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PRINCIPAL INVESTIGATOR:	Dr. Dusten Macdonald, MD
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Dusten Macdonald, MD Stephanie Ninneman, RN

E-Mail: dusten.m.macdonald.mil@mail.mil

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14. ABSTRACT

This program is intended to establish the infrastructure to provide state-of-the art targeted radiation therapy to military personnel and veterans with cancer. The research aspect of this project is intended to demonstrate whether 1) targeted radiation therapy with real time localization and tracking will allow use of a smaller planning treatment volume margin with a significant decrease in rectal and bladder volume treated and whether the use of such targeted therapy can occur within standard treatment times and thus feasible for routine clinical use, 2) whether the use of Vac-Lok® immobilization devices are necessary when patients are treated using the Calypso system, 3) whether Beacon® Transponder is of benefit in pelvic radiation therapy following prostatectomy, 4) whether 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) whether 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
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Targeted Radiation Therapy for Cancer Initiative Annual Report

Introduction

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

Body
Task Completion

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

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

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

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

A total of 23 non-study prostate cancer patients who did not otherwise qualify for a protocol have been treated with the Calypso system at MAMC. Non-protocol patients have allowed the providers to gain further proficiency with the Calypso unit. Six of these patients have been treated in the prone position. The experience and knowledge gained in this alternative positioning technique has 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 thus far we have treated 3 study patients in this position.

MAMC has now been routinely using the approved FDA surface transponders off protocol to monitor breathing motion during our standard breath-hold technique for treating left-sided breast cancer, which allows sparing of the heart. We have thus far treated 36 patients using these approved external beacons. The Calypso system provides a previously unavailable level of additional positional monitoring for these patients and we have gained considerable expertise with this technique. We have been selected to present 3 separate poster presentations (see appendices VII, VIII & IX) at upcoming professional meetings in September 2014 based on the data collected on our retrospective protocol. See Task 8 for further details on this protocol.

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

Thirty-one subjects have been consented and twenty-seven enrolled in the study with reduced PTV margins at MAMC to date. Thirteen of these subjects have completed the trial, twelve are in the follow-up phase, one is undergoing treatment, one patient died

while in the follow-up phase from lung cancer which was unrelated to study, three were screen failures that never started treatment and one is currently in the screening phase.

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1. Change of Research Monitor form COL Stephen Yoest, MC to LTC Jonathan Davison, MC. 2. Minor deviation regarding a subject who had a lab test slightly out of range. Report was submitted and acknowledged by the MAMC IRB without conditions. 3. Brooke Army Medical Center (BAMC) was added as a site and approved by all regulatory offices. 5. Continuing review was approved by the MAMC IRB from 17 July 2014 through 16 July 2015. The site will forward this approval to HRPO. All potential patients that are seen at the weekly multidisciplinary prostate cancer clinic and or by provider referral are being considered for participation and are given the option to partake.

We have given two presentations at a national conference and one here at Madigan, supported by the data collected from this trial thus far. Most recently we were selected to present our research data at The Western Section of the American Urological Association 90th annual meeting in October 2014. The first author, Kelly Sun, pre-medicine student volunteered her time to gather and analyze this data and will be presenting at the conference. We plan to continue our momentum and enroll new patients on this study until summer 2015, which includes a 1-2 year follow-up to assess for toxicity after treatment ends. Our ultimate goal is to get our work published in a renowned radiation oncology journal.

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

In an effort to boost enrollment, we collaborated with Brooke Army Medical Center and added them as a site on this protocol. BAMC is now actively recruiting patients.

This study is expected to enroll a combined total of up to 40 subjects from both centers.

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

The Radiation Therapy Oncology Group is a recognized leader in working to increase survival and improve the quality of life for cancer patients. We are excited about our recent endeavor in becoming an RTOG affiliate member. Having access to participating in RTOG clinical trials will open many research doors within our military setting and allow us to offer our patients the decision to participate in the most up-to-date radiation therapy techniques available.

We had originally planned to participate in RTOG 0938, but this trial has reached its accrual goal. We requested an amendment to the SOW to include RTOG 0924 under this task and it was recently approved. This is an equally important study for higher-risk prostate cancer patients. Participation in this national study will help us to continue to

establish Madigan as a "center of excellence" in targeted radiation therapy. Also, an added benefit with this trial is that it will not compete with our reduced PTV margins study (like 0938 would have).

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. We are in the process of working with RTOG on submitting this study to our local IRB as well as the NCI central IRB for approval.

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.*

Ten subjects have been enrolled in the immobilization study at MAMC to date. A total of thirteen signed consent; three were screen failures and never started treatment. Eight of these subjects have completed the study from consent to the one year follow-up, one is in the follow-up phase and one is currently on treatment. We continue to actively pre-screen all potential subjects and offer them participation in the trial.

We submitted an abstract to a professional conference, but were not chosen to present due to our limited data at the time. We hope to resubmit an abstract based on intra-fraction prostate motion and total treatment time for a future conference once we have compiled more data.

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1. Change of Research Monitor form COL Stephen Yoest, MC to LTC Jonathan Davison, MC. The continuing review package was submitted to MAMC IRB and is scheduled to be reviewed on 26 August 2014. The current review approval period is from 28 August 2013 through 27 August 2014.

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

This study has proven to be difficult to enroll since most patients who are intermediate to high-risk choose to have a prostatectomy. Our original goal of 20 subjects does not seem feasible at this time. A more attainable goal that would still allow us to gather enough data to support our study endpoints would be to enroll 10-15 subjects.

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.*

Eighteen subjects have been enrolled in the post-prostatectomy study at MAMC to date. A total of twenty-three have signed consent; five were screen failures and never started

treatment. Thirteen of these subjects have completed the study, four are in the follow-up phase and one was withdrawn during treatment due to an inability to accurately localize him to Calypso due to an anatomical shift that was occurring when using his calypso beacons.

Amendments, reviews and deviations that have occurred and been reviewed by the MAMC IRB in the last year include: 1. Change of Research Monitor form COL Stephen Yoest, MC to LTC Jonathan Davison, MC. 2. The current review approval period is from 23 October 2013 through 22 October 2014.

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. MAJ Madeera Kathpal, visiting from the Fort Sam Houston resident unit, presented the 2 most recent poster presentations supported by the data collected from this trial at the ASTRO 2013 Annual Meeting held on September 22-25 in Atlanta, Georgia, USA. MAJ Kathpal was the first author on both abstracts; "Differences Between Beacon-Localized and Cone-Beam CT (CBCT)-Localized Radiation Therapy to the Prostatic Fossa" and "Inter-Fraction Displacement of Electromagnetic Beacons in Patients Receiving Post-Prostatectomy Radiation Therapy."

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

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

This study is expected to enroll 20 subjects.

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

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

Our analysis to date of the CBCT data collected in Task 6 demonstrates that most patients would be appropriately treated with significantly decreased circumferential margins, however, a few patients are outliers who require more margin. It has been demonstrated by other groups that these outliers can be identified by analysis of target volume coverage during the first five

treatments, followed by margin adaptation based on this analysis. Therefore, this protocol will also include an adaptive radiation therapy component, by which each patient's first five fractions of radiation therapy will be analyzed for a pattern of excessive target volume motion, and margin adjustments will then be made to the patient's radiation treatment plan if necessary.

A protocol manuscript has been initiated and we hope to have it completed once we finish our analysis of the original post-prostatectomy clinical trial.

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

This study will include two phases and has the potential to dramatically alter the efficiency and efficacy of palliative radiation therapy. The primary goal of this study is to develop and validate a set of dosing guidelines that will allow widespread use of advanced technology radiation therapy techniques, such as IMRT and VMAT, in treating palliative patients. The main obstacle to overcome in reaching this goal is to establish practice patterns that allow simplified, though still safe, use of this technology in order to decrease the expense associated with these treatments. Currently, palliative patients with a single, or very few metastases, may be referred for stereotactic body radiation therapy, a time-consuming, expensive, and not widely applicable therapy. The other option for palliative patients tends to be simple 2-D or 3-D planned treatments which are not particularly conformal and are usually delivered over 10 fractions. Our study will seek to demonstrate the practicality of a middle ground between these two techniques – on the one hand bringing the benefits of intensity modulated dose escalation to palliative patients, but on the other hand maintaining simplicity, efficiency, and widespread applicability of treatment. The first phase of this study will involve a retrospective portion where we review the patients treated palliatively here at MAMC in the past, and by using their CT scan data compare dose that would be delivered to the target volume and nearby structures with a conformal "central-boost" plan vs. a conventional palliative plan. The second phase of this study will prospectively evaluate the feasibility of this strategy with specific quality of life outcome measurements.

We have completed the retrospective protocol (first phase as described above) and submitted it for Madigan IRB approval. Once approved, we will submit for HRPO approval.

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

> This study examines the precision and accuracy of radiation therapy using breath-hold technique for left-sided breast cancer patients treated with adjuvant radiation therapy, with the benefit of confirmatory tracking via the Calypso® 4D Localization System.
>
> We have concluded thus far that this technique demonstrates accuracy and precision that is well within the traditional 1 cm margin of error, allowing a potential decrease in planning margins.

We included 15 patients on our retrospective protocol. A total of 3 abstracts were selected for poster presentations. Two of the abstracts will be presented by the first author, MAJ Kathpal at the national radiation oncology conference (ASTRO), September 14-17 2014; "Deep Inspiration Breath Hold (DIBH) With Electromagnetic Surface Transponder Confirmation of Chest Wall Position for Adjuvant Therapy of Left-Sided Breast Cancer" and "Margins for Deep Inspiration Breath Hold (DIBH) With Electromagentic Confirmation of Chest Wall Position for Adjuvant Therapy of Left Breast Cancer ". The 3rd abstract, "Deep Inspiration Breath Hold (DIBH) With Electromagnetic Surface Transponder Confirmation of Chest Wall (CW) Position During Radiation For Left Breast Cancer" was also selected and will be presented also by MAJ Kathpal at the ASCO/ASTRO Breast Cancer Symposium September 4-6 2014. We are also working on 2 papers for 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 approximately 140 patients with the Calypso® 4D Localization System and continue to develop expertise as a center of excellence in targeted radiation therapy. This grant continues to facilitate continuing medical education for the staff at MAMC on image guided radiotherapy. Additional education materials and visits from other DOD providers will be coordinated in upcoming years of the project.

Active duty Army Radiation Oncologist resident, Madeera Kathpal has now completed five rotations at MAMC over the last 2 years. The resident learned advanced techniques of tumor targeting with the Calypso system and assisted in evaluating data and writing scientific papers under the guidance of the MAMC physicians. MAJ Kathpal worked on many projects under the guidance of MAMC physicians, including analyzing data from the post-prostatectomy trial and then writing/presenting 3 abstracts based on the findings at 2 national conferences and at Madigan's Research Day. She also contributed in developing our retrospective breast protocol as well as writing abstracts and papers based on our data analysis (as explained in the task above 2). She will be presenting this data in 3 separate poster presentations at 2 different national meetings. Dr. Kathpal has helped the team tremendously in our research endeavors. Her 5th and final rotation will be completed during August/September 2014. Dr. Kathpal was recently promoted to major and completed her residency program. She will start working as an attending radiation oncologist at Bethesda military treatment facility in Washington D.C., fall of 2014. 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.

We have also had a MAMC Radiology resident, and two medical students on research rotations and a pre-medical student assist in evaluating, preparing and writing abstracts based on the data gathered in our Reduced PTV Margins and Immobilization protocols.

We have hosted five educational conferences/visiting professorships in the area of urology and radiation oncology since the inception of this grant. We have committed to making these events an annual occurrence. We believe these educational events promote our site as a "center of excellence in target radiation therapy" and encourage physicians in the community to seek our expertise. Our most recent event was held on 28 July 2014. Dr. Bruce Montgomery, a professor of medicine and physician at the University of Washington and Seattle Cancer Care Alliance discussed, 'Recent Innovations in the Treatment of Metastatic Castrate Resistant Prostate Cancer'. The targeted audiences for this symposium were urologists, urology residents, radiation oncologists, and medical oncologists, internal medicine residents as well as some scientists from the Madigan Department of Clinical Investigation. We had a very large turnout with the highest attendance to date. We look forward to hosting the 6th annual symposium next year.

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

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

We have presented a total of 5 poster presentations at 2 prominent medical symposiums based on the continued findings of our research. We have been selected to present 4 more in September and October 2014. This will mark a total of 9 presentations at a professional conference. Also mentioned prior in this report, we have presented 2 presentation at Madigan research day. We hope to have the opportunity to present many more in the years to come.

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.

There was a delay in getting Brooke Army Medical Center added as an additional site on this grant to support the Reduced PTV margins protocol. This site now has full IRB and HRPO regulatory approval. They are currently pre-screening/recruiting new patients.

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 2 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 as well. We are very enthusiastic to expand our research in these different areas, while also advancing our important work in prostate cancer. The SOW was amended to reflect these changes. 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

None

Key Research Accomplishments

- Enrolled 27 on the Reduced PTV Margins protocol
- Enrolled 10 subjects on the Immobilization protocol
- Enrolled 18 subjects on the Post-prostatectomy protocol
- Treated 66 non-study patients with Calypso (including prostate and breast).
- Analyzed data on 15 patients enrolled in the retrospective breast cancer study.
- Developed a database of volumetric and dosimetric anatomical data correlated with patient quality of life outcomes for patients treated on the reduced PTV margins study.
- Developed a database of anatomical data describing quantitatively the morphology of the prostatic fossa measured on over 500 treatment-matched CT scans in post-prostatectomy patients receiving radiation therapy.
- Continued development of Madigan as a center of excellence in Targeted Radiation therapy, including continued success of our annual multidisciplinary educational conference/visiting professorship.
- Developed technical expertise in using Calypso surface beacons to track breathing motion in left-sided breast cancer, allowing sparing of the heart.

Reportable Outcomes

See appendix section of report for all abstracts presented/scheduled to be presented to date.

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 begin to mature.

Our currently underway analysis of our new database of post-prostatectomy anatomical information in over 500 treatment fractions will allow an unprecedented look at the inter- and intra- fraction changes in morphology of the prostatic fossa. Our planned participation in RTOG 0924 will allow us to contribute our expertise with Calypso localization to the national research question regarding necessary length of hormone therapy and the radiation target required for high-risk patients being treated with modern techniques. The continued accrual to our reduced PTV margins protocol, and participation of BAMC in this protocol, will lead to important quality of life outcomes publications in prostate cancer.

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

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 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.

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

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

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

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

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

APPENDIX III

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

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.

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

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

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

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

APPENDIX V

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

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

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

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 (**∑**)	1.2 /	2.7 /	1.4 /	
Random error(**σ**)	2.0 /	3.2 /	2.0 /	
Necessary margin (2.15∑ + 0.7**σ**)	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

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

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

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

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

Table 1:

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

APPENDIX IX

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

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.