold with Electromagnetic Confirmation of Chest Wall Position for Adjuvant Therapy of Left-Sided Breast Cancer: Technique and Accuracy," which we submitted to the Journal of Practical Radiation Oncology (PRO) based on this research, was accepted and is available online. We look forward to its upcoming publication.

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 have treated more than 200 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. A site visit to the Varian Medical Systems, which now owns Calypso ® technology, factory and headquarters in Palo Alto, California with members of the MAMC team was one such grant-supported educational event. On April 21st, 2016 the team met with members of the Varian staff, including Vice Presidents of Medical Affairs and Treatment & Imaging Solutions, to discuss upcoming improvements in radiation therapy treatment delivery and how our research fits into the wider context of treatment delivery in order to better understand the technological setting in which our findings will be used in clinics across the country.

Additional education materials and visits from other DoD providers will be coordinated as time allows through the remainder 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 three abstracts based on the findings at two 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 three separate poster presentations at two 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, four medical students on research rotations, a pre-medical student, as well as two radiation oncology residents assist in evaluating, preparing and writing abstracts based on the data gathered in our Reduced PTV Margins, Post-Prostatectomy, Immobilization, Breast, and Palliative protocols. Most recently, Charlton Smith, a radiation oncology resident from the Uniformed Services University of the Health Sciences completed a rotation at MAMC throughout the month of March, 2016 during which time he focused on drafting, under the guidance of MAMC physicians, a preliminary manuscript based on this research to be submitted to the International Journal of Radiation Oncology, Biology, Physics in the coming months.

We have also had an undergraduate research intern from The Geneva Foundation contribute to our research efforts, as well as two third-year Uniformed Services University (USU) medical students. Our recent abstract, which was published by ASCO (American Society of Clinical Oncology), allowed us to collaborate with two medical oncology colleagues who were coauthors on this study: Anthony Fadell, MD and Penelope Harris, MD.

We have hosted seven 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 targeted radiation therapy" and encourage physicians in the community to seek our expertise. Our most recent event was held on 17 June 2016. Dr. Ian Thompson, Director of the Cancer Therapy and Research Center of the University of Texas Health Science Center in San Antonio, discussed, 'Adaptive Trials and Other Modern Approaches to Cancer Therapeutic Trial Design'. The target audience for this symposium were urologists, urology residents, radiation oncologists and ancillary staff. Dr. Thompson's lecture was highly relatable to the work we are doing at MAMC and prompted much attendee participation during discussion.

We continue to collect information regarding problems and 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 stereotactic body radiation therapy (SBRT). 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 cause cancer cell death while minimizing exposure to surrounding healthy organs. We have successfully treated 22 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.*

Over the past year, we have had five abstract and one manuscript accepted for publication or presentation. On a national level, abstracts were presented via poster at ACRO, RSNA, and ACRO annual meetings. Locally, abstracts were presented at both MAMC and USUHS research days. In addition, the Journal of *Practical Radiation Oncology* published our manuscript online in January 2016. When tallied with past presentations, we have presented a total of 13 poster presentations and one oral presentation, as well as had one abstract published at seven prominent medical symposiums based on the continued findings of our research. Also mentioned prior in this report, we have given three oral presentations and two poster presentations at Madigan Research Day events. One manuscript based on our findings has also been published. Our next presentation, based on our palliative research, will be presented in the fall of 2016 at the American Society for Radiation Oncology (ASTRO) 2016 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, because they are located in California. However, since MAMC falls under the cooperative group, SWOG, we are able to participate in RTOG studies that are encompassed within SWOG.

Insufficient time remaining: This was of great concern to us as our work continues to yield exciting results, and our momentum has increased tremendously. Now that our request for a one year no-cost extension has been granted, we feel confident that we will meet and even exceed our timelines and associated goals. As a side-result of our research, we have discovered applications for this technology beyond prostate cancer and are now able to use electromagnetic beacon transponders in treating breast cancer and

lung cancer as well. We have also had success in tracking breathing motion in conjunction with SBRT treatments for lung cancer. Continuing our current momentum with professional presentations and manuscript submissions based on these studies is an important step that fits one of the main goals of our award – establishing MAMC as a "center of excellence" in targeted radiation therapy. We are enthusiastic to push forward with our research in analyzing comprehensive data as our remaining study participants complete their follow-up visits. We are grateful to be given the opportunity to carry on our research and continue to offer service personnel and their families who suffer from these types of cancers this state-of-the-art treatment.

Key Personnel Updates:

- Dr. Christopher Premo is now the local MAMC Principal Investigator on all of the protocols. Dr. Premo completed a one month rotation at our site in 2015 as a radiation oncology resident. During this time he became familiar with our research and contributed by writing and presented an abstract based on our palliative study to the RSNA 2015 annual meeting. Since that time, Dr. Premo completed his residency and transitioned to the role of staff radiation oncologist at MAMC as Dr. Macdonald retired from the Army and left the department. Dr. Macdonald remains as the overall PI of the grant and an associate investigator on all protocols.

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 124 non-study patients with Calypso (including prostate, breast, SBRT 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.

- Built a database categorizing the cost and treatment time for 2,959 palliative fractions delivered to 156 patients in addition to survivorship of all palliative patients treated between June 2006-December 2007 and January 2013-June2014.

- Constructed a database to track patient excursion and treatment time for more than 550 fractions delivered under the Immobilization study.

- Created a database tracking precise breathing motion and breath hold stability in three axes in left-sided breast cancer patients.

- 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.

- Developed procedures for using Calypso surface beacons to track breathing motion in stereotactic body radiation therapy lung cancer patients thus minimizing radiation to surrounding healthy organs.

- Presented our research findings orally and in poster form at national conferences and Madigan Research Day.

Reportable Outcomes:

See appendix section of 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.

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.

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 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. Final cumulative analysis 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 submissions, we had the opportunity to collaborate with the MAMC Radiology Department, a collaboration which we hope will expand. We also were able to include members of the Pathology Department in our visiting professorships, including a substantial number of primary care providers in our visiting professorships over the years as well as medical oncologists, and we hope to continue to foster future research collaboration with these groups. We continue to work closely with MAMC 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 illiococcygeus (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.

MATHERIALS/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

					Necessary PTV margins				
Axial CT slice location and reference structure	**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.

MATHERIALS/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 = $2.15\sum + 0.7\boldsymbol{\sigma}$), 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 ($\sum$)	1.2 /	2.7 /	1.4 /	
Random error($\boldsymbol{\sigma}$)	2.0 /	3.2 /	2.0 /	
Necessary margin ($2.15\sum + 0.7\boldsymbol{\sigma}$)	4.0 /	8.1 /	4.4 /	

APPENDIX VIII

Abstract: Deep Inspiration Breath Hold (DIBH) With Electromagentic 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 ± 2SD and CW excursion ±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 ± 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 D. (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 Christensen[1]:

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 recoupment 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.*

** 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 presented Madigan Army Medical Center's 2016 Annual Research Day, Tacoma, WA.*

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
Abstract: Anorectal Angle and Bowel Toxicity Following Radiation Therapy for Prostate Cancer. *

** Mitchell D, Tinnel B, Brand T, Huang R, Gossweiler M, Ninneman S, Wendt S, Macdonald D. (17-19 March 2016). Anorectal Angle and Bowel Toxicity Following Radiation Therapy for Prostate Cancer. Poster presented the ACRO 2016 Annual Meeting, Orlando, FL.*

PURPOSE/OBJECTIVES: Some elements of bowel toxicity following radiation therapy (XRT) for prostate cancer – such as urgency, frequency, or fecal leakage – may be related to anal canal geometry and musculature. In a hypothesis-generating study presented at the 2013 ASTRO/RSNA Cancer Imaging and Radiation Therapy Symposium we reported a statistically significant correlation between larger anorectal angle (ARA) and self-reported bowel toxicity in a sample of 10 patients. We have since continued to accumulate data and herein report our evaluation of this potential association with a larger cohort.

MATERIALS/METHODS: We studied 28 consecutive patients with low-to-intermediate risk prostate cancer treated on a prospective clinical study with definitive intensity-modulated radiation therapy (IMRT). Patients completed the EPIC quality of life questionnaire at baseline and at four post-treatment time points. We averaged EPIC bowel scores from the final day of treatment and 1 month post-treatment to get an acute toxicity score, and averaged scores at 4 and 10 months post-treatment to get a chronic toxicity score. We tabulated EPIC scores so that a score of 100 reflected a "perfect score" (no toxicity). ARA was measured on the mid-sagittal slice of treatment planning CT scans as the angle formed by the intersection of the central axes of the lower rectum and anal canal. Patients were divided by the mean ARA (104°) into two groups, "large ARA" and "small ARA." We used a two-tailed t-test to compare mean EPIC scores of the two groups at each time point at alpha level 0.05.

RESULTS: ARA ranged from 86° to 131.5°, with both mean and median values of 104°. There was no statistically significant difference between small and large ARA groups in baseline EPIC bowel scores, not in acute or chronic toxicity scores. Mean EPIC scores and p values for each comparison are shown in Table 1.

CONCLUSIONS: In this group of 28 patients there appears to be no association between a larger ARA and increased bowel toxicity following XRT for prostate cancer. There was some evidence of increased baseline bowel symptoms in men with larger ARA which was not statistically significant.

Table 1: Mean EPIC bowel scores +/- standard deviation for each group at each time point.

	Baseline	Acute	Chronic
Small ARA	95.7 ± 5.1	87.3 ± 11.1	90.1 ± 14.5
Large ARA	91.8 ± 7.0	84.2 ± 14.2	88.8 ± 10.4
p value	0.098	0.518	0.808

Appendix XIV
Abstract: Cost and Efficiency of Multi-Site Palliative Radiation Therapy. *

* *Adams B, Wendt S, Premo C, Valentich D, Tinnel B, Ninneman S, Ayres J, Mitchell D, Macdonald D. (12 May 2016). Cost and Efficiency of Multi-Site Palliative Radiation Therapy. Poster presented at the Uniformed Services University of the Health Services' (USUHS) Annual Research Day, Bethesda, Maryland.*

PURPOSE/OBJECTIVES: The term "disruptive innovation" describes a process wherein a simpler, cheaper, but inferior product gains a foothold with less demanding customers and is then propelled along a unique and rapid improvement trajectory. Patients receiving palliative radiation therapy could be considered one such "less-demanding" group ripe with innovation opportunities. For example, although in raw terms we have the capability to target multiple lesions with palliative radiation therapy in each treatment encounter, little has been done to make multi-site palliation (MSP) a convenient reality. To begin a discussion on this subject, we ask the questions: Is treatment time per site treated reduced when patients receive palliative treatment to more than one site in a given encounter? And, do current billing methods reimburse appropriately for the added time needed to treat multiple sites?

MATERIALS/METHODS: We reviewed palliative treatment at a military hospital from January 2013 through June of 2014. This included 72 patients with 111 episodes of radiation therapy. We divided this group into MSP episodes (45) and single site episodes (SSP – 66). We further divided the groups into those MSP and SSP episodes which included the use of intensity modulated radiation therapy (IMRT) and/or volumetric arc therapy (VMAT) and those MSP and SSP episodes which did not. For each of these groups we then calculated the cost per episode of treatment including the professional and technical cost of consultation, simulation, planning, and treatment using 2015 CPT codes and the 2015 Medicare fee schedule. The treatment time per site was likewise calculated for all groups. Likewise, we calculated treatment time per site for all four groups using digital time-stamps from the first image taken or beam-on for each treatment to the completion of the last beam to calculate daily treatment times, and adding 5 minutes to each daily treatment time to account for patient movement and set-up time. Using an unpaired t-test, we then made comparisons between the MSP and SSP groups with and without the use of IMRT/VMAT: (1) daily treatment time per site treated, (2) cost per site treated and (3) cost per minute of treatment.

RESULTS: When compared to SSP, MSP had a statistically significant decrease in daily treatment time per site by 3:40, cost per site by $2,589.73 and cost per minute per site by $11.47. Group stratification to include or exclude IMRT/VMAT yielded the following results: When MSP using only IMRT/VMAT was compared to SSP using only IMRT/VMAT, there was a statistically significant decrease in daily treatment time per site by 1:36 and cost per site. When MSP and SSP were compared excluding IMRT/VMAT, there was similarly a statistically significant decrease in daily treatment time per site by 4:42 and cost per episode by $653.25.

Mean values and results of unpaired t-tests are displayed in Table 1:

	All MSP Episodes (45)	**All SSP Episodes (66)**	**P-value**
Daily treatment time per site (min:sec)	10:54	14:43	<0.0001
Cost per site	$1,901.34	$4,491.07	<0.0001

Cost per minute	$33.63	$45.10	0.0318
	MSP IMRT & VMAT Only (6)	**SSP IMRT & VMAT Only (20)**	**P-value**
Daily time per site (min:sec)	12:21	13:57	<0.0001
Cost per site	$4,378.13	$9,821.34	<0.0001
Cost per minute	$47.05	$56.13	0.3869
	MSP excluding IMRT & VMAT (39)	**SSP excluding IMRT & VMAT (46)**	**P-value**
Daily time per site (min:sec)	10:31	15:13	<0.0001
Cost per site	$1,520.30	$2,173.55	0.002
Cost per minute	$31.57	$40.31	0.154

CONCLUSIONS: Overall, multi-site palliative therapy reduces overall treatment time and cost per site compared to single-site palliative therapy. When groups were stratified to include or exclude IMRT and VMAT, cost per minute of treatment time was not statistically significant between the two groups. Innovations which streamline MSP could benefit many patients and contribute to increased savings and decreased treatment time.

Appendix XV
Abstract: Use of Simultaneous Multi-Site Radiation Therapy Palliation: Patterns of Care at a Military Hospital. *

* *Wendt S, Premo C, Valentich K, Tinnel B, Adams B, Eyres J, Harris PJ, Fadell AJ, Macdonald D. (3-7 June 2016). Use of Simultaneous Multi-Site Radiation Therapy Palliation: Patterns of Care at a Military Hospital. Published for the 2016 ASCO Annual Meeting, Chicago, IL.*

BACKGROUND: The purchase and implementation of new radiation therapy technologies, such as intensity modulated radiation therapy (IMRT), volumetric arc therapy (VMAT), or on-board imaging (OBI), is expensive, and therefore these new technologies are primarily applied only to curative treatment. However, it is inevitable that benefits of their use will eventually accrue to palliative patients. For example, the technique of simultaneous multi-site palliation (MSP) is significantly improved by OBI and advanced radiation delivery technologies. We analyzed patterns of care for palliative radiation therapy in a military hospital from 2006 to 2014, and report here our findings in relation to changes in the use and costs associated with the delivery of MSP over that span.

METHODS: All patients treated with palliative intent from June 2006 – December 2007 (Group A) and from January 2013 – June 2014 (Group B) were retrospectively reviewed in this IRB-approved study. This included 75 and 72 evaluable patients, respectively. We calculated the percentage of MSP patients in each group. We then calculated the cost of treating each patient using 2015 CPT codes and the 2015 Medicare fee schedule, and compared mean cost per treated site using a pared t-test. Using just group B (to represent a modern cohort) we also compared mean cost per treated site for MSP patients to the cost per treated site for patients treated single-site-at-a-time.

RESULTS: In group A, 31% of palliative patients received MSP, and in group B, 47% received MSP. IMRT/VMAT/ARC therapy was used in 0% of group A patients and in 21% of group B patients. Mean radiation therapy cost per treated site was not quite statistically significantly different between the two groups, ($2765.04 in group A and $3451.18 in group B, $p = 0.0693$). In group B the mean radiation therapy cost per treated site was significantly less in the MSP cohort than in the single-site-at-a-time cohort (MSP $2220.09 per treated site compared to $4552.68, $p = 0.0006$).

CONCLUSIONS: Although new radiation therapy technologies are expensive, they open the door for increased use of MSP in palliative patients. In modern practice, MSP provides cost benefits to patients when analyzed in terms of cost per treated site.

Appendix XVI
Abstract: Cost and Efficiency of Multi-Site Palliative Radiation Therapy.*

* *Wendt S, Premo C, Valentich K, Tinnel B, Ninneman S, Adams B, Ayres J, Mitchell D, Macdonald D. (25-27 September 2016). Cost and Efficiency of Multi-Site Palliative Radiation Therapy. Poster to be presented at the 2016 ASTRO Annual Meeting, Boston, MA.*

PURPOSE/OBJECTIVES: The term "disruptive innovation" describes a process wherein a simpler, cheaper, but inferior product gains a foothold with less demanding customers and is then propelled along a unique and rapid improvement trajectory. Patients receiving palliative radiation therapy could be considered one such "less-demanding" group ripe with innovation opportunities. For example, although in raw terms we have the capability to target multiple lesions with palliative radiation therapy in each treatment encounter, little has been done to make multi-site palliation (MSP) a convenient reality. To begin a discussion on this subject, we ask the questions: is treatment time per site treated reduced when patients receive palliative treatment to more than one site in a given encounter? And, do current billing methods reimburse appropriately for the added time needed to treat multiple sites?

MATERIALS/METHODS: We reviewed palliative treatments at a military hospital from January 2013 through June 2014. This included 72 patients. We divided this group into those who received treatment to two or more sites per fraction (MSP – 18 patients), and those who received treatment to only a single site per fraction (SSP – 38 patients). 16 patients received treatment to an average of between 1 and 2 sites per fraction and this middle group was not further analyzed. 5 MSP patients (27.8%) received IMRT or VMAT treatment compared to 16 SSP patients (42.1%). The average number of fractions received was 7.80 for MSP patients and 7.94 for SSP patients. We used digital time-stamps from the first image taken or beam-on for each treatment to the completion of the last beam to calculate daily treatment times, and added 5 minutes to each daily treatment time to account for patient movement and set-up time. We also calculated the professional and technical costs of consultation, simulation, planning, and treatment for each patient using 2015 CPT codes and the 2015 Medicare fee schedule. Using an unpaired t-test, we then made three comparisons between the MSP and SSP groups: (1) daily treatment time per site treated, (2) total cost per site treated, and (3) total cost per minute of treatment time.

RESULTS: Mean values and results of unpaired t-tests are displayed in Table 1:

	Daily treatment time per site (min:sec)	Cost per site treated	Cost per minute of treatment time
MSP	12:20	$2222.46	$27.60
SSP	14:25	$4683.29	$40.80
p-value	0.253	0.006	0.008

CONCLUSIONS: Current technology and work flow does not lead to significant time savings per site for MSP patients and current Medicare payment does not compensate for the additional treatment time involved in multi-site palliation. Innovations which streamline MSP could benefit many patients and would have disruptive potential.

Appendix XVII
Manuscript: Deep Inspiration Breath Hold with Electromagnetic Confirmation of Chest Wall Position for Adjuvant Therapy of Left-Sided Breast Cancer: Technique and Accuracy*

* *Kathpal, Madeera, Brent Tinnel, Kelly Sun, Stephanie Ninneman, Cynthia Malmer, Stacie Wendt, Sheena Buff, David Valentich, Marisa Gossweiler, and Dusten Macdonald. "Deep Inspiration Breath Hold with Electromagnetic Confirmation of Chest Wall Position for Adjuvant Therapy of Left-sided Breast Cancer: Technique and Accuracy." Practical Radiation Oncology (2016): n. pag. Web. <http://dx.doi.org/10.1016/j.prro.2015.12.008>.*

Abstract
Purpose: With most patients now living long after their breast cancer diagnosis, minimizing long-term side-effects of breast cancer treatment, such as reducing late cardiac and pulmonary side effects of radiation therapy (RT), is particularly important. It is now possible to use an electromagnetic tracking system to allow real-time tracking of chest wall (CW) position during the delivery of RT. Herein we report our experience using electromagnetic surface transponders as an added measure of CW position during deep inspiration breath hold (DIBH).

Methods and materials: We conducted a single institution IRB-approved retrospective review of 15 female LBC patients treated between July 2012 and June 2013 with conventional whole breast radiation. We compared daily port films with treatment- planning DRRs to establish daily set-up accuracy, and then used Calypso tracings to compare the position of the CW during the daily port film with the position of the CW during that day's treatment to determine the reproducibility of the breath hold position. Finally, we created competing treatment plans not using DIBH and used a paired t-test to compare mean heart (MH) and left anterior descending coronary artery dose (LAD) between the two techniques.

Results: Mean total error (inter- and intra-fraction) was dominated by inter-fraction error and was greatest in the longitudinal direction with a mean of 2.13 mm and 2 standard deviations (SD) of 8.2 mm. DIBH significantly reduced MH and LAD dose versus free breathing (FB) plans (MH 1.26 Gy v 2.84 Gy, $p \leq 0.001$), (LAD 5.49 Gy v 18.15 Gy, $p \leq 0.001$).

Conclusions: This study demonstrates that DIBH with electromagnetic confirmation of CW position is feasible, and allows potential improvement in the accurate delivery of adjuvant RT therapy for breast cancer.
Introduction

Manuscript
Introduction
Breast cancer remains the most prevalent cancer and a leading cause of cancer death among women.[1] More than 230,000 women will be diagnosed with breast cancer in the United States this year, and many will receive radiation therapy (RT) as part of their initial breast cancer treatment. Adjuvant RT is known to reduce local recurrence, which in turn increases breast cancer specific survival and overall survival.[2] With most patients now living long after their breast cancer diagnosis, the medical community bears increased responsibility to minimize long-term side-effects of treatment for breast cancer. This is particularly true in regards to reducing late cardiac and pulmonary side effects of RT.

In 2013, New England Journal of Medicine published an article reporting on cardiac toxicity incurred in 2168 women treated for breast cancer in Sweden and Denmark between 1958 and 2001. In this group, 963 women suffered major coronary events and 1205 were used as controls. They found that rates of major coronary events increased linearly with mean dose to the heart by a relative rate of 7.4% per Gy, with no apparent low-dose threshold. The risk was noted to start within five years of treatment and to continue for at least 20 years.[3]

Electromagnetic beacon transponders (Calypso® 4D Localization System, Calypso Medical Technologies, Seattle, WA, USA) are widely used for real-time tracking of prostate motion during RT for prostate cancer. More recently, the FDA has approved the use of electromagnetic beacon transponders designed to be placed on the body surface during RT. Therefore, it is now possible to use an electromagnetic tracking system to allow real-time tracking of chest wall (CW) position during the delivery of RT. We recognized this benefit for patients with left-sided breast cancers (LBC) and developed a protocol using electromagnetic surface transponders to track CW position during deep inspiration breath hold (DIBH). Our standard procedure included daily port films as the primary method of verifying CW position.

In the present study, we review the entire treatment course for 15 breast cancer patients treated with this technique. By using an auto-match function verified by visual confirmation to compare daily port films with treatment-planning DRRs we established daily set-up accuracy. We then used Calypso tracings to compare the position of the CW during the daily port film versus that day's treatment to determine the reproducibility of the breath hold (BH) position. Finally, we created competing treatment plans, not using DIBH, to establish the benefit in reduction of dose to the heart with this technique.

Methods and materials

Patient Population

We conducted a single institution IRB-approved retrospective review of 15 female LBC cancer patients treated between July 2012 and June 2013 with conventional whole breast radiation. Candidates for this study were patients with non-invasive or invasive LBC who were able to comfortably hold their breath for about 20 seconds at the time of initial simulation.

Patients were between 42 and 70 years old, with a median age of 55 years. The majority of patients had negative nodal status, were estrogen receptor (ER) positive, and received adjuvant systemic therapy (Table 1). All patients were treated with 6 MV photons through opposed tangents to a dose of 50 Gy in 25 fractions followed by a lumpectomy cavity boost. One patient had a supraclavicular field treated, also in DIBH position. One patient was treated with a couch kick, which required minor adjustments in interpreting the Calypso reports.

Simulation

Patients were placed supine on a breast board on the CT scanner table. The physician then outlined field borders and a marker was placed on the sternum about halfway between the

superior and inferior borders of the marked field, which would eventually be the BH mark. Lateral level marks as delineated by the external lasers in this position were also marked.

A free breathing (FB) CT simulation scan was performed to determine if DIBH technique was required. The treating physicians examined the FB CT and approximated how much heart would be in the field using standard tangents. If the treating physician determined the patient would benefit from DIBH during treatment, additional steps during the simulation were performed, as outlined below.

DIBH Technique

After ensuring the patient was straight and properly aligned, the patient was instructed to perform a DIBH. Longitudinal (i.e. cranio-caudal) movement of the BH mark was observed, measured, and recorded. The patient was coached and asked to repeat the DIBH until the longitudinal movement of the BH mark was reproducible. The external Calypso beacon pair was then placed on the BH mark and another CT scan was performed with the patient in DIBH. After the physician approved the scans and technique, permanent tattoos replaced the leveling and BH marks and an additional straightening mark was placed on the sternum inferior to the BH tattoo.

Treatment Planning

Both FB and DIBH CT scans were transferred to the treatment planning system. All planning was performed on the DIBH CT scan using the Pinnacle treatment planning system. All patients were treated with opposed tangents with the least amount of tangent segments possible in order to minimize time required for the DIBH technique. Physical wedges were not used; however dynamic wedges (EDW) were acceptable in lieu of segments if the BH time did not exceed approximately 20 seconds per field. The lasers were localized at the BH tattoo. The CAX was placed 2-cm posterior and 3-cm lateral to the BH tattoo.

Each Calypso beacon was assigned as a point in Pinnacle, which provided the beacon coordinates for entry into the Calypso System. The medial beacon was identified in the Calypso system as the left mid-base with a medium transponder frequency. The black ringed beacon pointing superiorly was the apex beacon and had the lowest frequency. The CAX and beacon coordinates from the Pinnacle treatment plan had the following tolerances: Lateral: 3.0-cm, Longitudinal: 4.0-cm, Vertical: 5.0- cm, Geometric Residual: 0.3 cm and Rotational Alignment: 30 degrees.

Treatment Setup

The patient was set up on a breast board as at the time of simulation. While FB, the patient was leveled and straightened using external lasers and the leveling marks, BH mark, and the anterior straightening mark. The patient was then directed to perform a DIBH. The therapists observed the subsequent location of the BH tattoo to confirm the DIBH was of a similar magnitude to that during simulation. The patient then performed another DIBH and was shifted so the light field cross-hairs aligned with the BH mark. The therapists placed the beacon pair on the patient and

verified that the light field cross-hairs bisected the beacons during DIBH (Figure 1A). Also, during DIBH, SSD was set to 98-cm at the BH mark. Finally, a standard lateral shift of 3-cm (patient moved right, isocenter moved left) was applied (Figure 1B). The therapists then had the patient perform a final preparation DIBH, so the Calypso unit could localize and begin to track the two beacons.

Treatment

From outside the treatment room, therapists requested the patient take a DIBH and a single-exposure port film was acquired. If this was unsatisfactory, the patient was repositioned by coaching BH technique (if Calypso tracings indicate a difference between set-up BH and port film BH) or table shift until a satisfactory port film was taken.

The average number of ports taken per day of treatment was 1.5 with the majority of patients having either one or two ports taken per day. 98.4% of these images were closed-field ports, so did not contribute significant additional heart dose. Additional dose to lung and soft tissue within the treated field is estimated to be within 1% of the planned treatment dose.

During treatment, therapists monitored the Calypso tracings and stopped the beam, if necessary, to constrain beam-on CW position to within about 2-mm of the port film CW position. Because beacons track the relative position of the chest wall – i.e. the difference in CW position between the time of port film and the time of treatment – small differences in beacon placement on the CW from day to day were not considered a source of error. Therefore these differences, which are thought to be in the range of <1mm, were not measured.

Retrospective measurement of port film alignment in comparison to DRR's

Each patient's treatment planning digitally-reconstructed radiograph (DRR) was auto-matched (with visual confirmation of accuracy) to each day's port film. The positional difference between the actual port and the now positionally optimized port was recorded in three dimensions along the lateral, vertical, and longitudinal axes. Auto- match parameters were set so the area of interest was in line with the outer corners of the planned field edge before the auto-match was conducted. The auto-match was performed twice for each port film. Using this data, the mean initial positioning error was calculated to represent inter-fraction motion. While the beacons are radiopaque, they typically do not appear in the port films as they are positioned either outside, or at the border of, the imaged field.

Mathematical recreation of the three-dimensional position of the target tissues

Maximum intra-fraction excursions were determined by examining Calypso tracings that portray the position of surface beacons through the port film and treatment (Figure 2). High, low, and best fit positions of the CW were recorded for each daily port film and treatment beams. The high and low points represent the largest and smallest excursions, respectively, superiorly, anteriorly, and to the left during treatment along the longitudinal, vertical, and lateral axes. The best fit measurement represents the position the patient spent the most time in during beam-on time. This position was compared to that during port filming from the same day, and this

difference was recorded as the intra- fraction motion of the CW for that beam. The intra-fraction motion from each beam was then combined with the auto-shift measurements which aligned that day's port film with the treatment plan DRR to determine the total precision of the patients' three- dimensional position in relation to the planned treatment (Figure 3).

Mean heart (MH) and left anterior descending coronary artery (LAD) dose

The heart was contoured in every patient according to RTOG guidelines. The LAD was contoured superiorly from the beginning of the left atrium, down to the apex inferiorly. In addition to the DIBH treatment plan, a second plan was created using the FB CT scan and the same anatomical beam entry and exit points as the DIBH plan (Figure 4). The FB and DIBH treatment plans' heart and LAD mean doses were calculated and recorded from each dose-volume histogram. Three FB scans were unable to be analyzed because of incomplete heart visualization. We used a paired t-test to compare MH and LAD dose with and without DIBH and CW excursion during DIBH to that during beam-on.

Results

The mean number of treatment BHs per fraction was 2.3. 23% of treatment beams were interrupted to adjust for suboptimal BH or CW position. The inter-fraction positioning error data is presented in Table 2 as mean values in the vertical (anterior/posterior), longitudinal (superior/inferior), and lateral (left/right) directions. The mean positional error of the daily port films by auto-match comparison to the DRR of the DIBH simulation CT was 0.61-mm posteriorly, 2.16-mm inferiorly, and 0.42-mm to the left. The difference from the Calypso beacon position during treatment to the position at the time of port film, or the mean intra-fraction motion (Table 2), was 0.11-mm anteriorly, 0.10-mm superiorly, and 0.09-mm to the left. The greatest variability in intra-fraction motion was in the longitudinal direction; in that axis 95% of treatments (2SD) fell within 3.1-mm of the port film position. The total precision of the study technique was determined by combining the two previous measures for each treatment. The mean total precision (Table 2) was 0.47-mm posteriorly, 2.13-mm superiorly, and 0.51-mm to the left.

We compared DIBH CW position during the entire BH (plateau) to position during beam-on (Table 3). The mean (SD) CW motion during the entire DIBH was 4.2 (2.8) mm, 5.0 (4.0) mm, and 2.5 (2.3) mm in the vertical, longitudinal, and lateral axes respectively. Overall, this was significantly larger than the CW motion during beam-on of 1.3 (0.9) mm, 1.7 (1.4) mm, and 1.1 (1.2) mm in the vertical, longitudinal, and lateral axes respectively ($p<0.001$ in all dimensions).

Table 4 shows the dosimetric comparison of (MH) dose and mean LAD dose between the FB and BH simulation CTs. DIBH significantly reduced MH and LAD dose versus FB plans (MH 1.26 ±0.51 Gy v 2.84 ±1.55 Gy, $p\leq0.001$), (LAD 5.49 ±4.02 Gy v 18.15 ±8.78 Gy, $p\leq0.001$).

Discussion

Our study shows electromagnetic confirmation of CW position is technically feasible, allows for verification of BH reproducibility to within 3.1-mm (2SD) in 95% of fractions, and allows

therapists to constrain beam-on time to the most reproducible and stable portion of each BH. With our technique, DIBH during irradiation of left-breast cancer patients reduced the MH and LAD dose by at least 50%.

The importance of minimizing dose to the heart during adjuvant RT for LBC has become increasingly clear as this issue has been studied over the past decade. For example, long-term mortality from heart disease after RT was studied using the United States SEER cancer registry. Women with left-sided tumors were compared to ones with right-sided tumors. For women treated in the 1970s and 1980s, cardiac mortality 10 years or longer after radiation treatment was higher in women with left-sided tumors.[4] Similar findings were seen in 961 patients with stage I or II breast cancer treated with adjuvant RT at the University of Pennsylvania between 1977 and 1994. At 20 years after treatment, an increased risk of cardiac mortality was seen in patients treated for left versus right breast cancers. Diagnosis of chest pain, coronary artery disease and myocardial infarction was also statistically higher in left-sided patients.[5]

A group from Canada specifically studied mortality from myocardial infarction after RT.[6.7] An increased risk of fatal myocardial infarction was found in women with LBC compared to right-sided cancers. This difference was most evident in women younger than 60 years of age. Internal mammary chain irradiation, use of adjuvant chemotherapy with adjuvant radiation and smoking have all been shown to increase risk of cardiovascular disease in 10-year survivors of breast cancer.[8]

The physiologic basis for the increased risk of cardiac mortality following RT for breast cancer has been proposed to be radiation-associated coronary damage. A group from University of Pennsylvania demonstrated an increase in SPECT myocardial perfusion stress testing or transthoracic stress echocardiogram abnormalities a median of 15 years after treatment. Nearly half of the left breast cancer patients with these abnormalities underwent cardiac catheterization with nearly all showing coronary stenosis involving the LAD artery.[9]

Certainly many groups have studied the use of DIBH to assist in limiting heart dose during adjuvant RT for breast cancer. For example, Giraud et al. reported on the benefits of using BH technique in the treatment of patients with breast cancer. They found a significant reduction in volume of lung and heart treated when using BH versus FB during treatment. They also found a reduction in maximum dose to the contralateral breast. There was no difference in early or late toxicity between the two treatment modalities.[10]

To our knowledge, we are the first to report a careful study of the use of electromagnetic transponders to track CW position when using DIBH technique. Our study shows that the CW is not necessarily stable during DIBH. Tracking CW motion allowed our therapists to limit beam-on time to the most stable portions of the BH.

We were able to couple retrospective analysis of daily port films with Calypso tracings, which allowed us to make conclusions regarding the accuracy of this treatment technique. The inter-fraction error we determined from the port films dominated these measurements, with 2SD for longitudinal errors of nearly 8-mm. On the other hand, intra-fraction motion, or the comparison of CW position at the time of port film to that at the time of beam-on was shown to be small,

with 2SD for longitudinal errors of 3.1-mm. It is apparent that often these two errors occurred in opposite directions, such that the average of the daily combination of inter-fraction and intra-fraction error was very similar to the inter-fraction error alone.

There is a small added cost to this method of verification. Using daily port films adds 20 additional port film charges in addition to the five that would be billed during a course of treatment verified with weekly ports alone. With the Centers for Medicare & Medicaid Services reporting the 2015b national payment amount for radiology port films in a hospital at $10.78, this equated to an average additional cost of $215.60 per course of treatment. At present, there is no additional charge for using Calypso tracking during treatment.

Finally, our dosimetric comparison demonstrated that in this carefully selected group, DIBH technique does reduce mean dose to the heart, as well as dose to the LAD artery. Our study does suffer from significant limitations, with the primary limitation being a small sample size. Other limitations include the inaccuracies inherent in using an auto-match algorithm to compare port films to DRR's, and the fact that measurements of CW position from Calypso tracings were obtained manually. However, we feel that the use of an auto-match algorithm allowed us to objectively compare films, and the errors potentially introduced by making manual measurements from Calypso tracings should be very small.

In conclusion, we have demonstrated that DIBH with electromagnetic confirmation of CW position is feasible, and allows potential improvement in the accurate delivery of adjuvant RT for LBC.

References

1) "Breast Cancer Statistics." Centers for Disease Control and Prevention. Centers for Disease Control and Prevention, accessed 18 Sep 2015. http://www.cdc.gov/cancer/breast/statistics/index.htm.
2) Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet 2005; 366:2087-2106.
3) Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. NEJM 2013; 368(11):987-98.
4) Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in the IS SEER cancer registries. Lancet Oncol 2005; 6:557-565.
5) Harris EE, Correa C, Hwang WT, et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. JCO 2006; 24:4100-4106.
6) Paszat LF, Mackillop WJ, Groome PA, et al. Mortality from myocardial infarction following postlumpectomy radiotherapy for breast cancer: a population-based study in Ontario, Canada. IJROBP 1999; 43:755-762.
7) Paszat LF, Mackillop WJ, Groome PA, et al. Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the surveillance, epidemiology, and end-results cancer registries. JCO 1998; 16:2625-2631.
8) Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. JNCI 2007; 99:365-375.
9) Correa CR, Litt HI, Hwang WT, et al. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. JCO 2007; 25:3031-3037.

Figure Legends:

Figure 1: (A) Laser alignment with beacons placed on sternum for breast treatment on treatment table. (B) Photo demonstrating position of the beacons in relation to BH tattoo. BH, breath hold.

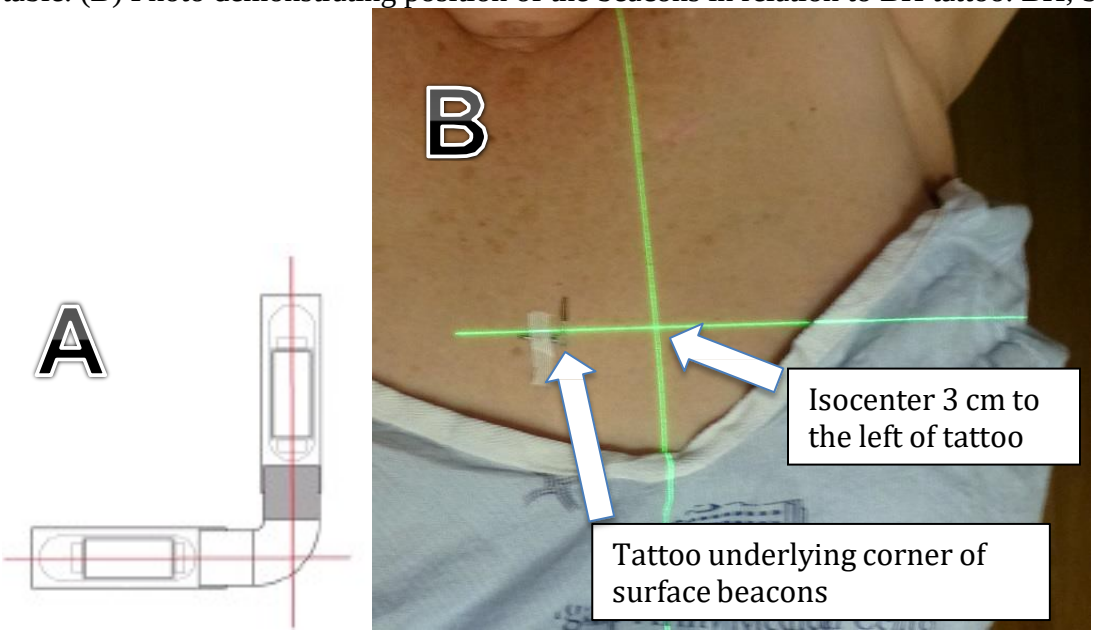

Figure 2: (A) Transponder tracking report showing CW position in all three axes at the time of daily port film (vertical blue line), FB (yellow highlight), DIBH [mean distance between max and min values (green arrows)], and beam-on time (red highlight / shaded area). (B) Example of a transponder tracking report with a split-beam during the second tangent. CW, chest wall; FB, free breathing; DIBH, deep inspiration breath hold; Sup, superior; Inf, inferior; Ant, anterior; Post, posterior.

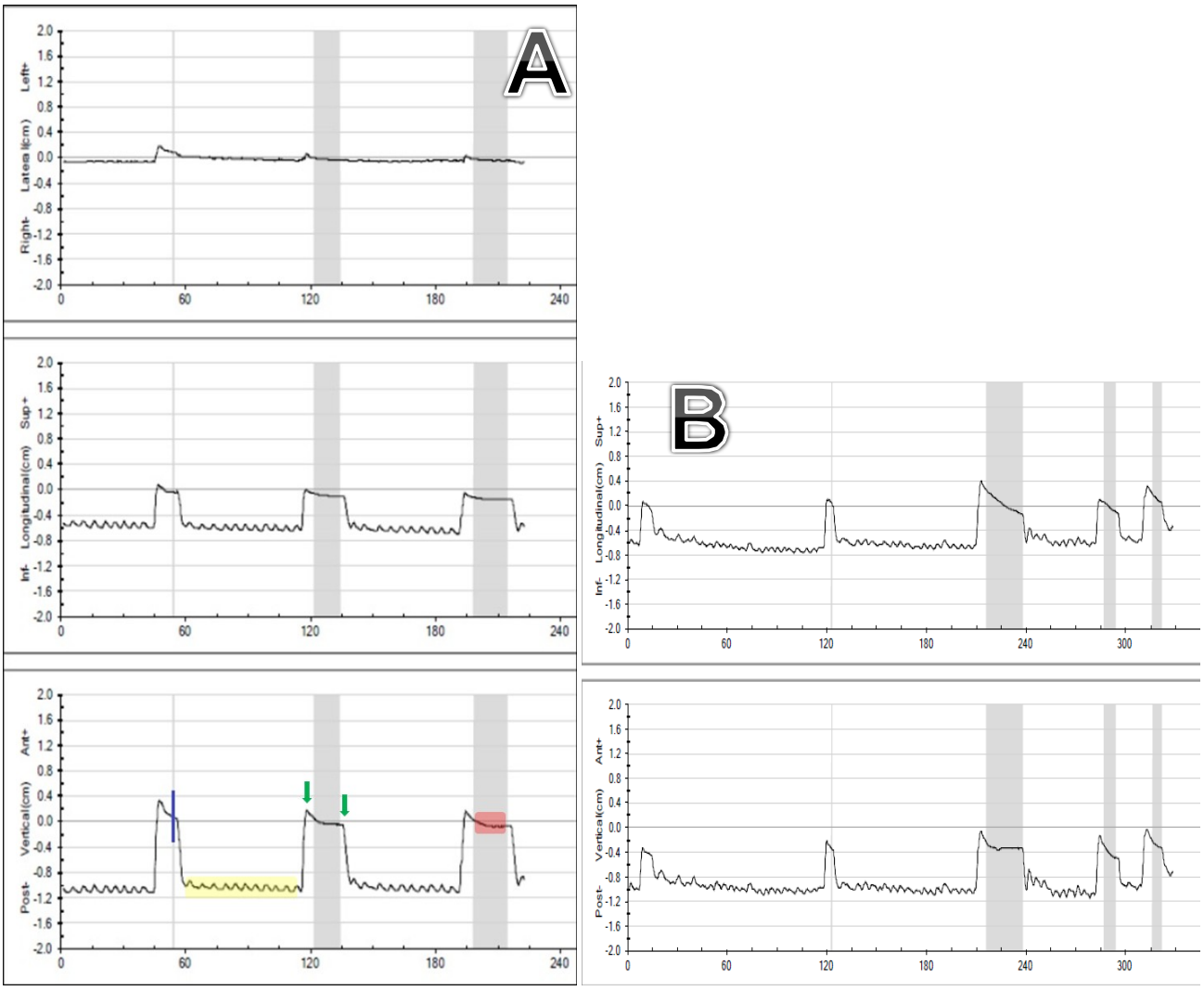

Figure 3: Depiction of measurements used to determine the inter-fraction error (Step 1), the intra-fraction motion (Step 2), and the necessary PTV margin (Step 3). PTV, planning treatment volume; DRR, digitally reconstructed radiograph.

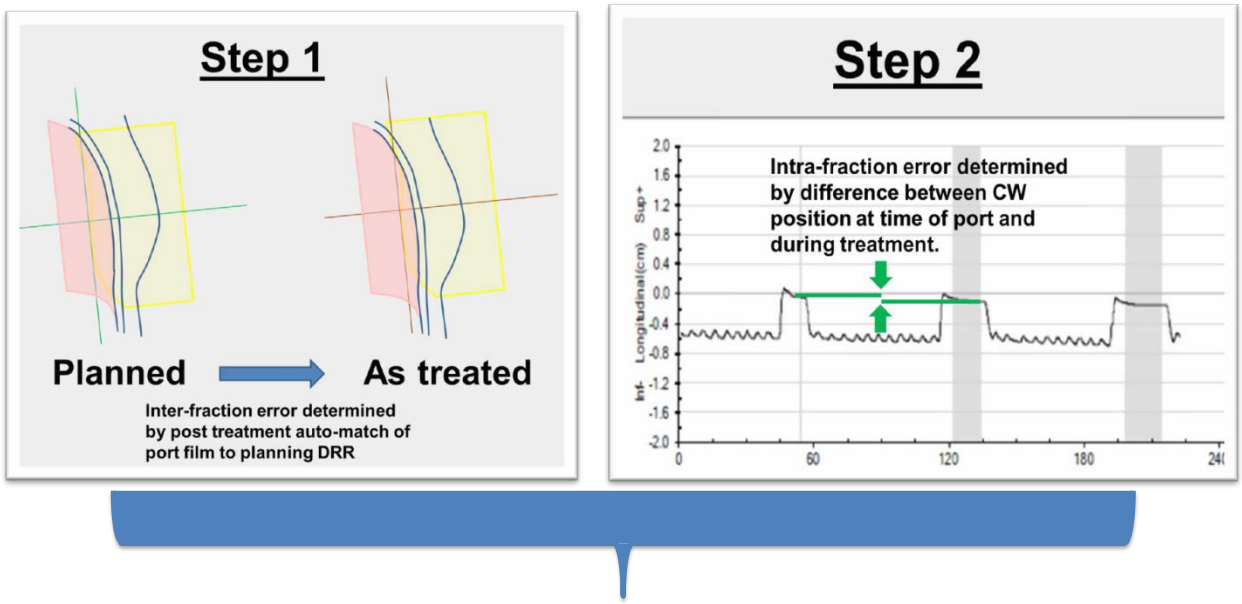

Figure 4: DIBH CT scan with isodose lines showing sparing of heart (left); FB CT scan at same slice as DIBH scan showing inclusion of heart within the tangent (right). CT, computed axial tomography.

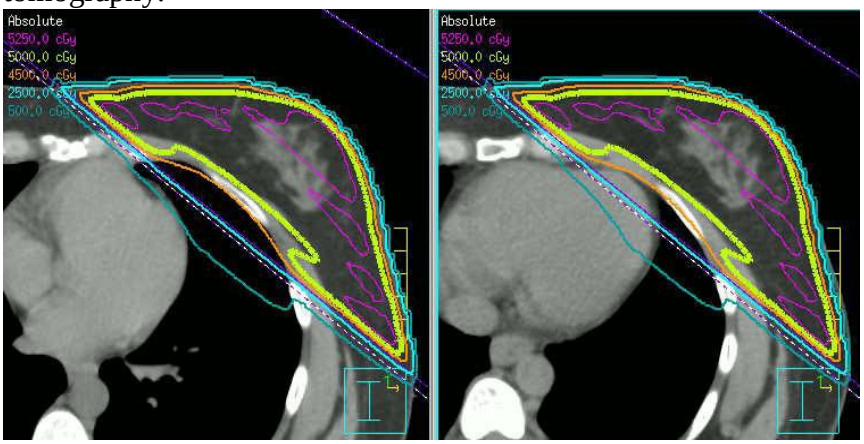

Table 1: Patient Characteristics.

Table 1: Patient Characteristics	
Characteristic	
Age	
Range	42-70
Median	55
Pathologic Stage	
0	8
IA	2
IB	0
IIA	4
IIB	1
Nodal Status	
Negative	12
Positive	3
Tumor Size (cm)	
0 – 0.5	4
> 0.5 – 1.0	4
>1.0 – 2.0	4
> 2.0	3
Receptor Status	
Estrogen Receptor Positive	14
Her-2 Receptor Positive	2
Triple Negative	1
Hormone Therapy	
Yes	11
No	4
Adjuvant Chemotherapy	
Yes	4
No	11

Table 2: Mean Inter-fraction positional error based on comparison between daily port film and DRR of the DIBH simulation CT, Mean Intra-fraction Motion (mm) with 2 SD, and Mean Total Precision (mm) with 2 SD. 2 SD, two standard deviations.

	Longitudinal	Vertical	Lateral	
Inter-Fraction Error	2.16 Inf	0.61 Post	0.42 Left	Mean
	7.9	4.4	3.8	2 SD
Intra-Fraction Error	0.10 Sup	0.11 Ant	0.09 Left	Mean
	3.1	2.3	2.5	2 SD
Total Precision	2.13 Sup	0.47 Post	0.51 Left	Mean
	8.2	4.9	4.6	2 SD

Table 3: Mean CW Excursion ±1SD During Entire DIBH and During Beam-On ($p<0.001$ in all dimensions). LR, left/right; SI, superior/inferior; AP, anterior/posterior.

	Lateral (LR)	Longitudinal (SI)	Vertical (AP)
CW excursion during DIBH	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

Table 4: Mean Heart and LAD Dose between FB and BH Scans (Gy). $p<0.001$ for both heart and LAD comparisons. BH, breath hold; LAD, left anterior descending coronary artery

	Heart			LAD	
	FB	**BH**		**FB**	**BH**
Mean	2.84	1.26		18.15	5.49
2 SD	3.10	1.03		17.57	8.04
Range	1.43 – 6.79	0.60 – 2.16		3.12–35.16	3.10 – 10.93

Appendix XVIII
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 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 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 ASCO/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 presented at the 101st Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA), Chicago, IL.

17. Mitchell D, Tinnel B, Brand T, Huang R, Gossweiler M, Ninneman S, Wendt S, Macdonald D. (17-19 March 2016). Anorectal Angle and Bowel Toxicity Following

Radiation Therapy for Prostate Cancer. Poster presented at the ACRO Annual Meeting, Orlando, FL.

18. 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 presented Madigan Army Medical Center's 2016 Annual Research Day, Tacoma, WA.

19. Adams B, Wendt S, Premo C, Valentich D, Tinnel B, Ninneman S, Ayres J, Mitchell D, Macdonald D. (12 May 2016). Cost and Efficiency of Multi-Site Palliative Radiation Therapy. Poster presented at the Uniformed Services University of the Health Services' (USUHS) Annual Research Day, Bethesda, Maryland.

20. Wendt S, Premo C, Valentich K, Tinnel B, Adams B, Eyres J, Harris PJ, Fadell AJ, Macdonald D. (3-7 June 2016). Use of Simultaneous Multi-Site Radiation Therapy Palliation: Patterns of Care at a Military Hospital. Published for the 2016 ASCO Annual Meeting, Chicago, IL.

21. Wendt S, Premo C, Valentich K, Tinnel B, Ninneman S, Adams B, Ayres J, Mitchell D, Macdonald D. (25-27 September 2016). Cost and Efficiency of Multi-Site Palliative Radiation Therapy. Poster to be presented at the 2016 ASTRO Annual Meeting, Boston, MA.

22. Kathpal, Madeera, Brent Tinnel, Kelly Sun, Stephanie Ninneman, Cynthia Malmer, Stacie Wendt, Sheena Buff, David Valentich, Marisa Gossweiler, and Dusten Macdonald. "Deep Inspiration Breath Hold with Electromagnetic Confirmation of Chest Wall Position for Adjuvant Therapy of Left-sided Breast Cancer: Technique and Accuracy." Practical Radiation Oncology (2016): n. pag. Web. <http://dx.doi.org/10.1016/j.prro.2015.12.008>.