Scientific Article

Evaluating the potential benefit of reduced planning target volume margins for low and intermediate risk patients with prostate cancer using real-time electromagnetic tracking

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Abstract

Purpose: The aim of this study is to quantify and describe the feasibility, clinical outcomes, and patient-reported outcomes of reduced planning target volume (PTV) margins for prostate cancer treatment using real-time, continuous, intrafraction monitoring with implanted radiation frequency transponder beacons.

Methods and materials: For this prospective, nonrandomized trial, the Calypso localization system was used for intrafraction target localization in 31 patients with a PTV margin reduced to 2 mm in all directions. A total of 1333 fractions were analyzed with respect to movement of the prostate, pauses and interruptions, and dosimetric data. Pre- and posttreatment quality-of-life scores were tracked at baseline, during treatment, and up to 24 months after treatment.

Results: The mean time of daily treatment was 10 minutes, with 96.1% of all treatments falling within a 20-minute treatment window standard. On average, beacon motion exceeded 3 mm during active treatment only 1.76% of the time. The average length of treatment interruption was 34.2 seconds, with an average of 1 interruption every 3.39 fractions. The displacement or excursion of the prostate was the greatest in the superior or inferior dimension (0.11 mm and 0.09 mm, respectively) and anterior or posterior dimension (0.07 mm and 0.13 mm, respectively), followed

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by the left or right dimension (0.05 mm and 0.06 mm, respectively). At 6 months, patients demonstrated a smaller change in Expanded Prostate Cancer Index Composite scores than the ProtecT comparator group (decreased short-term morbidity). However, in the Bowel and Urinary domains at 12 and 24 months, there was no significant difference.

Conclusions: Our data confirm and support that the use of Calypso tracking with intensity modulated radiation therapy reliably provides minimal disruption to daily treatments and overall time of treatment, with the PTV only moving outside of a 3-mm margin < 2% of the time. The use of a 3-mm PTV margin provides adequate dosimetric coverage while minimizing genitourinary and gastrointestinal toxicity.

Introduction

Radiation therapy is an effective treatment option for many men with localized prostate cancer. The use of advanced radiation techniques including intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) have been shown to reduce gastrointestinal (GI) and genitourinary (GU) toxicities, even in the setting of dose escalation.[1-3] The addition of daily image guided radiation therapy (IGRT) has led to a further reduction in the dose adjacent to organs at risk and improved toxicity rates by reducing planning target volume (PTV) margins.[4] Several systems have been devised to more precisely localize the target compared with skin markings, including daily ultrasound localization, cone beam computed tomography (CBCT), and implanted fiducial markers or gold seeds with daily orthogonal pretreatment portal imaging. The implementation of these methods have allowed for a reduction in PTV expansion to 5 to 7 mm.[5-7]

In the past decade, there has been increasing research into intrafraction motion of the prostate related to changes in treatment planning, dosimetry, and radiation-associated toxicities.[8-20] However, PTV margins still vary widely depending on immobilization and IGRT technique. Recent protocols have mandated PTV margins of 5 to 10 mm, and only in the setting of extremely hypofractionated radiation therapy (SBRT) have margins of <5 mm been considered acceptable in most practices.[21] Many institutions are now using a 5-mm posterior expansion in the setting of IGRT with conventional fractionation. Real-time electromagnetic tracking of the prostate allows for the real-time tracking of internal organ and patient movement, which can allow for a further decrease in PTV margin. In theory, this would lead to a reduction in doses to adjacent organs at risk and reduction in late toxicities.

The current study is a prospective trial using the Calypso four-dimensional localization system to treat patient volunteers with prostate cancer with a clinical target volume to PTV margin of only 3 mm. We evaluated the feasibility, clinical outcomes, and patient-reported quality-of-life outcomes of reduced PTV margins for prostate cancer treatments using real-time continuous intrafraction monitoring with implanted radiation frequency transponder beacons.

Methods and materials

Patient Population

Men with low or intermediate risk of prostate cancer per the National Comprehensive Cancer Network risk groups were treated with definitive IMRT using reduced PTV margins in a prospective, single-institution, non-randomized trial. The eligibility criteria included age > 40 years, histologically confirmed prostate adenocarcinoma, cT1a-cT2c, Gleason score ≤7, prostate-specific antigen ≤15, and Zubrod performance score of 0 or 1. Patients with high risk (per the National Comprehensive Cancer Network), node-positive, or metastatic disease were excluded as well as patients with a history of connective tissue or inflammatory bowel disease, active implanted devices, or prior prostate cancer treatments other than androgen deprivation therapy (ADT). Patients with maximum anterior–posterior separation through the torso minus the height of the center of the prostate >17 cm were excluded as well for technical reasons. We obtained approval from our institutional review board and ethics committee. Patients provided consent prior to enrollment in this trial.

Treatment planning and margins

Three Calypso Beacon Transponders were implanted in the prostate via rectal ultrasound guidance per the manufacturer's instructions 4 to 7 days prior to computed tomography simulation. Computed tomography simulation was performed with a full bladder and empty rectum (and daily treatment), with coaching on behavioral and dietary modifications to achieve these goals. Lower extremity Vac-Lok bags were used for immobilization. The normal tissues were contoured per the Radiation Therapy Oncology Group

Table 1 Patient characteristics

Study		ProtecT study	AIM study	PROST-QA cohort
Number enrolled	31	545	64	153
Age (y)				
Median	69		69	69
Range	50-82		55-86	47-83
Age group, n (%)				
<60	3 (10)		3 (5)	22 (14)
60-69	14 (45)		35 (55)	66 (43)
≥70	14 (45)		26 (41)	65 (42)
PSA (ng/mL)				
Mean	5.8 (±2.6)		8.3 (±6.2)	6.8 (±4.3)
Median	5.79	4.8	6.7	5.8
Range	1.5-11.3		0.6-36.8	0.5-25.8
Group, n (%)				
<4 ng/mL	7 (23)		9 (14)	31 (20)
4-10 ng/mL	22 (71)		41 (64)	96 (63)
>10 ng/mL	2 (6)		14 (22)	26 (17)
ADT				
Yes	0		21	0
No	31		43	153
Gleason score on biopsy, n (%)				
<7	12 (39)	423 (78)	32 (5)	97 (63)
7	19 (61)	108 (20)	26 (41)	56 (37)
>7	0 (0)	14 (3)	6 (9)	0 (0)
Clinical stage, n (%)				
T1	20 (65)	429 (79)	32 (50)	123 (80)
T2	11 (35)	116 (21)	31 (48)	30 (20)
T3	0 (0)	0 (0)	1 (2)	0 (0)
Overall cancer risk				
Low	12 (39)		15 (23)	61 (40)
Intermediate	19 (61)		41 (64)	88 (58)
High	0 (0)		8 (13)	4 (3)
Other characteristics				
Mean BMI (±SD)	27.2 (3.9)		28.1 (4.6)	28.5 (5.4)
Mean prostate volume, mL (±SD)	45.3 (15.9)		61.0 (25.9)	50.0 (27.0)

ADT, androgen deprivation therapy; BMI, body mass index; PSA, prostate-specific antigen; SD, standard deviation.

guidelines. The gross tumor volume was defined as the entire prostate. The apex was defined by either prostate magnetic resonance imaging or urethrogram.

For men with low risk prostate cancer, the clinical target volume (CTV) equaled the gross tumor volume without expansion. For men with intermediate risk prostate cancer, the CTV equaled the prostate, proximal 1 cm of the seminal vesicles, plus a 3-mm expansion of the prostate (minus rectum and bladder) to account for possible extraprostatic extension. The PTV for all patients was a 3-mm uniform expansion from the CTV. CBCT was typically used once weekly to confirm bladder filling and empty rectum. The prescription dose was 77.4 Gy in 1.8 Gy fractions. The coverage goals included $V_{77.4\ Gy}$ ≥100% of the CTV and $V_{77.4\ Gy}$ ≥98% of the PTV. The maximum dose allowed to the bladder and rectum was 105% (81 Gy). Other constraints for the rectum included $V_{78\ Gy}$ ≤5% (and $V_{78\ Gy}$ <10 cm^3), $V_{75\ Gy}$ ≤15%, $V_{70\ Gy}$

≤25%, $V_{65\ Gy}$ ≤35%, and $V_{50\ Gy}$ ≤60%. Other constraints for the bladder included $V_{80\ Gy}$ ≤15%, $V_{75\ Gy}$ ≤25%, $V_{70\ Gy}$ ≤35%, and $V_{65\ Gy}$ ≤50%. All patients received static field IMRT, typically with 7 fields and occasionally up to 9. VMAT was not used because our clinic had not fully implemented VMAT at the time of the beginning of the trial.

Target localization and tracking

Treatments were delivered using the Calypso Beacons for localization and continuous, real-time tracking with the Calypso system. A 2-mm tracking threshold was utilized such that, if the beacons moved more than 2 mm from their planned position, the therapists intervened to pause the beam until either the beacons returned to an acceptable range on their own or the patient was realigned. In general, a deviation that persisted for >10 seconds would prompt repositioning.

Patient-reported outcomes

Patients completed the full Expanded Prostate Cancer Index Composite (EPIC) questionnaire[25] prior to radiation therapy, at Week 5 of radiation therapy, at the last fraction of radiation therapy, and at 3, 6, 12, 18, and 24 months after the start of radiation therapy. Three key domains were assessed: Bowel, urinary, and sexual function. We compared morbidity to ProtecT, a contemporary, well-studied cohort of patients who underwent prostate external beam radiation therapy (EBRT; 3-dimensional conformal radiation therapy) using conventional PTV margins.[22] Differences between baseline scores and follow-up EPIC scores were compared between the Calypso and ProtecT patients. Per previous analyses of EPIC scores in prostate cancer radiation therapy, a clinically relevant change in quality of life was defined as a difference from baseline to follow-up that was greater than half a standard deviation of the baseline value.[26]

Results

A total of 31 patients were enrolled in our single-institution study between May 2009 and June 2015. Patient characteristics can be found in Table 1. A total of 1333 fractions (or treatments) were recorded during this time. The follow-up time of patients ranged between 12 and 60 months with formal follow-up as part of the study at 15 months, with a mean follow-up time of 22.45 months.

The mean time of daily treatment was 10 minutes with a standard deviation of 4.80 minutes (minimum: 4 minutes; maximum: 71 minutes). Of all treatments, 96.1% fell within the standard of a 20-minute treatment window. On average, the PTV only spent $1.76\% \pm 1.69\%$ of beam-on time outside of the 2-mm treatment window.

The average length of a treatment interruption was 34.2 seconds, with an average number of interruptions of 0.30 interruptions per fraction, which is equivalent to an interruption every 3.39 fractions. Each interruption was either a pause, during which the prostate returned to within 2 mm of its planned position on its own, or a reposition that required a couch position intervention by the radiation therapist. The average length of a pause was 17.6 seconds, and the median length was 6 seconds. The average reposition time was 40.5 seconds with a median of 28.5 seconds. Given the disparity between the mean and median for both pauses and repositions, the data is likely skewed by outliers and the median values are more indicative of common pause and reposition times. These data are summarized in Table 2.

The greatest variation in displacement or excursion of the prostate in 3 dimensions was in the superior or inferior dimension (maximum excursion of the prostate during beam-on: 1.1 ± 0.9 mm or 0.9 ± 0.9 mm, respectively) and anterior or posterior dimension (0.7 ± 1.1 mm or

Table 2   Interruption length and breakdown

	Interruption Time (s)	Pause Time (s)	Reposition Time (s)
Mean	34.2	17.55	40.51
SD	33.79	37.56	51.21
Median	19.68	6	28.5
Minimum	1	1	2
Maximum	601	301	501

SD, standard deviation.

1.3 ± 0.7 mm, respectively). Left or right movement was found to a lesser degree (0.5 ± 0.6 mm or 0.6 ± 0.6 mm, respectively). These data are summarized in Table 3 and Figure 1.

All 31 patients were able to achieve a standard of 98% PTV coverage at 77.4 Gy, with a mean of $98.4\% \pm 0.5\%$. The mean rectal volumes at $V_{78\ Gy}$, $V_{75\ Gy}$, and $V_{70\ Gy}$ were $2.7\% \pm 1.6\%$, $8.2\% \pm 3.2\%$, and $14.2\% \pm 5.3\%$, respectively. The mean bladder volumes at $V_{80\ Gy}$, $V_{75\ Gy}$, and $V_{70\ Gy}$ were $1.0\% \pm 1.7\%$, $7.5\% \pm 4.2\ \%$, and $10.8\% \pm 6.2\%$, respectively. These data are summarized in Table 4.

The EPIC questionnaire response rate during the follow-up was 95%. Three volunteers stopped completing the questionnaires after 6 to 18 months of follow-up and others did not fully complete every questionnaire. For each domain at baseline, our cohort had similar or slightly lower scores than the comparator group, which indicates a higher prevalence of baseline symptoms that impair quality of life. At 6 months, patients demonstrated a smaller change in scores (ie, better health-related quality of life) than the comparator group in the bowel, urinary, and sexual domains, but this change was only statistically significant in the urinary and sexual domains ($P = .14$; $P = .03$; and $P < .01$, respectively). However, in the bowel and urinary domains at 12 and 24 months, the EPIC scores of patients in the ProtecT trial returned closer to baseline levels, whereas patient scores continued to decrease or remain stable such that there was no significant difference in the EPIC scores of the 2 groups in these domains. In addition, in the sexual domain, patients showed significantly smaller follow-up change in scores at all points of follow-up, but this comparison is confounded by the use of 6 months of ADT in the ProtecT trial.

In the ProtecT cohort at 6 months, a clinically meaningful decline is demonstrated in all 3 domains compared with a clinically meaningful decline only in the bowel scores in the patient group at that time point. At subsequent time points, patients in the ProtecT trial did not demonstrate a clinically meaningful decline in urinary symptoms. Table 5 and Figure 2 summarize the patient reported EPIC scores and changes from baseline for patients and the radiation therapy arm of the ProtecT trial.

Table 3 Maximum prostate excursion or displacement during beam-on

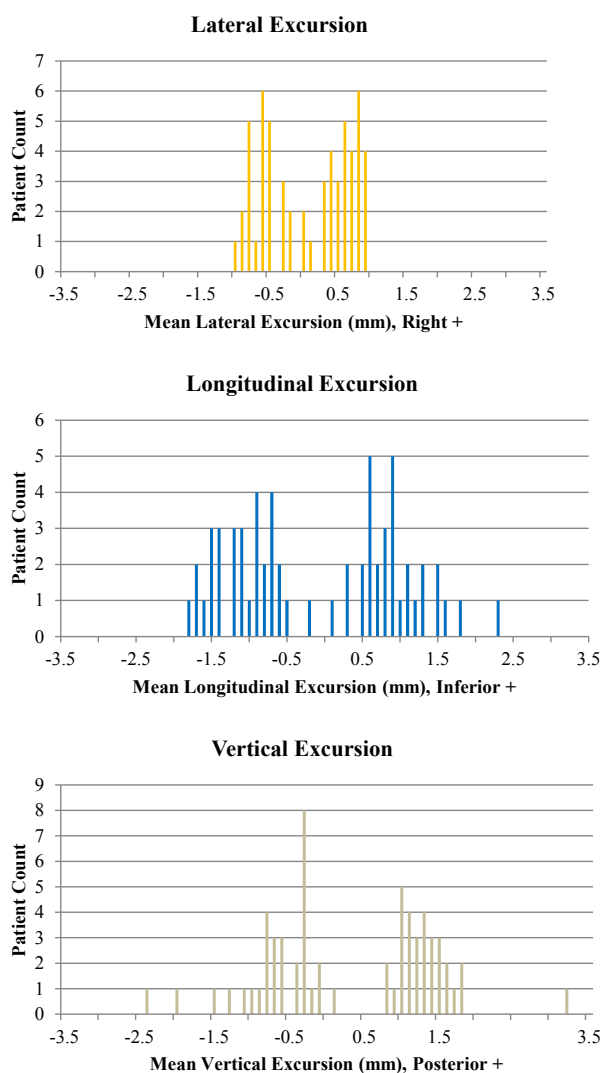| Displacement (mm)						
	Left	Right	Superior	Inferior	Anterior	Posterior
Mean	0.5	0.6	1.1	0.9	0.7	1.3
SD	0.6	0.6	0.9	0.9	1.1	0.7
Median	0.5	0.6	1.0	0.9	0.4	1.3
Minimum	−1.1	−1.2	−1.4	−1.2	−4.0	−1.1
Maximum	6.7	6.0	10.7	11.5	11.4	4.5

SD, standard deviation.

Discussion

In the recent ProtecT trial, EBRT had little effect on urinary continence, a stable long-term effect on sexual function, and a worsening effect on bowel function (with recovery) when compared with prostatectomy.[22] Of note, all men in the radiation arm of this trial also received ADT. In addition, the radiation technique was 3-dimensional conformation radiation therapy. To improve EBRT's toxicity profile, many efforts have been made to improve radiation delivery techniques, including inter- and intrafraction monitoring, to decrease dose delivery to organs at risk.

A common concern about smaller PTV margins is intrafraction motion. There is significant time between obtaining on-board kV imaging and the completion of the daily radiation fraction with multiple field IMRT plans, which leaves more time for intrafraction motion. Using the same technology, Shelton et al. in their study of 37 patients demonstrated that treatment time was the strongest predictor of observed displacements, and that VMAT was associated with reduced motion.[23] Langen et al. reported similar findings that the likelihood of prostate gland movement increased with time, and emphasized the importance of initiating treatment quickly after initially imaging the patient and minimizing overall time of treatment to decrease the likelihood of prostate drift.[13] In a comparison of VMAT with electromagnetic tracking to IMRT with and without electromagnetic tracking, Hall et al. found that VMAT was associated with a decreased time of delivery per treatment.[24] In addition, the researchers found that using VMAT with electromagnetic tracking did not cause a significantly different treatment time compared with previous methods overall.[24] Hall et al. had an average treatment time of 13.81 minutes with VMAT with Calypso tracking.[24]

Our data show a lesser mean treatment time of 10.0±4.80 minutes using the same technologies with IMRT. We suspect that by using VMAT, treatment times would be even shorter. In addition, our data show encouraging reproducibility, with 96.1% of all treatments falling within a standard treatment time of 20 minutes.

Figure 1 Patient Mean Prostate Excursion/Displacement During Beam-On.

Our data confirm and support that using Calypso tracking is time efficient and reproducible.

Our study is one of the first to demonstrate minimal disruption to daily treatments using this new technology. Langen et al. had only 17 of 550 fractions (3.1%) with interventions; however, their protocol did not dictate any interventions on the basis of observed prostate displacement.[13] In a similar study for patients undergoing prostate SBRT with Calypso tracking, Lovelock et al. demonstrated an average of 1.74 interventions or fraction required, with an increase in time of dose delivery of approximately 65 seconds.[12] Even with strict margins <2 mm to require an intervention, we only required 1 intervention every 3.39 fractions, with a mean added time of 34.2 seconds per intervention. Each pause (ie, self-return of the prostate to within 2 mm) was a median of 6 seconds long, and each reposition was a median of 28.5 seconds in duration. Pauses do not appear to contribute significantly

Table 4 Dosimetric data

	PTV	Rectum			Bladder		
	V$_{77.4}$ (≥98%)	V$_{78}$ (≤5%)	V$_{75}$ (≤15%)	V$_{70}$ (≤25%)	V$_{80}$ (≤15%)	V$_{75}$ (≤25%)	V$_{70}$ (≤35%)
Mean	98.4%	2.7%	8.2%	14.2%	1.0%	7.5%	10.8%
SD	0.5%	1.6%	3.2%	5.3%	1.7%	4.2%	6.2%
Minimum	98.0%	0.0%	1.3%	3.5%	0.0%	2.5%	3.7%
Maximum	99.9%	6.4%	14.9%	23.0%	7.8%	16.6%	27.0%

PTV, planning target volume; SD, standard deviation; V$_x$, coverage goal of x Gy.

to treatment time, but repositions tend to be slightly longer.

In addition, we noted that in a few rare instances, repositions required anywhere from 5 to 8 minutes and were likely due to rectal gas, which may have distorted the prostate and required a CBCT and repositioning. However, given the relatively low rate of interventions (1 intervention every 3.39 fractions) and the relatively small amount of time added on average by either an intervention or pause, our data show that Calypso tracking reliably provides minimal disruption to daily treatments and overall time of treatment. Implementing the Calypso tracking worked seamlessly in our clinic workflow and did not negatively impact patient care.

Many previous studies have tracked prostate intrafraction motion and its displacement or excursion has been well described in the literature.[8,13-17,20,23] Mayyas et al. used Calypso tracking and found standard deviations for intrafraction prostate motion of 1.3, 1.5, and 0.6 mm (2 standard deviation values would be 2.6, 3.0, and 1.2 mm) in the anterior or posterior, superior or inferior, and left or right directions, respectively, in a study of 27 patients.[15]

Shelton et al. also found that shifts were greater in the anterior or posterior and superior or inferior dimensions and were likely related to organ motion, and left or right motion was less and likely related to patient motion.[23] Langen et al. described that the prostate's displacement in all directions was >3 mm for 13.6% of the time, and >5 mm for 3.3% of the time on average.[13] Lin et al. looked at respiratory-induced prostate motion and found an oscillatory pattern of the prostate in the anterior or posterior and superior or inferior directions, with 99% of patients showing an average respiratory-induced motion between 0.2 and 2.0 mm.[19]

In our study, we found prostate motion to be similar to slightly lower than what has generally been described

Table 5 Patient-reported morbidity comparison (EPIC Scores[a])

Domain	Our Study (n = 31)			ProtecT (n = 545)			P-value
	Score, mean (SD)	Mean difference[b] (95% CI)	Clinically meaningful decline[c]	Score, mean (SD)	Mean difference[b] (95% CI)	Clinically meaningful decline[c]	
Bowel							
Baseline	94.1 (6.6)	—	—	94.8 (6.9)	—	—	—
6 mo	90.5 (12.2)	−3.6 (−8.5 to 1.3)	Yes	86.3 (16.0)	−8.5 (−10.4 to −6.6)	Yes	.14
12 mo	87.8 (14.2)	−6.3 (−11.8 to −0.8)	Yes	90.5 (12.2)	−4.3 (−5.8 to −2.8)	Yes	.47
24 mo	88.1 (13.7)	−6.0 (−11.4 to −0.6)	Yes	89.3 (12.8)	−5.5 (−7.0 to −4.0)	Yes	.86
Urinary							
Baseline	88.9 (10.6)	—	—	93.2 (8.3)	—	—	—
6 mo	87.2 (13.3)	−1.7 (−7.7 to 4.3)	No	84.7 (13.8)	−8.5 (−10.3 to −6.7)	Yes	.03
12 mo	85.2 (14.4)	−3.7 (−10.0 to 2.6)	No	91.9 (9.0)	−1.3 (−2.7 to 0.1)	No	.36
24 mo	84.3 (14.4)	−4.6 (−10.9 to 1.7)	No	91.4 (9.8)	−1.8 (−3.2 to −0.4)	No	.31
Sexual							
Baseline	48.9 (31.8)	—	—	63.6 (23.1)	—	—	—
6 mo	41.1 (30.1)	−7.8 (−23.2 to 7.6)	No	31.9 (27.1)	−31.7 (−35.8 to −27.6)	Yes	< .01
12 mo	36.7 (26.2)	−12.2 (−26.7 to 2.3)	No	43.2 (27.6)	−20.4 (−24.5 to −16.3)	Yes	< .01
24 mo	41.7 (29.2)	−7.2 (−22.4 to 8.0)	No	43.4 (25.9)	−20.2 (−24.1 to −16.3)	Yes	< .01

CI, confidence interval; EPIC, Expanded Prostate Cancer Index Composite; SD, standard deviation.
  [a] Scores range from 0 to 100, and higher scores indicate better patient-reported quality of life.
  [b] Change from baseline to follow-up, calculated from within-patient differences.
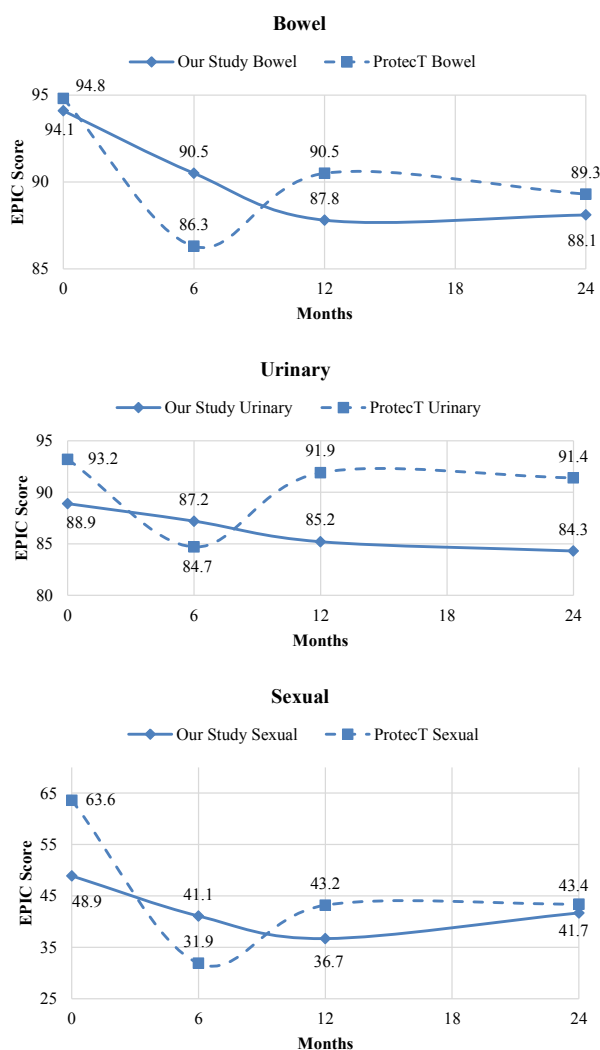 [c] Mean difference >0.5 SD from baseline value.

Figure 2   EPIC Scores.

focused on rectal toxicity, our bladder dosimetry data at $V_{80\ Gy}$, $V_{75\ Gy}$, and $V_{70\ Gy}$ show values that are in line with modern dosimetry standards to decrease GU toxicity.[21]

Patient-reported, health-related outcomes measured by EPIC questionnaire were generally improved or similar when compared with those of the ProtecT radiation therapy arm. Most notably, at 6 months of follow-up, the urinary domain was significantly improved in our study, and changes in sexual function scores remained significantly better compared with those of ProtecT. Although the initial decrements were smaller in our study, the ProtecT radiation therapy cohort showed a trend to return closer to baseline while our study showed stability/small decrements in bowel and urinary scores throughout 24 months of follow-up.

Modeling studies have previously estimated that 3-mm PTV margins in prostate cancer can decrease rectal toxicities by reducing volume of acute normal tissue damage, which can predict late tissue damage.[27,28] This may suggest that the decreased short-term morbidity observed in our study may translate into long-term improvements in morbidity that we were unable to observe in our smaller patient group.

Some observed differences in EPIC scores between our patients and those in the ProtecT trial may be related to differences in technique, lower doses used in the ProtecT trial (74 Gy in 37 fractions), and the fact that all men in the radiation arm of the ProtecT trial were treated with short-term ADT. An ADT-related reduction in prostate size could lead to improved EPIC scores.

Our analysis of patient-reported, health-related outcomes compared with those of the ProtecT radiation therapy arm is consistent with previous analyses of our cohort to the AIM and Prost-QA studies,[26,31] where pre- and post-treatment EPIC-26 survey scores for bowel, urinary irritation/incontinence, and sexual function were compared.[32] A clinically meaningful decline was demonstrated in 2 domains in our study, 1 domain in the AIM study, and 3 domains in the Prost-QA cohort study (Table 6). Furthermore, mean decrements between pre- and posttreatment scores were significantly lower in the AIM study compared with those in our cohort in the urinary irritation domain ($P = .0009$). Our cohort's results were most similar to those of Prost-QA patients, but worse than the AIM non-neoadjuvant hormonal therapy study cohort in the urinary irritation domain.

Upcoming areas of interest include hypofractionation of localized prostate cancer treatment because prospective trials, such as the Conventional versus Hypofractionated High-Dose Intensity Modulated Radiotherapy for Prostate Cancer trial, have shown noninferiority of hypofractionated treatment and the possibility to decrease

previously in the literature. This is in line with research by Bell et al. in a smaller study of only 3 patients, with findings of mean intrafraction motion of ≤ 0.2 cm in all directions.[8] Additionally, the prostate spent only 1.76% of the time outside of our planned tracking constraint of 2 mm. These are strong indicators that 3 mm margins are feasible and safe.

We would expect that a decrease in PTV margin would lead to a decrease in normal tissue toxicity. Michalski et al. showed that IMRT was associated with a reduction in acute GI and GU toxicity, and that keeping $V_{70\ Gy}$ and $V_{75\ Gy}$ at $<15\%$ and $<10\%$, respectively, was associated with lower rates of GI toxicity.[2] Our V_{70Gy} of 14.2% and $V_{75\ Gy}$ of 8.2% fell within these margins and would thus be associated with a reduction in toxicities as described by Michalski et al.[2] Zelefsky et al. found that, with interfraction monitoring using fiducial markers versus a similar non-IGRT cohort, there was significant reduction in late urinary toxicity.[9] Although previous studies have

Table 6   Patient-reported morbidity comparison between studies (EPIC Scores[a])

EPIC domain/study (n)	Pretreatment mean (SD)	Post-treatment mean (SD)	Mean difference (95% CI)	Clinically meaningful decline[b]
Bowel/rectal				
This study (31)	94.1 (18.1)	83.81 (15.4)	−10.5 (−11.5 to −9.5)	Yes
AIM non-NHT study (41)	91.8 (19.2)	89.8 (17.6)	−1.9 (−9.0 to 5.1)	No
Prost-QA cohort (148)	94.4 (10.8)	78.5 (20.9)	−16.0 (−19.4 to −12.5)	Yes
Urinary irritation				
This study (31)	88.8 (18.8)	70.6 (20.5)	−18.2 (−19.3 to −17.1)	Yes
AIM non-NHT study (38)	84.5 (18.0)	80.6 (23.0)	−4.0 (−10.0 to 2.1)	No
Prost-QA cohort (148)	86.6 (14.3)	70.1 (20.7)	−16.5 (−19.8 to −13.3)	Yes
Urinary incontinence				
This study (31)	90.8 (20.3)	86.8 (20.1)	−4.2 (−5.0 to −3.4)	No
AIM non-NHT study (43)	93.0 (12.5)	86.3 (21.0)	−6.7 (−12.1 to −1.3)	Yes
Prost-QA cohort (138)	92.5 (13.1)	84.6 (20.5)	−7.9 (−11.0 to −4.8)	Yes
Sexual				
This study (31)	48.9 (32.5)	41.0 (31.8)	−7.7 (−9.1 to −6.3)	No
AIM non-NHT study (43)	50.9 (32.1)	50.9 (26.9)	0.0 (−8.6 to 8.6)	No
Prost-QA cohort (133)	63.5 (27.8)	51.5 (30.0)	−12.0 (−15.4 to −8.5)	No

CI, confidence interval; EPIC, Expanded Prostate Cancer Index Composite; NHT, non-neoadjuvant hormonal therapy; SD, standard deviation.

[a] Scores range from 0-100, and higher scores indicate better patient reported quality of life.

[b] Mean difference >0.5 SD from baseline value.

toxicities.[29,30] Further areas of study include the study of intrafraction monitoring in the setting of hypofractionated treatments and prostate SBRT. Concern remains about late toxicities in these treatment regimens, but one way to help reduce this may be with smaller PTV margins and tighter rectal or bladder constraints.

The limitations of our study include the relative small size of the patient population and the fact that the study was performed at a single institution. Future studies that incorporate larger patient populations and more treatment centers may point toward more generalizable ways of incorporating Calypso tracking into routine dosimetric planning and daily treatments.

Conclusions

Our data confirm and support that using Calypso tracking is reliable to provide minimal disruption to daily treatments and overall time of treatment, with the PTV only moving outside of a 3-mm margin <2% of the time. IMRT with Calypso tracking presents an effective way to track the prostate in real time. Using 3-mm PTV margins provides adequate dosimetric coverage while also minimizing GU and GI toxicity. Our decreased, observed, short-term morbidity may translate into long-term improvements in morbidity that we were unable to observe in our smaller patient group. Hypofractionation and prostate SBRT are ongoing areas of research for which Calypso tracking with reduced PTV margins may serve as an important tool to improve accuracy and minimize toxicity.

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