Prostate tumor alignment and continuous, real-time adaptive radiation therapy using electromagnetic fiducials: Clinical and cost-utility analyses

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Abstract

**Objective:** To evaluate the accuracy, utility, and cost effectiveness of a new electromagnetic patient positioning and continuous, real-time monitoring system, which uses permanently implanted resonant transponders in the target (Calypso® 4D Localization System and Beacon® transponders, Seattle, WA) to continuously monitor tumor location and movement during external beam radiation therapy of the prostate.

**Materials and methods:** This clinical trial studied 43 patients at 5 sites. All patients were implanted with 3 transponders each. In 41 patients, the system was used for initial alignment at each therapy session. Thirty-five patients had continuous monitoring during their radiation treatment. Over 1,000 alignment comparisons were made to a commercially available kV X-ray positioning system (BrainLAB ExacTrac, Munich, Germany). Using decision analysis and Markov processes, the outcomes of patients were simulated over a 5-year period and measured in terms of costs from a payer’s perspective and quality-adjusted life years (QALYs).

**Results:** All patients had satisfactory transponder implantations for monitoring purposes. In over 75% of the treatment sessions, the correction to conventional positioning (laser and tattoos) directed by an electromagnetic patient positioning and monitoring system was greater than 5 mm. Ninety-seven percent (34/35) of the patients who underwent continuous monitoring had target motion that exceeded preset limits at some point during the course of their radiation therapy. Exceeding preset thresholds resulted in user intervention at least once during the therapy in 80% of the patients (28/35). Compared with localization using ultrasound, electronic portal imaging devices (EPID), or computed tomography (CT), localization with the electromagnetic patient positioning and monitoring system yielded superior gains in QALYs at comparable costs.

**Conclusions:** Most patients positioned with conventional tattoos and lasers for prostate radiation therapy were found by use of the electromagnetic patient positioning and monitoring system to have alignment errors exceeding 5 mm. Almost all patients undergoing external beam radiation of the prostate have been shown to have target organ movement exceeding 3 mm during radiation therapy delivery. The ability of the electromagnetic technology to monitor tumor target location during the same time as radiation therapy is being delivered allows clinicians to provide real time adaptive radiation therapy for prostate cancer. This permits clinicians to intervene when the prostate moves outside the radiation isocenter, which should decrease adverse events and improve patient outcomes. Additionally, a cost-utility analysis has demonstrated that the electromagnetic patient positioning and monitoring system offers patient outcome benefits at a cost that falls well within the payer’s customary willingness to pay (WTP) threshold of $50,000 per QALY. © 2008 Elsevier Inc. All rights reserved.

**Keywords:** Prostate; Radiation therapy; Localization; Monitoring; Radiofrequency; Electromagnetic

1. Introduction

Despite recent technological advances in diagnosis and management, prostate cancer has become the most common newly diagnosed cancer and second leading cause of cancer death in men in the United States [1]. The effectiveness of radiation therapy, the mainstay of prostate cancer treatment [2], is limited by morbidity produced by exposure of adjacent normal tissues to nontherapeutic ionizing radiation. Due to the contiguous radiosensitive tissues of the urethra,
bladder, and rectum, as well as uncertainty as to the exact tumor location during radiation, patients may receive a suboptimal radiation dose to the tumor itself and/or excessive radiation to surrounding normal tissue.

Initial patient positioning for radiation therapy is typically performed with the aid of skin marks or tattoos and laser alignment. Other localization technologies, such as megavoltage (MV) port films or electronic portal imaging devices (EPIDs) are used prior to treatment to verify the alignment of the target organ and treatment beam. Technological advances, such as three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), allow for more precise conformity of the treatment beams to the target shape. Other target localization and patient positioning technologies currently in use include ultrasound-based (e.g., NOMOS BAT® system [3]) and ionizing radiation-based systems (e.g., BrainLAB ExacTrac® [4]).

Yet, even with more precise initial positioning, without an accurate, continuous, real-time monitoring system used during the radiation therapy delivery, sources of geometric variations, such as organ motion, organ deformation, patient movement, and other causes of positioning uncertainty, can still result in the excessive irradiation of normal tissues and/or suboptimal tumor treatment.

This article describes the results of the initial clinical trials of a continuous, real-time alignment and monitoring system for external radiation therapy of the prostate based on permanently implanted transponders, electromagnetically energized, and monitored by a flat panel array positioned over the target area.

Payers, such as Medicare, Medicaid, and commercial insurers, typically consider $50,000 per quality-adjusted life year (QALY) to be the upper threshold of their willingness to pay (WTP) [5] for new pharmaceuticals and medical devices. Cost-utility analyses were performed to compare the costs and benefits of the electromagnetic patient positioning and monitoring system with currently available positioning systems.

2. Materials and methods

2.1. Calypso® 4D Localization System with Beacon® transponders

The Calypso® 4D Localization System has been cleared for marketing by the U.S. Food and Drug Administration (FDA) for target organ positioning and monitoring during delivery of radiation therapy in prostate cancer patients.

The Calypso® System has 5 main components: implanted Beacon® transponders, the console, the array (which is attached to the console), the optical localization subsystem, and the monitoring station. It is to be used only with a nonconductive table top.

Each transponder consists of a sealed biocompatible glass capsule containing a miniature electronic circuit (a copper coil wound on a ferrite core). Transponders are 1.85 mm in diameter by 8.7 mm in length. The transponder circuits are passive and do not contain an internal energy source. The transponders resonate when excited by the non-ionizing electromagnetic field generated by the array. Once excited, each transponder briefly emits a signal at a frequency specific to that transponder, which is detected by the array. A minimum of 2 functioning transponders are necessary for functioning of the electromagnetic patient positioning and monitoring system.

The console is a moveable unit that is used in the radiation therapy treatment room. It contains the electronic power supply, system components that generate and detect the electromagnetic signals used for patient setup and continuous target position monitoring, and a dedicated computer with touch screen display. The software interprets the shape of the transponder signal measured across the array to determine the position of each transponder. The array is attached to the console by means of a mechanical arm, which allows manual positioning of the array and carries the power and data transfer cables.

The array contains source coils, sensors, and optical targets. Source coils inside the array generate electromagnetic fields in the 300 to 500 kHz frequency range. Each of the transponders resonates at a specific frequency. Multiple sensors inside the array measure the strength and orientation of the resonant signals from the transponders. This information is then used by proprietary Calypso® software to determine and continuously monitor the target position with respect to the array.

Nine infrared (IR) targets embedded on the top of the array enable the optical localization subsystem to detect and continuously monitor the array’s position relative to the linear accelerator’s isocenter. The optical localization subsystem is comprised of 3 infrared cameras permanently mounted on the walls or ceiling of the treatment room. These cameras continuously monitor the array’s position relative to the linear accelerator’s isocenter. An optical calibration procedure must be performed periodically to ensure that the isocenter of the optical localization system coincides with linear accelerator’s isocenter. Three cameras are used in order to provide redundancy in the event that an individual camera is obscured by personnel, the linear accelerator gantry, or by other machinery in the room.

The console and optical system located in the treatment room are connected via Ethernet to the monitoring station located in the control area outside the treatment room. The monitoring station receives and interprets data from the console. Data is continuously transferred between the console and the monitoring station to enable the radiation therapists or operators to monitor the target position relative to machine isocenter in real-time. Localization and monitoring information is presented to the radiation therapist using simple and objective on-screen graphics as well as numer-
tical data. If the target position exceeds the preset monitoring limits, the color of the on-screen graphics changes and an audible alarm alerts the user when the target stays out of the preset monitoring limits for more than 5 seconds. Fig. 1 shows the Calypso® 4D Localization System with all its components. Fig. 2 shows a screen shot of the graphical display of the target monitoring.

The Calypso® System provides 2 important functions: initial localization and continuous tracking. The system was designed to localize 95%+ of all males based on an extensive morphometric analysis during the design of the Calypso® System. For continuous tracking, the transponders must be 23 cm or less from the detection array placed over the patient. It is not just the patient’s gross weight that determines this cutoff distance but body habitus, such as a barrel shaped chest or very protuberant abdomen, patient variables that are difficult to predict until an attempt is made to continuously track the patient on the treatment table.

2.2. Patient selection

All studies were conducted after review and approval and under the supervision of the relevant Institutional Review Boards under an FDA investigational device exemption (IDE). Eligible patients were over age 18 years with histologically confirmed diagnosis of prostate cancer and a planned course of treatment using external beam radiation therapy only with implanted fiducial markers (i.e., gold markers). All patients had intact prostates. (Minor post-transurethral prostate resection defects were allowed at the investigator’s discretion.) Exclusion criteria included: prior nonhormonal treatment for prostate cancer, stage IV prostate cancer, patients ineligible for prostate biopsy, history of abdomino-perineal resection, planned brachytherapy, allergy to local anesthetics, patients with any permanently implanted medical devices that have an energy source, (e.g., pacemakers, defibrillators, neurostimulators, and drug infusion pumps), prosthetic implants in the abdomen or pelvis, vascular implants, history of prostatitis, history of recent acute and/or chronic bleeding disorders, patients on anticoagulant or antiplatelet therapy, patients for which the maximum anterior-posterior separation through the torso minus the height of the center of the prostate exceeded 23 cm, abnormal baseline INR (international normalized ratio) or PTT (partial thromboplastin time), platelet count < 75,000 mm³, or creatinine > 2.0 mg/dl.

The data reported in this manuscript were from the FDA pre-market approval study. In this study, the FDA defined the exclusion criteria and limited the study subjects to early stage patients. In the final FDA approved product label, there are no restrictions due to clinical stage, the only limitations for the use of Calypso® System are bleeding disorders or other medical comorbidities that preclude transponder insertion (basically the same contraindications as for prostate biopsy) or conditions such as patients with pacemakers or bilateral artificial hip replacements that might interfere with or be contraindications to the use of radiofrequency excitation. Written informed consent was obtained from all participants. Patient characteristics are summarized in Table 1.

In actual clinical practice, the specific anatomy in 10% to 15% of patients permits localization but not continuous tracking. Rarely, a patient cannot be localized, such as a massively obese patient (exceeding 350 lbs.). Generally, these same patients cannot undergo external radiation therapy as most radiation therapy treatment tables are limited to patients weighing less than 350 to 400 lbs.¹

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¹ Data not shown; clinical experience of coauthors.
Table 1
Summary of patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean value ± SD (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at implant (y)</td>
<td>66 ± 9 (range: 46–79)</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>199 ± 36 (range: 145–321)</td>
</tr>
<tr>
<td>Prostate volume (cc)</td>
<td>34 ± 21 (range: 10–140)</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>9.4 ± 12.2 (range: 0–74.2)</td>
</tr>
<tr>
<td>Prior hormone therapy</td>
<td>15 (35)</td>
</tr>
<tr>
<td>Gleason score: Grade 5</td>
<td>0 (0)</td>
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<tr>
<td>Grade 6</td>
<td>26 (61)</td>
</tr>
<tr>
<td>Grade 7</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Grade 8</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Major: Grade 3</td>
<td>35 (81)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Minor: Grade 2</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>31 (72)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Clinical T stage: T1A</td>
<td>1 (2)</td>
</tr>
<tr>
<td>T1C</td>
<td>30 (70)</td>
</tr>
<tr>
<td>T1</td>
<td>1 (2)</td>
</tr>
<tr>
<td>T2A</td>
<td>7 (16)</td>
</tr>
<tr>
<td>T2B</td>
<td>1 (2)</td>
</tr>
<tr>
<td>T2C</td>
<td>2 (5)</td>
</tr>
<tr>
<td>T3B</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Clinical N stage N0</td>
<td>27 (63)</td>
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<tr>
<td>NX</td>
<td>16 (37)</td>
</tr>
<tr>
<td>Clinical M stage M0</td>
<td>30 (70)</td>
</tr>
<tr>
<td>MX</td>
<td>13 (30)</td>
</tr>
</tbody>
</table>

2.3. Implantation of transponders

At each investigational site, transponder implantations were performed by a single physician. These included 2 urologists, 2 radiation oncologists, and 1 interventional radiologist. The transponders were implanted with 14-gauge needles at the apex and left and right bases of the prostate under transrectal ultrasound guidance. All the patients were implanted with 3 transponders using a local anesthetic and prophylactic antibiotics. Transponder localization and stability were confirmed by a postimplantation CT scan followed by a second CT scan between 4 and 14 days after the implant, which was then used for treatment planning. All transponder implantations were performed from July 2005 through March 2006.

Transponder labeling is simply for insertion guideline, such that some reasonable spacing between transponders will be the end result, i.e., >5 mm. It does not matter if the transponders are placed in the coronal, sagittal, or transverse planes because each transponder has its own magnetic centroid point. The Calypso® System is not dependent on the final anatomical location within the prostate, as long as the transponders are retained in the prostate or the peri-prostatic tissue. The relationship between the transponders and the volume of tissue the radiation oncologist wishes to treat (e.g., prostate, prostate and seminal vesicles) is established by CT imaging performed for radiation therapy planning. In this planning process, the transponders are referenced to the radiation treatment isocenter, which is the virtual point about which the physician defined radiation volume is actually delivered. Thus at radiation treatment, the Calypso® System is actually checking the target alignment to beam isocenter, such that the prescribed radiation volume (as defined by CT/physician input step) is delivered to the intended target.

Prostate size does not matter because the Calypso® System relates to the treatment isocenter about which the physician defined (by CT) radiation volume is delivered. In fact, the Calypso System works in the post-prostatectomy setting as well.2

2.4. Study design

Follow-up CTs after the implant were used to determine the relative stability of the transponders. Transponder and treatment isocenter coordinates were determined using standard treatment planning software and entered into the monitoring station. Tumor movement thresholds (5 mm at 4 sites and 3 mm at 1 site) were selected at the discretion of the site investigator. Both isocenter localization and centroid localization were used in the study. The type of localization depended on the implanted transponder geometry and selection of target isocenter. Of the 41 patients who completed radiation therapy,3 28 patients had isocenter localization (68%) and 13 patients had centroid localization (32%). Standard external beam prostate cancer treatment protocols were used at the site investigator’s discretion. Regimens varied from 76 to 81 Gy, administered in 38 to 45 sessions, using 5 to 7 beams.

Patients were initially aligned using conventional methods (triangulation of skin tattoos with lasers). The electromagnetic patient positioning and monitoring system was then used to confirm alignment. Patients were then repositioned, as necessary, using the measured off-sets from the electromagnetic patient positioning and monitoring system. Body size prevented continuous monitoring during radiation therapy for a total of 6 patients at 3 of the 5 sites. Thirty-five patients had continuous target monitoring during most therapy sessions.

On 6 occasions during the course of therapy (dry run, fractions 1, 10, 20, 30, and last), direct comparisons were made between the electromagnetic patient positioning and monitoring system and the kV X-ray positioning system (BrainLAB Excactrac®). For the comparison sessions, the electromagnetic system was first used for localization, followed by a kV X-ray single image localization followed by another electromagnetic system localization. After a portion of the therapy beams was delivered, the set of comparative measurements were repeated and the treatment session was subsequently completed.

2 Data not shown; clinical experience of coauthors.
3 One patient chose not to receive external radiation after transponder implantation and withdrew from the study. An additional patient had undergone implantation but had not completed therapy at the time of the data compilation.
During the therapy session, the radiation therapy technician monitored the target motion at the monitoring station for an indication that the target had moved outside the designated monitoring limits (e.g., 5 mm or 3 mm depending on the institution) and then responded according to individual regimens adopted at each site. There were 4 types of user responses tabulated from least to greatest level of intervention when organ motion exceeded monitoring limits: no action; delayed initiation of radiation beam until target returned within limits; realigned patient between beams (if the excursion occurred during beam delivery, the user did not stop the radiation beam); and stopped beam and either waited for the excursion to resolve, or entered the room and realigned the patient. Figs. 3, 4, 5, 6, and 7 demonstrate 5 types of motion that were characterized across the cohort: persistent excursions, self-resolving excursions, drifting excursions, high frequency transient excursions, and a stable target.

### 2.5. Cost-utility analysis

A cost-utility Markov model was constructed and analyzed using TreeAge™ Data Pro version 8.0 software (TreeAge Software, Inc., Williamstown, MA). All probability values were based on evidence from published peer-reviewed clinical studies and data from national healthcare databases. The term “cost” as it is used in the model and discussion thereof, represented the Centers for Medicare and Medicaid Services Fee Schedule national nonadjusted reimbursement values (2006) for applicable Current Procedural Terminology (CPT; American Medical Association) and Ambulatory Payment Classification (APC) codes for outpatient physician services and supplies. The nonadjusted average wholesale price (AWP) based on the 2005 Red Book (Thomson Medical Economics, 2005) was used as the cost for pharmaceutical treatment of complications or androgen ablation therapy. The cost of the electromagnetic patient positioning and monitoring system was estimated based on the average cost of the comparable technologies (ultrasound, EPID, or CT). The cost and probability variables for the complications were the averaged values of acute and late Radiation Therapy Oncology Group (RTOG) grades 2 and 3 rectal and urinary toxicities. Grade 4 toxicities were rare and considered insignificant to the model. Cost and disutility values for the complications were the total estimated values for 60 months of observation and treatment. Utility values were derived from health state preference assessments from published studies and based on a scale from 0 to 1, with 0 representing death and 1 denoting a state of perfect health. Due to a lack of clinical data, the rate of achieving biochemical no evidence of disease (bNED) control in the study population was assumed to be equivalent to the estimated rate for the population receiving conformal radiotherapy. Due to the nature of the study design and the lack of data from comparable real-time monitoring technologies, the cost-utility analysis was limited to analyses of initial positioning errors and did not include the benefits assumed with continuous real-time electromagnetic patient monitoring.
3. Results

3.1. Transponder implantation experience

The implantation procedures were generally uneventful and well tolerated by the patients. All patients (43/43) had implantation configurations that met the qualifications for use with the electromagnetic patient positioning and monitoring system (i.e., 2 or 3 transponders available for detection). Table 2 lists the symptoms reported by the 41 patients who have completed therapy and the 1 patient who withdrew from the study. Fifty-two percent of patients (22/42) reported symptoms after the implantation procedure. The rate of reporting of these symptoms is well within the range of symptoms reported after similar procedures (implantation of gold fiducials, transrectal ultrasound-guided prostate biopsy) [6,7].

One patient reported pain associated with insertion and manipulation of the transrectal ultrasound probe. The implanting physician commented that the prostate seemed hard, making it more difficult than usual to insert the introducer. The apex transponder was deposited in the apex-rectal border. The transponder position was stable, and the transponder configuration was used with the electromagnetic patient positioning and monitoring system over the course of therapy. During the implantation procedure of 1 patient, the physician encountered resistance when trying to withdraw the introducer from the channel that runs through

![Fig. 5. Drifting excursion. Representation of target organ motion tracing over a 10-minute period of time. Of note is the persistent, progressive, combined inferior (red) and longitudinal (green) displacement that began about 2.5 minutes into the tracing, reached five mm at 4 minutes into the tracing and continued increasing throughout the period of the tracing.](image1)

![Fig. 6. High frequency transient excursions. Representation of target organ motion tracing over a 10-minute period of time. Of note are the repetitive, brief, combined superior (red) and longitudinal (green) displacements, each lasting less than 30 seconds with prompt return to a stable baseline. The vertical displacements are of greater magnitude than the simultaneous lateral displacements and often exceed 10 mm.](image2)

![Fig. 7. Stable target. Representation of target organ motion tracing over a 10-minute period of time. Of note is the absence of either transient excursions or baseline shift. Over the 10-minute recording, the lateral axis (blue) shifted less than 2 mm while there was essentially no shift in the other 2 axes.](image3)

Table 2
Post implantation patient-reported symptoms

<table>
<thead>
<tr>
<th>Reported symptoms</th>
<th>n = 42</th>
<th>Number reporting (n = 22)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td>17</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Hematochezia</td>
<td>7</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Pain*</td>
<td>5</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>IPSS Symptomsb</td>
<td>7</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Hematospermia</td>
<td>4</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Dysuria</td>
<td>3</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>1</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Otherc</td>
<td>1</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

* Pelvic, testicular, scrotal, or rectal pain.

b International Prostate Symptom Score.

c Suspected vasovagal reaction after implantation procedure.
the end of the ultrasound probe after depositing the first transponder. The ultrasound probe was damaged in the process. After an investigation, it was concluded that the probe cover had become caught between the introducer and the channel, preventing the introducer from being withdrawn from the channel. The remaining 2 transponders were implanted during a subsequent visit, and the patient progressed through the study without further incident. In 1 patient, the apical transponder was deposited near the urethra and observed by the implanter on ultrasound to move immediately toward the bladder. The transponder was documented to be in the bladder on the post-implant CT scan. The patient was instructed to strain his urine, passed the transponder without sensing it pass, and retrieved the transponder in the strained urine. No clinical sequelae were observed. This patient subsequently withdrew from the study in order to pursue another form of therapy instead of external beam radiation therapy.

3.2. Transponder reliability

All 123 transponders (41 patients) were functional over a full course of radiation therapy. The calculated 95% confidence interval for an individual transponder being functional exceeded 97%. In the event of a single non-responsive transponder in a patient, the electromagnetic patient positioning and monitoring system will still operate as intended.

3.3. Accuracy of initial conventional positioning

Data were collected on the distance between conventional laser/tattoo patient positioning and alignment indicated by the electromagnetic patient positioning and monitoring system. The root-sum-squared (RSS) of the lateral, longitudinal, and vertical components of localization discrepancies as shown by the electromagnetic patient positioning and monitoring system were calculated for 1,524 fractions in 41 patients. In over three-quarters of the measured fractions, the correction to conventional positioning directed by the electromagnetic patient positioning and monitoring system was greater than 5 mm. Over 10% of patients had an initial positioning misalignment exceeding 15 mm.

3.4. Time for patient alignment

Time-to-alignment data using the electromagnetic patient positioning and monitoring system were analyzed for a total of 1,057 treatment fractions from 4 clinical sites. The mean alignment time ranged from 70 to 121 seconds (1.17 to 2.02 minutes) across the 4 sites with an overall cumulative mean of 104 seconds (SD 50) (or 1.73 minutes; SD 0.83). In a subset analysis of 5 patients (139 fractions), time-to-align data using laser and tattoos were compared with data for alignment of the electromagnetic patient positioning and monitoring system. The mean time required for the initial alignment of tattoos and lasers was 1.33 minutes (SD 0.58; range 0.33 to 3.95) compared with 1.98 minutes (SD 1.33; range 0.35 to 10.58) for alignment using the electromagnetic patient positioning and monitoring system. In actual clinical practice, there is little or no difference in the patient time in treatment room with or without use of the Calypso® System.  

3.5. Comparison of electromagnetic patient positioning and tracking system and kV X-ray localization

In order to validate the accuracy of the Calypso® System in initial positioning, a series of comparisons were made with an FDA approved kV X-ray positioning system (BrainLAB ExacTrac®). A total of 1,027 comparisons between the electromagnetic system and kV X-rays were computed during the study. The computed average and standard deviation of the vector length difference (RSS) between the electromagnetic patient positioning and monitoring system and kV X-ray localizations were 1.9 ± 1.2 mm. The mean RSS vector difference in measurements did not exceed 3 mm at any center. There were no discernible differences depending on tumor position, patient anatomy, or prior hormone therapy. Accordingly, the Calypso® System was demonstrated to be as accurate as other FDA-approved positioning technology, with, however, the added advantage of the ability to continuously monitor the target organ during radiation therapy.

3.6. Target movement during therapy sessions

The 35 localize and track patients who were continuously monitored for target position during treatment delivery had a total of 1,157 fractions tracked (mean 33, range 20 to 40). There was considerable variation across patients. In 362 fractions (31.3%), Center-specified tracking limits were exceeded. Ninety-seven percent (34/35) of patients had target motion that exceeded tumor movement thresholds at some point during their radiation therapy. Users intervened at least once during the therapy of 80% of patients (28/35). Users delayed radiation in 2.7% of fractions, realigned patients in 8.2% of fractions, and stopped the beam during 0.4% of fractions. In the majority of fractions across all patients, the user did not intervene or change the course of action in response to the target motion exceeding the movement thresholds. Interventions were at the discretion of the investigator.

3.7. Acute radiation-induced toxicities

Preliminary data (which were limited to adverse events reported during the 8 weeks of treatment) revealed that 15
of 41 (37%) patients reported acute urinary symptoms, which were attributed to the effects of radiation therapy. There were no reported acute rectal toxicities. Among the 15 patients, there were 13 (30%) complaints of International Prostate Symptom Score (IPSS) ([8]) symptoms, 2 (5%) accounts of dysuria, and 1 report (2%) of pain on ejaculation. One patient (2%) had hematuria. Overall, the toxicities were minor and transient with only 4 patients requiring medical (pharmacologic) intervention. Based on the RTOG scoring criteria, 11 patients (27%) had Grade 1 and 4 (10%) had Grade 2 urinary toxicities during treatment. There was no Grade 3 or 4 urinary toxicities. Additional details of the study design and results have previously been published [9].

3.8. Cost-utility analysis

Using decision analysis and Markov processes, the outcomes of patients were simulated over a 5-year period and measured in terms of costs from a payer’s perspective and QALYs. Table 3 summarizes the results of the baseline cost-utility analyses for the localization technologies. In the baseline cost-utility analysis (CUA), EPID was the least costly localization method and, therefore, did not generate an incremental cost effectiveness ratio (ICER). CT localization was not a cost effective option and was “dominated” by ultrasound due to the latter’s lower cost and greater effectiveness. Because of its dominated position, the CT strategy was eliminated from the analysis and the ICER of the electromagnetic patient positioning and monitoring system was calculated relative to ultrasound.

Compared with localization using ultrasound, the electromagnetic patient positioning and monitoring system yielded superior gains in QALYs at comparable costs. Specifically, over 5 years, patients localized with the electromagnetic patient positioning and monitoring system prior to each radiation therapy session gained an average net health benefit of approximately 2.47 QALYs at $5,432 per QALY. Compared with ultrasound, the electromagnetic patient positioning and monitoring system generated an incremental benefit of approximately 43 quality-adjusted life days (QALDs), resulting in an incremental cost effectiveness ratio (ICER) of approximately $14,053 per QALY. This ICER fell well within the payers’ customary willingness-to-pay (WTP) threshold of $50,000 per QALY [5].

4. Discussion

The International Commission on Radiation Units and Measurements (ICRU) defines the following treatment margins in radiation treatment planning: gross tumor volume (GTV): the confirmed target that is palpable or visible by physical or radiological examination; clinical target volume (CTV): the GTV plus a margin to account for areas of suspected involvement; planning target volume (PTV): the CTV plus a margin to account for geometric variations in its shape and location due to organ motion, organ deformation, and patient set-up [10]. Wider margins result in increased risk that the maximal therapeutic dose cannot be administered without potential damage to the adjacent normal structures. Conversely, smaller margins are suboptimal because they compromise adequate dose coverage of the CTV in the case of target motion or positioning error. Traditionally, the PTV consists of a single, uniform margin applied to the CTV [11]. Numerous studies have applied various calculations and algorithms to determine appropriate PTV margins. In general, the PTV margin must account for set-up error and organ motion. The margin width that achieves the desired radiation dose distribution while minimizing normal tissue exposure may also be dictated by organ localization and immobilization techniques. Margins exceeding 5 mm have been associated with normal tissue exposure and perturbations in the prescribed dose [12]. Thus, it is evident that without accurate means of monitoring prostate motion continuously throughout treatment delivery, in real-time, normal tissues will continue to be irradiated in order to maintain a PTV adequately large to include the affected areas, while accounting for geometric uncertainties. Only by reducing the PTV can the radiation exposure of normal tissues be minimized [13]. Use of the electromagnetic patient positioning and monitoring system provided an accurate method of monitoring prostate motion continuously throughout treatment delivery, allowing clinicians to adopt the delivery of radiation to changes in tumor location. The ability to provide continuous tumor location information in real time, termed Adaptive Radiation Therapy, is distinctive. It allows clinicians to reduce treatment margins and to deliver higher doses of radiation in fewer treatments for prostate cancer.

Currently available advanced localization and positioning systems include ultrasound-based, as well as ionizing-radiation-based (EPIDs, CT, and stereoscopic X-ray) tech-
nology, and all methods provide a single snapshot of the target and all but CT provide only a two-dimensional image of the target. At the time of this writing, there are no FDA cleared, commercially available systems in the United States that permit continuous, real-time target monitoring during radiation therapy of prostate cancers other than the electromagnetic patient positioning and monitoring system reported herein.

This trial included a direct comparison with a currently marketed kV X-ray positioning system using radiographic images of the implanted fiducial markers with over 1,000 comparative measurements performed in the 41 patients studied. Although conformational issues prevented simultaneous comparison with the electromagnetic patient positioning and monitoring system and the kV X-ray system, comparisons of measurements performed in sequence revealed a mean difference in displacement measurements of less than 3 mm between the 2 systems despite the nonsimultaneous nature of the comparison. (There was a difference of up to 3 minutes between comparative measurements.) While the study did not permit the determination of which system was more correct, a consistent difference of less than 3 mm is clearly within the intended safety margin, and significantly more accurate than conventional patient alignment.

Although the present study does not include any long-term follow-up reporting of radiation-associated gastrointestinal or genitourinary symptomatology, it is a logical assumption that more accurate initial alignment to the intended treatment isocenter and the ability to realign and/or pause treatments if target motion outside limits occur during treatment will reduce the radiation to adjacent normal structures and, thus, the incidence of symptomatology. The lack of reported acute radiation-associated gastrointestinal symptoms may be an indication that the use of this system has resulted in decreased irradiation of adjacent tissues as many reports cite much higher incidence of acute rectal symptomatology [14,15].

Just considering the accuracy in initial patient positioning, the electromagnetic patient positioning and monitoring system was demonstrated to be a cost-effective alternative to currently available advanced positioning systems (ultrasound, EPIDs, and CT). Costs were comparable and there was an incremental net benefit resulting in an incremental cost-effectiveness ratio (ICER) of approximately $14,053 per QALY compared with the next most cost-effective alternative technology, well within the payers’ customary WTP threshold of $50,000 per QALY.

5. Conclusions

This preliminary multi-center clinical trial has shown that most patients positioned with conventional tattoo and lasers for prostate radiation therapy have alignment errors exceeding 5 mm. Almost all patients undergoing external beam radiation of the prostate have target organ movement exceeding 5 mm during one or more treatment fractions. The electromagnetic patient positioning and monitoring system has been demonstrated to be accurate in initial patient set-up without any clinically important technician delay. It has been shown to be comparable in accuracy to a commercially marketed kV X-ray localization system, and offers the opportunity to continuously monitor target organ motion during therapy and intervene if the prostate moves outside the radiation isocenter. If differences in reported radiation-induced side effects (primarily bowel, urinary tract, and sexual symptoms) and bNED outcomes are due to variations in the actual location of the intended target tissue during radiation, then the ability of the Calypso® System to continuously monitor and adapt the radiation may result in improved outcomes with fewer complications. In addition, cost-utility analysis has demonstrated that the electromagnetic patient positioning and monitoring system described herein exhibits the greatest incremental cost effectiveness ratio of the studied alternative technologies, and its calculated ICER ($14,053) lies well within the payers’ usual willingness to pay threshold of $50,000.

References


