Implantation of electromagnetic transponders following radical prostatectomy for delivery of IMRT

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Introduction: *Radiation therapy (RT) after radical prostatectomy (RP) has been associated with a survival benefit in both the adjuvant and salvage setting. Nevertheless, optimal targeting of the prostate bed following surgery remains challenging. The Calypso 4D Localization System (Calypso Medical Technologies, Seattle, WA, USA) is a target positioning device that continuously monitors the location of three implantable electromagnetic transponders. We describe our technique of ultrasound-guided placement of these transponders into the prostate bed for adjuvant and salvage RT.*

Methods: *Seventeen patients presenting to Fox Chase Cancer Center for postoperative RT underwent transrectal ultrasound-guided placement of Calypso beacons. The three transponders were placed approximately 1 cm apart in a triangular fashion around the vesico-urethral anastomosis and in the retrovesicular tissue.*

Results: *All patients were successfully implanted without periprocedural complications. Appropriate beacon position was confirmed by CT scan performed at the time of RT simulation. Intensity-modulated radiation therapy was delivered at a dose of 68 Gy (range 64-68). Treatment was well-tolerated with no Grade 3 or 4 toxicities. Grade > 2 enteritis was not observed, and there were no cases of rectal bleeding. Genitourinary toxicity was noted in 10 patients and consisted of Grade 1 and 2 frequency and dysuria. No patient developed gross hematuria or urinary retention. All patients (9/9) with at least 6 months of follow up after treatment had an undetectable PSA.*

Conclusions: *The placement of Calypso transponders for adjuvant/salvage RT is a safe and efficacious method for treatment targeting with an acceptable acute toxicity profile.*

Key Words: prostate cancer, radical prostatectomy, Calypso transponders, adjuvant radiation, salvage radiation

Introduction

Despite the stage migration which has been noted in prostate cancer during the prostate-specific antigen (PSA) era, extraprostatic disease continues to be detected in 38%-52% of patients undergoing radical prostatectomy (RP),[1,2] and 5-year biochemical recurrence (BCR) rates after surgery remain between 15%-40%.[3,4] Therefore, considerable attention has focused on evaluating secondary local treatments in order to improve patient outcomes. In particular, radiation therapy (RT) after RP has been assessed in both the adjuvant and salvage settings.

Indeed, the initial reports from multiple contemporary randomized trials of adjuvant RT versus observation both noted that adjuvant treatment provided improvements in BCR-free survival and clinical recurrence-free survival.[5-7] An update from one of these trials, which

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included longer follow up, demonstrated a decrease in mortality with adjuvant radiation as well.[6] Likewise, a separate recent study found that salvage RT was associated with a three-fold increase in prostate cancer-specific survival.[8]

The delivery of RT to the prostatic fossa after surgery requires precise localization of the target region in order to maximize dose to the area of interest and limit toxicity to adjacent organs such as the rectum and bladder. In patients being treated with primary RT for prostate cancer, prostate position has been shown to vary daily,[9] and can be influenced by bladder and rectal volumes.[10] Various methods to limit or compensate for this positional variation have been employed, including quantifying interfraction differences with imaging,[11-13] utilizing rigid immobilization devices for patients, and skin tattooing. More recently, the placement of radiopaque fiducial markers[14-17] and electromagnetic transponder beacons (Calypso Medical Technologies, Seattle, WA, USA)[19,20] have been introduced as a method to further improve targeting precision. A multi-institutional experience using the Calypso system, which relies on a wireless magnetic tracking system, during primary RT for prostate cancer has been reported.[12]

For patients who require RT following RP, however, limited data exist regarding the optimal method to achieve target localization. A single study reported placing gold seed fiducial markers into the prostatic bed of 10 patients who were undergoing adjuvant or salvage radiotherapy.[13] However, the use of the electromagnetic transponders has not, to our knowledge, been previously described in this setting. Here, then, we report our initial experience with the implantation of transponder beacons into the prostatic bed of patients after RP to aid in target localization for adjuvant and salvage RT. Technique for beacon placement, acute toxicities, and early oncologic outcomes are reported.

Materials and methods

After Institutional Review Board approval was obtained, we retrospectively reviewed our prospectively maintained radiation therapy database to identify 17 patients who underwent electromagnetic transponder implantation prior to receiving postoperative RT. Two patients received adjuvant RT and 15 patients received salvage RT. Adjuvant therapy was defined as radiation treatment delivered to patients after RP with an undectable PSA but high risk pathological features, such as positive surgical margins, extracapsular extension, or seminal vesicle invasion. Salvage therapy was defined as RT delivered to patients with a detectable and/or rising PSA after surgery. Patients were initially evaluated with a magnetic resonance imaging (MRI) simulation of the prostate bed, whereby the patient is placed in a supine position and immobilized in an alpha cradle cast (Smithers Medical Products, Akron, OH, USA). A closed 1.5T MRI –simulator is used to acquire a non-contrast volumetric scan. The patient is scanned in the supine position in the alpha cradle. The scan encompasses approximately 1 cm above the bladder to 1 cm below the penile bulb using 3 mm axial slice thickness with a T2-weighted 3-dimensional turbo spin-echo sequence. The MRI images are processed for image distortion correction. The patient is then sent for Calypso beacon placement.

The preprocedure regimen for beacon placement is similar to that of a transrectal ultrasound-guided prostate needle biopsy. An oral antibiotic, most commonly a quinolone, is prescribed starting the day before the procedure and continued for 3 days after the procedure. All anticoagulant medications are withheld for 7 days before the procedure date. The morning of the procedure an enema is given to empty the rectal vault in an effort to better visualize the vesico-urethral anastomosis.

For transponder implantation, the patient is placed in the left lateral decubitus position on the examining table. Using the sagittal orientation on the ultrasound probe, the vesico-urethral anastomosis is imaged. Five cc of 1% lidocaine are administered to the left and right of the vesico-urethral anastomosis for local anesthesia. Another 5 cc of 1% lidocaine is then injected anterior to the rectal wall to create separation between the urethra, bladder, and rectum. This injection helps to create a space for placement of the beacons. Transponders are placed in a triangular separation pattern, taking care to place the beacons at least one cm apart from one another, in accordance with the manufacturer's instructions. Transponders were placed in all patients in an identical location pattern, with one beacon on either lateral aspect of the vesicourethral anastomosis and one in the retrovesical tissue approximately at the level where the seminal vesicles had been. Successful placement was confirmed in all cases by ultrasound during the procedure and then subsequent CT during treatment planning. The endorectal probe is then removed, and the patient is discharged with standard post-prostate needle biopsy instructions.

One week later, a non-contrast CT scan is obtained according to the following parameters (FOV = 48 cm; matrix = 512 x 512): from 2 cm above the iliac crest to 2 cm above the femoral heads with 1 cm slice thickness; from 2 cm above the femoral heads to the bottom of the ischial tuberosities using 3 mm slice thickness; and from the bottom of the ischial tuberosities to 12 cm caudal

using 1 cm slice thickness. The resultant images are transferred to a treatment planning workstation where a CT-MRI fusion is performed employing chamfer matching and maximization of mutual information techniques. Once the fusion is complete, the critical structures are contoured, including the prostatic fossa, bladder and rectum, as well as the femoral heads, skin and small bowel. The transponder beacons are also identified during this process and their location is stored in the computer. An intensity-modulated RT (IMRT) plan is generated that will cover the planned target volume while limiting the dose to the bladder and rectum.

The Calypso beacons are used for daily target localization and tracking. The stored location of the beacons is where the transponders are expected to be found during daily RT treatments. During each treatment session, the Calypso system compares the expected location of the transponders to their actual location. If the transponders actual location is found to be significantly different from the expected location, a repeat CT scan would be performed to re-contour the critical structures in relation to the new location of one of the transponders.

During treatment, urinary and bowel symptoms are assessed weekly for toxicity. After treatment, patients are seen at 3 and 6 months, and every 6 months thereafter with a serum PSA and symptom assessment. We reviewed the charts of these patients to evaluate the acute toxicity profile during treatment, as well as the American Urological Association Symptom Scores (AUA-SS) and Sexual Health Inventory for Men (SHIM) scores pre- and post-RT.

Results

A total of 17 men treated with IMRT post-RP underwent transrectal ultrasound-guided placement of Calypso electromagnetic transponder beacons into the prostatic fossa prior to RT. Daily on-line image guidance adjustments were made according to the location of the transponders, Figures 1 and 2. Transponder beacon placement proceeded without complications in all 17 patients. Specifically, during the implantation and throughout the IMRT course, no cases of hematuria, urinary retention, febrile illness, or rectal bleeding occurred.

Fifteen patients were implanted with transponders for salvage radiotherapy, while 2 patients had transponders placed for adjuvant radiation. Table 1 displays the patients' demographics and their pathologic data from RP. Five patients (29.4%) each had high risk prostate cancer (Gleason score 8-10) or

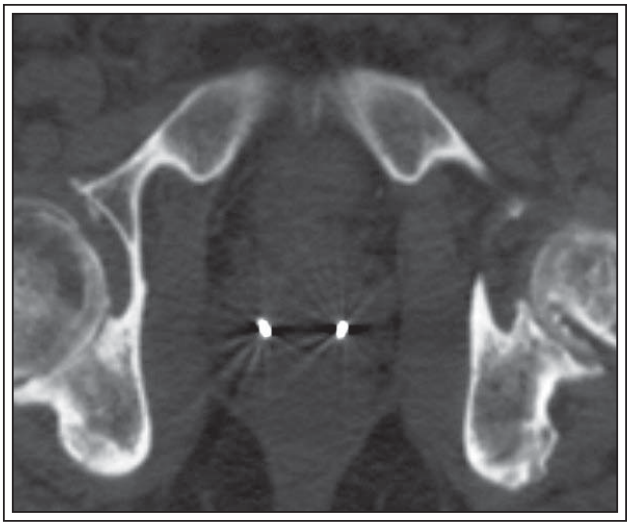

Figure 1. Axial CT image of 2 electromagnetic transponder beacon in prostatic bed.

positive surgical margins. Seven patients (41.2%) had extracapsular extension and 4 patients (23.5%) had evidence of seminal vesicle invasion in their pathologic specimens, respectively.

Median pretreatment PSA was 0.1 (range < 0.1 ng/dL-5.8 ng/dL). All patients received IMRT, with a median dose of 68 Gy (range 64-68). Treatment was well-tolerated, with no Grade 3 or 4 toxicities. Grade > 2 enteritis was not observed as well, and there were no cases of rectal bleeding. Genitourinary toxicity was noted in 10 patients, and consisted of Grade 1 and 2 frequency and dysuria. No patient developed gross hematuria or urinary retention.

Nine patients (52.9%) had at least 6 months of follow up after the completion of treatment. All of these patients had a PSA value that was undectable (≤ 0.1) at 6 months. In addition, no changes were

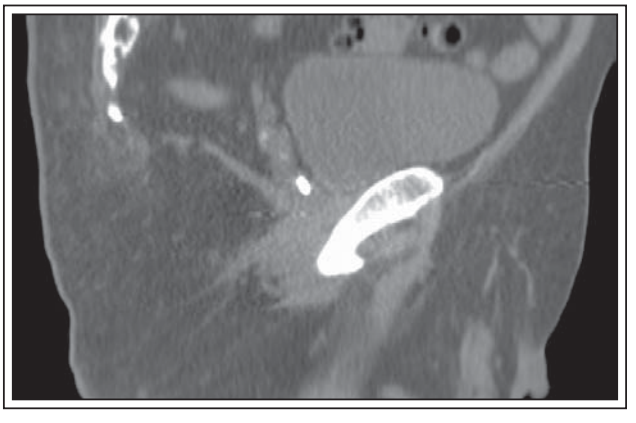

Figure 2. Sagittal CT image of electromagnetic transponder beacon in prostatic bed.

TABLE 1. **Patient demographics**

Median age	65 (range = 51-74)	
Median preoperative PSA (ng/dL)	6.5 (range = 0.9-37.3)	
Pathologic Gleason score	Gleason 6	4 patients
	Gleason 7 (3+4)	3 patients
	Gleason 7 (4+3)	5 patients
	Gleason 8-10	5 patients
Pathologic tumor stage	pT2a	2 patients
	pT2b	2 patients
	pT2c	2 patients
	pT3a	7 patients
	pT3b	4 patients
Surgical margin status	Negative	12 patients
	Positive	5 patients

noted in the AUA Symptom Score or SHIM score in these nine patients who had completed treatment. The median pre-treatment AUA-SS was 5 and the median post-treatment AUA-SS was 3. Similarly, the median pre- and post-treatment SHIM scores were 5.

During treatment, transponder actual location did not differ significantly from the expected location that was stored in the computer during treatment planning. For all 17 patients, a repeat CT scan was not necessary, signifying that the transponder location was durable and stable. Furthermore, the transponders moved very little during daily treatments. By convention, a greater than 5 mm intrafraction movement in any direction would result in a cessation of the daily fractionated dose and a realignment of the Calypso system. During treatment for these 17 patients, the targeted volume moved less than 5 mm in all three-dimensional directions as evidenced by the lack of need for realignment.

Discussion

The goals of radiotherapy are to deliver the maximum amount of radiation to the intended target tissue while limiting toxicities to surrounding structures. The ability to localize the intended target is paramount in accomplishing these purposes. Unfortunately, the position of the prostate and the prostatic fossa after RP is especially subject to motion and positioning errors due to the bony pelvic anatomy,[14] bladder volumes,[10] and rectal distension.[10]

Several methods have been developed to limit target position variability on an interfraction basis. For example, immobilization devices such as an alpha cradle have been used to reduce patient positioning errors. Alternatively, target position movement may be limited by placement of a rectal balloon filled with air.[15] In addition, investigators have used different imaging techniques, including CT scans, ultrasonography, and MRI to localize the prostate and make daily realignments prior to treatment.

More recently, implanted fiducial markers, including gold seeds and electromagnetic beacon transponders, have been used to localize the prostate and make daily target adjustments during radiotherapy for prostate cancer. These techniques have been shown to be technically feasible and appear to improve the precision of treatment.[12,16-22] However, the reports to date have largely been limited to patients undergoing primary RT. Little data exist on the optimal method to target the prostate bed for post-RP RT. Efforts have included external imaging modalities such as 3-D ultrasonography[23] and imaging of radiopaque surgical clips.[24]

A single previous series reported the implantation of gold seed fiducials in patients undergoing RT following RP.[13] Specifically, Schiffner et al described their experience in 10 patients and found that the use of image-guided target localization was a valuable tool to correct for daily target motion and thereby decrease positioning error.[13] The authors noted that the procedure was safe with no instances of seed migration or toxicities attributable to the implantation.

Here, we report our experience with implanting electromagnetic transponder beacons into the prostatic bed in patients undergoing adjuvant or salvage radiotherapy. Three beacons are placed in a triangular pattern around the vesico-urethral anastomosis and in the retro-vesicular tissue. The procedure is very similar to the technique employed for transrectal prostate biopsy,

a procedure familiar to all urologists. To date, we have noted no adverse events attributable to the procedure. No patient experienced a post-procedure febrile illness, urinary retention, hematuria, or rectal bleeding.

To our knowledge, this study represents the first description of the technique of implanting electromagnetic transponder beacons into the prostatic bed for patients undergoing adjuvant or salvage RT following RP. The use of the wireless beacons allows for daily target positioning correction, offering the opportunity to maximize the amount of radiation that can be delivered to the prostatic bed while minimizing adjacent organ exposure. There appears to be excellent stability of the beacons after placement and during treatment. The actual and expected locations of the transponders correlated very well such that recontouring was not necessary. Furthermore, intrafracion motion was minimal. The acute toxicity profile was excellent, and short term functional and oncologic outcomes appear promising. Whether the use of transponder beacons in this setting will impact the clinical endpoints of biochemical recurrence and survival in a meaningful way remains to be evaluated with larger patient numbers and long term follow up.

Conclusions

We describe the implantation of electromagnetic transponder beacons into the prostate bed to improve the delivery of IMRT during post-prostatectomy radiation therapy. This technique is feasible, associated with an excellent toxicity profile, and demonstrated promising short term oncologic and functional outcomes. □

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