Technical Innovations & Patient Support in Radiation Oncology 31 (2024) 100267

Contents lists available at ScienceDirect

Technical Innovations & Patient Support in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/technical-innovations-and-patient-support-in-radiation-oncology

Research Article

Clinical implementation of real time motion management for prostate SBRT: A radiation therapist's perspective

Joanne Mitchell [a,c,e,*], Duncan B. McLaren [a,c], Donna Burns Pollock [a], Joella Wright [a], Angus Killean [a], Michael Trainer [b], Susan Adamson [a], Laura McKernan [a], William H. Nailon [b,c,d]

[a] Department of Clinical Oncology, Edinburgh Cancer Centre, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK
[b] Department of Oncology Physics, Edinburgh Cancer Centre, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK
[c] Institute of Genetics and Cancer, University of Edinburgh, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK
[d] School of Engineering, the University of Edinburgh, the King's Buildings, Mayfield Road, Edinburgh EH9 3JL, UK
[e] College of Medicine and Veterinary Medicine, the University of Edinburgh, UK

ARTICLE INFO

Keywords:
Adaptive radiotherapy
Prostate cancer
Real-time tracking
SBRT prostate

ABSTRACT

Background and purpose: The adoption of hypo-fractionated stereotactic body radiotherapy (SBRT) for treating prostate cancer has led to an increase in specialised techniques for monitoring prostate motion. The aim of this study was to comprehensively review a radiation therapist (RTT) led treatment process in which two such systems were utilised, and present initial findings on their use within a SBRT prostate clinical trial.
Materials and Methods: 18 patients were investigated, nine were fitted with the Micropos RayPilot™ (RP) system (Micropos Medical, Gothenburg, SE) and nine were fitted with the Micropos Raypilot Hypocath ™ (HC) system. 36.25 Gray (Gy) was delivered in 5 fractions over 7 days with daily pre- and post-treatment cone beam computed tomography (CBCT) images acquired. Acute toxicity was reported on completion of treatment at six- and 12-weeks post-treatment, using the Radiation Therapy Oncology Group (RTOG) grading system and vertical (Vrt), longitudinal (Lng) and lateral (Lat) transmitter displacements recorded.
Results: A significant difference was found in the Lat displacement between devices (P=0.003). A more consistent bladder volume was reported in the HC group (68.03 cc to 483.7 cc RP, 196.11 cc to 313.85 cc HC). No significant difference was observed in mean dose to the bladder, rectum and bladder dose maximum between the groups. Comparison of the rectal dose maximum between the groups reported a significant result (P=0.09). Comparing displacements with toxicity endpoints identified two significant correlations: Grade 2 Genitourinary (GU) at 6 weeks, P=0.029; and no toxicity, Gastrointestinal (GI) at 12 weeks P=0.013.
Conclusion: Both the directly implanted RP device and the urinary catheter-based HC device are capable of real time motion monitoring. Here, the HC system was advantageous in the SBRT prostate workflow.

Introduction

Ultra hypofractionated SBRT, for the treatment of prostate cancer is not yet standard of care in the UK. However, there is growing evidence supporting its adoption because of the potential for therapeutic benefit and the convenience of fewer fractions of radiotherapy [1–4]. Acute toxicity reported by patients in the PACE-B trial showed no increase in gastrointestinal (GI) or genitourinary (GU) RTOG side effects in those treated with five fraction SBRT when compared to conventional fractionation schedules [5]. More recently long-term follow-up of these patients has reported similar results, with the study concluding that five fraction SBRT should now become the standard of care for patients with low or intermediate risk prostate cancer [6,7].

The increased dose per fraction, strict planning margins and steep dose gradients required for SBRT mean that any geographical errors in dose delivery can result in significant adverse toxicity to the bladder and rectum, the main organs at risk (OAR) in prostate radiotherapy [8–10]. Whilst advanced radiotherapy techniques, such as volumetric modulated arc therapy (VMAT) and image guided radiotherapy (IGRT), enable the accurate delivery of highly conformal radiotherapy [11–13] this level of precision comes with extra concerns and can still result in a geographical miss of the tumour [14]. More specifically, the position of

* Corresponding author at: Edinburgh Cancer Centre, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK.
E-mail address: Joanne.Mitchell@nhslothian.scot.nhs.uk (J. Mitchell).

https://doi.org/10.1016/j.tipsro.2024.100267
Received 30 March 2024; Received in revised form 10 July 2024; Accepted 3 August 2024
Available online 5 August 2024

the prostate gland has been shown to systematically drift in the inferior and posterior direction after initial set up [14–19], most probably caused by fluctuations in the shape and size of the bladder and rectum. However, evidence also suggests that intra-fraction motion occurs randomly and is variable between treatment fractions and patients, with real time monitoring suggested as the most appropriate method to account for this variance [16].

A number of possible approaches exist for monitoring prostate motion [20,21]. When treatment is delivered using a conventional linear accelerator pre- and post-treatment planar imaging via kilovoltage (kV) and volumetric CBCT with fiducial marker matching is the most commonly used method [22,23]. However, these methods are not able to provide continuous, real-time information on the position of the prostate gland. Monitoring real-time, intra-fractional position requires the use of specialised motion management strategies such as the magnetic resonance (MR) linear accelerator (MR Linac) (Elekta, Stockholm, Sweden), Cyberknife® (Accuray, Sunnyvale, CA), Elekta Clarity® (Elekta, Stockholm, Sweden) and the Calypso® (Varian Medical System, Palo Alto, CA) systems [21,23–25]. Whilst real time motion monitoring using the MR Linac and Cyberknife® systems requires an initial significant investment in specialised equipment the Elekta four-dimensional (4D) Clarity® system and the Calypso® 4D localization system are both examples of linear accelerator-based motion monitoring devices. The Clarity system is able to track the prostate gland via transperineal ultrasound with an accuracy of < 1 mm in the anterior/posterior (Ant/Post), superior/inferior (Sup/Inf) and left/right (L/R) directions [26]. The Calypso® system uses implanted electromagnetic transponders (beacons) and an array containing source and receiver coils to detect and monitor prostate motion [27]. The Micropos System (Fig. 1) is another linear accelerator-based approach suitable for monitoring intra-fraction prostate motion. The system consists of an electromagnetic transmitter, a receiver couch top fitted with 16 antennae to detect the co-ordinates of the transmitter, and software to calculate displacement of the transmitter against a reference position. The system has gone through two iterations since it was first developed. In the first system, known as Raypilot (RP) (Fig. 2A) the transmitter was implanted and placed, via transperineal insertion, into the prostate gland where it remained for the duration of the treatment. In the second system, known as Hypocath (HC) (Fig. 2B), the transmitter is placed within a urinary catheter before insertion within the urethra where it can be removed and re-inserted with relative ease.

The aim of this study was to comprehensively report on the clinical implementation of the RP and HC devices as methods for monitoring real time prostate motion when treating a cohort of SBRT prostate patients. Preliminary data on the clinical utility, acute patient toxicity and overall performance of both devices is reported and compared to changes observed on CBCTs taken as part of the treatment procedure. The additional information, which the use of such a device provides to RTTs, is discussed alongside the key role of the RTT in this pathway. This includes, device insertion, on-treatment monitoring, image interpretation and device removal, all of which are undertaken by suitably trained RTTs.

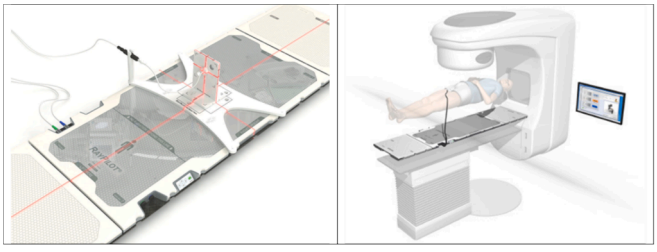


Fig. 1. Left: RayPilot couch insert which includes the antenna array required to communicate with the wired transponder shown here in the quality assurance jig. Right: Raypilot couch on treatment machine showing wired connection to patient.

Materials and methods

Ethical considerations

Patients were consented to the PRINTOUT trial [28] (Using breath analysis to PRedIct Normal TissUe and Tumour response during prostate cancer SBRT), a non-randomised cohort observational study (UKNCT04081428, IRAS 240335), which was granted ethical approval by Southeast Scotland ethics committee on March 10th 2018 with sponsorship via the Academic and Clinical Central Office for Research and Development (ACCORD) (NHS LOTHIAN/UoE).

Study recruitment

Data from the first 18 patients recruited to the PRINTOUT study matching the entry criteria of low (T1-2, PSA<10 ng/ml, Gleason $3 + 3 = 6$) or intermediate risk (T1-T2, PSA 10–20 ng/ml, Gleason score ≤ 7 ($3 + 4$ only)) prostate cancer were included.

Device insertion

For the first nine of these patients the RP transmitter was fitted under local anaesthetic into the prostate gland via transperineal insertion at the same time as three gold fiducial markers were inserted (Fig. 2A). This device would remain in situ, being removed on completion of all five treatment sessions. The next nine patients were fitted with the newly developed catheter-based HC system (Fig. 2B). With the HC system the transmitter sits within a urinary catheter and can therefore be placed into the patient as part of a normal catheterisation process. These patients attended an initial appointment for gold marker seed insertion with a dummy catheter fitted at the time of imaging for treatment planning. The planning catheter was removed on completion of pre-treatment imaging with the HC treatment catheter inserted on day one of treatment and remaining in the urethra until all treatment fractions were delivered. Device insertion was by a suitably trained RTT and once inserted the bladder was drained of urine and up to 150 ml of sterile water was injected into the balloon. Gentle tension was placed on the catheter until resistance was felt indicating that the balloon was positioned at the bladder neck. The catheter was next taped to the patient's leg to ensure a reproducible position. This procedure would be repeated at every treatment fraction.

Radiotherapy treatment planning imaging

All patients underwent a multi-parametric, radiotherapy planning MR image scan on a Siemens Magentom Aera® 1.5 Tesla wide bore scanner (Siemens Healthineers, Erlangen, Germany), fitted with a flat radiotherapy couch top. Standard rectal suppository bowel preparation was used by all patients. Those patients fitted with the RP device followed the standard departmental bladder preparation protocol by emptying their bladder followed by drinking approximately 330 ml of water 30 min prior to scanning. Those patients fitted with the HC device had their bladder drained of urine and up to 150 ml of sterile water inserted into the catheter prior to the MR scan. On completion of the scan all patients underwent a radiotherapy planning CT scan on a Phillips Brilliance® big bore scanner (Philips, Amsterdam, The Netherlands), with images acquired at 1 mm slice thickness. All patients were positioned supine and were supported by a standard head support and indexed knee and feet support. Scan length was from L3/4 intervertebral space superiorly to 2 cm below the ischial tuberosities. On completion of the planning MRI and CT scans patients fitted with HC had their planning catheter removed whilst for those patients fitted with the RP transmitter, the device remained in situ. A rigid image fusion, matching against fiducial markers and the urethra, was performed on

Fig. 2. A – RayPilot transducer element with wired connection. B – Hypocath catheter based device with balloon for insertion.

the Eclipse ® (Varian Medical System, Palo Alto, CA) treatment planning system, with dose and positional validation of this approach supported by a previous in-house study.

Target Delineation, planning and dose constraints (as per pace Trial)

Clinical Target Volumes (CTV) were defined by an experienced site-specific clinical oncologist with the prostate gland outlined as defined in the low-risk category. For patients classified as intermediate risk the CTV included the prostate and the first 1 cm of the proximal seminal vesicles. Margins of 5 mm in the anterior, superior, lateral and inferior directions with 3 mm posteriorly were applied to create the Planning Target Volume (PTV). A dose of 36.25 Gy was prescribed to the PTV to be delivered over 5 fractions in 7 days with treatment commencing on a Wednesday and completing on the following Tuesday. VMAT plans were prepared, 6MV with 3 full arcs, on the treatment planning system adhering to the dose constraints listed in Table 1.

Treatment verification

Treatment was delivered on a TrueBeam ® (Varian Medical System, Palo Alto, CA) linear accelerator. All patients were positioned supine on the Raypilot receiver couch top, which was fitted within the existing treatment couch top. The position of the transmitter was registered to the couch, which was subsequently shown on the display screen at the treatment console. On-treatment verification was followed as per the standard departmental protocol for VMAT techniques. Prior to delivery of the first treatment arc, KV images and a CBCT were acquired. Orthogonal KV images were matched to the fiducial markers, with a zero-tolerance level set. A pre-treatment CBCT was then acquired and matched against the planning CT to assess PTV coverage and OAR structures. If, in the case of the RP patients, the bladder volume was deemed to be an inadequate match to that of the planned volume and the volume of rectum covered by a pre-determined 36 Gy contour level, overlaid from the original treatment plan, was too large, the patient was removed from the treatment couch and instructed to drink water or take a further rectal enema. A further post-treatment CBCT was acquired on completion of treatment for further data collection and analysis.

Table 1
Dose constraints for VMAT planning.

Target	Required coverage
PTV_3625	V95% =99 %
CTV	V100% = 99 %
OAR	**Dose Constraint**
Rectum	V18.1 Gy < 50 %
	V29Gy < 20 %
	V36Gy < 1 cc (optimal)
	<2cc (mandatory)
Bladder	V 18.1 Gy < 40 %
	V37Gy < 10 cc
Prostatic Urethra	V42Gy < 50 %
Femoral Head	V14.5 Gy < 5 %
Penile Bulb	V29.5 Gy < 50 %
Testicular	Blocking Structure
Bowel	V18.1 Gy < 5 cc

Continuous monitoring

During treatment the position of the prostate gland was tracked continuously using the RP or HC systems. Real-time positional data was displayed in both graphical and numerical form on a monitor at the treatment console. A minimum of two suitably trained RTTs were responsible for each treatment session, with one RTT monitoring the patient and one RTT monitoring the real-time tracking data. An action level of 2 mm in X, Y and Z directions was set, where the direction of positive shifts was in the left, anterior and superior directions respectively. A protocol was also prepared for manually stopping the beam by the RTTs should prostate motion exceed this tolerance level. This protocol also included information on restarting treatment after the prostate returned to within tolerance. For analysis purposes the real-time data in each direction was measured from an initial reference position and was recorded at one second intervals.

Analysis

All patient data for analysis was retrospectively gathered from the Aria® (Varian Medical Systems, Palo Alto, CA) Record and Verify (R&V) database and the RP/HC reports, which were generated for each treatment session. Average displacement values, OAR volumes, delivered dose and the toxicity experienced by the patients were examined for possible correlations between these variables and prostate gland motion. Statistical analysis was carried out to test for any statistically significant differences between the two groups (RP v HC), and thus how the transmitter is positioned in the patient. Average displacements recorded in each direction (Lat, Lng, Vrt) were tested for a significant difference between the devices and the acute toxicities reported by the patients.

Image analysis

A total of 198 datasets, 18 planning CT datasets along with 180 CBCT data sets, gathered over 90 treatment fractions, were available for evaluation which allowed for a comparison in changes to the OAR's in the patients being investigated. The radiotherapy structure set assigned to the treatment plan was copied to create a further research structure set, which was named 'Printout'. On the printout structure set, new bladder and rectum organ contours were added for the planning CT and each pre- and post-CBCT dataset associated with every patient. The prefix 'PO' was assigned along with the fraction number and whether the CBCT was taken before or after treatment delivery (e.g. POBladder1pre), which allowed the study contours to be easily identified. Each

pre- and post- treatment CBCT was blended against the planning CT. Bladder and rectum organ contours were outlined on each image and saved against a new plan 'Printout' (Fig. 3). Study plans were calculated and compared against the actual treatment plan used for treatment. Bladder and rectum organ volumes and delivered dose metrics were used in the analysis.

Reported outcomes

Toxicity scores

Acute GU and GI toxicity scores were collected (RTOG) on completion of treatment (TP1) and at six weeks (TP2) and 12 weeks (TP3) after treatment. Statistical analysis between RP and HC groups was undertaken along with examination of any correlation in direction of displacement and grading of toxicity experienced by the patients.

Results

Patient demographics

The data from 18 consecutive patients, recruited between Nov 2018 and July 2022 is reported for the nine patients fitted with the RP and HC devices. Patients in the RP cohort reported baseline median PSA levels of 9.7 (range 7.1 to 12.9). Baseline GU RTOG toxicity scores in these patients were in the range 0 (n = 6) to 1 with baseline GI RTOG toxicity scores also in the range of 0 (n = 8) to 1 (n = 1). Five patients in the RP group had a Gleason score of 6 and were classified as being in the low-risk category, with four patients classified as intermediate risk with a Gleason score of 7. Patients in the HC cohort reported baseline median PSA levels of 13.6 (range 2.8 to 17.3). Baseline GU toxicity ranged from 0 (n = 5) to 1 (n = 4) and baseline GI toxicity was also in the range 0 (n = 8) to 1 (n = 1). All patients in the HC group were classified as intermediate risk with a Gleason score of 7.

Intra- fractional displacement

The real time displacement data, during treatment delivery from the RP and HC systems is shown as an average value per patient across all five treatment fractions (mm) in Fig. 4. Independent T-tests or Wilcoxon tests[1] were used to interrogate the data with a significance level of $P<0.05$. Results returned values of P=0.63 Lng; P=0.003 Lat; P=3.603 Vrt indicating a significant difference in lateral displacements between the devices.

Data highlighting motion greater than 2 mm, indicating a manual treatment interruption, is shown per patient as a unit of time and as a percentage of the overall session time across all treatment fractions in Fig. 5. Mean values indicate that those in the RP group experienced a greater percentage of overall treatment session time interrupted with 8.56 % (Lat), 9.02 % (Lng) and 5.67 % (Vrt). In comparison those in the HC group experienced 4.36 % (Lat), 8.78 % (Lng), 8.94 % (Vrt) of interrupted session time. Independent T-tests or Wilcoxon tests were used to test for any statistically significant difference in values between the RP and HC devices with a significance level of $P<0.05$. Results returned values of P=0.8371 Lat; P=0.4131 Lng; P=0.4807 Vrt indicating no significant difference between the devices.

CBCT analysis

Pre- and post-treatment CBCT data were assessed, and results presented as an overall on-treatment average value.

Bladder

Combined analysis of the pre- and post-treatment CBCTs in the RP group demonstrated overall average bladder volumes of 132.05 cc to 483.70 cc (SD 33.02 cc to 135.49 cc). Cumulative mean dose delivered to each patient, as per DVH analysis, ranged from 4.27 Gy to 12.1 Gy (SD of 0.3 Gy to 4.98 Gy) and dose maximum of 37.2 Gy to 38.5 Gy. By comparison in the HC group mean bladder volume was in the range of 196.11 cc to 313.85 cc with (SD 20.18 cc to 50.38 cc). Cumulative mean dose in this group ranged from 5.2 Gy to 13.12 Gy with SD per individual patient in the range of 0.3 Gy to 4.98 Gy and dose maximum 37.47 Gy to 42.36 Gy. Independent T-tests or Wilcoxon tests were used to test the values between the RP and HC groups for statistical significance using a significance level of $P<0.05$. No statistically significant differences were observed for: average on-treatment bladder volume (P=0.870); maximum dose to the bladder (P=0.364); mean dose to the bladder (P=0.162).

Rectum

Pre and post CBCT analysis demonstrated combined average rectal volumes, in those patients fitted with the RP device, were in the range of 38.89 cc to 99.45 cc with SD 2.03 cc to 39.83 cc. Cumulative mean dose, as per pre and post DVH analysis, to the rectum in this group of patients ranged from 10.48 Gy to 20.54 Gy, SD 0.78 Gy to 1.74 Gy and dose maximum 36.79 Gy to 38.22 Gy. Pre and Post CBCT analysis of those patients fitted with the HC device reported rectal volumes in the range 36.56 cc to 196.11 cc with a SD ranging between 3.89 cc to 26.79 cc. DVH analysis demonstrated cumulative mean dose ranging between 12.19 Gy to 18.61 Gy, SD 0.56 Gy to 1.96 Gy with a dose maximum of 36.89 Gy to 41.32 Gy. Independent T-Tests or Wilcoxon tests were used to test the values between the RP and HC groups for any statistical significance using a significance level of $P<0.05$. No significance was observed between average rectal volumes, or the mean rectal dose received between the groups: mean rectal dose (P=0.499); average rectal volume (P=0.489). A P value of P=0.009 was reported when comparing the maximum rectal dose, between the RP and HC groups indicating a statistically significant difference. Fig. 6 summarises the dose and volume relationships between the two groups.

Toxicity scores and real time displacement

RTOG reported toxicity values and the frequency of reporting are displayed in the Table 2. Independent T-tests or Wilcoxon tests were used to compare toxicity and average on-treatment shifts between the RP and HC groups to examine for any statistical significance, with a significance level of $P<0.05$ set, the results of which are shown in Table 3.

Discussion

This study has reported on the clinical experience, with a particular focus on the role of the RTT, of real-time motion monitoring of the prostate gland during a course of prostate SBRT. The RP and HC displacements along with the pre- and post- CBCT images taken during each treatment fraction have been analysed and examined along with the acute toxicities reported by each patient.

Displacements

As previously documented the prostate gland is known to move during the time it takes to deliver a radiotherapy fraction [25,27]. In line with other studies [19,27,29,30] this study also demonstrated motion that was predominantly in the Vrt (A/P) and Lng (S/I) direction. Overall, on-treatment vertical motion ranged from −1.71 mm (posterior) to + 0.11 mm (anterior) from initial reference position, with the largest shift

[1] Data was first tested for normality, with the appropriate statistical test then used to test for statistical significance.

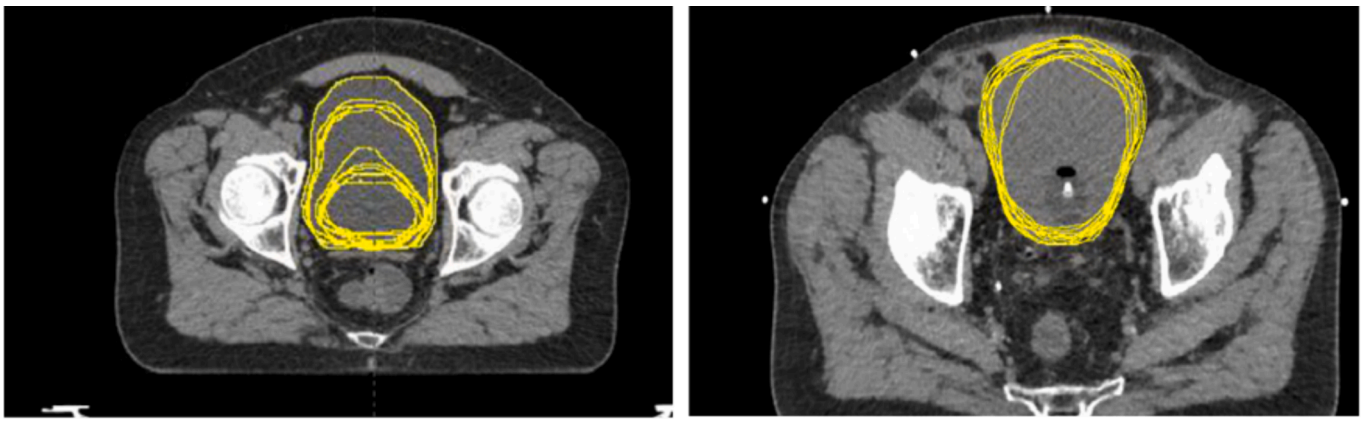


Fig. 3. CBCT image showing variation in bladder contours throughout the five fraction course of treatment. Bladder contours in the RayPilot group varied significantly more than in the Hypocath group.

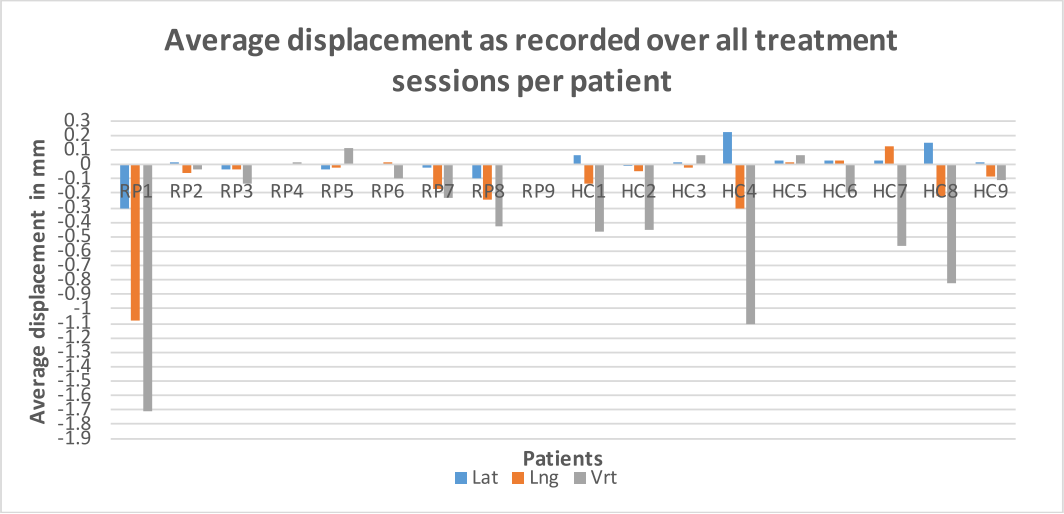


Fig. 4. Average on treatment shifts in each direction for all Raypilot and Hypocath patients.

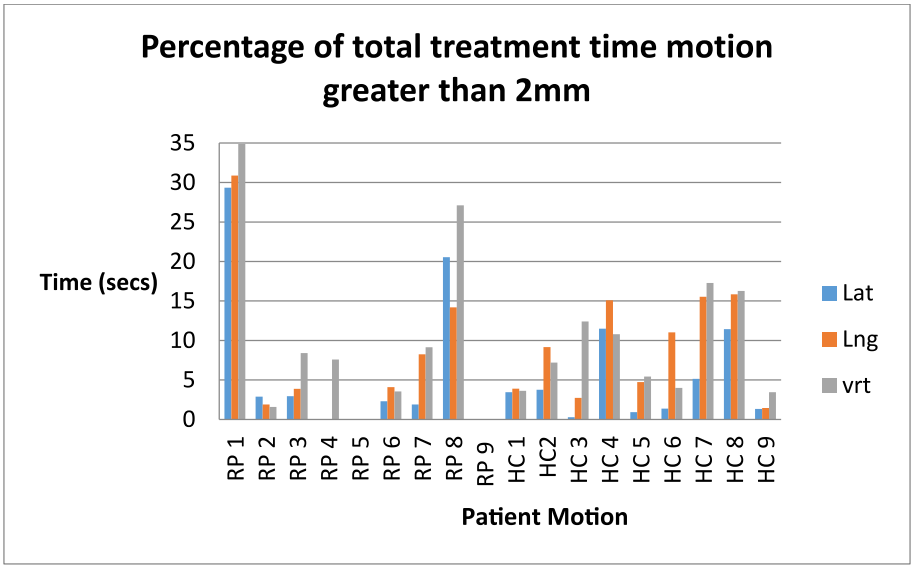
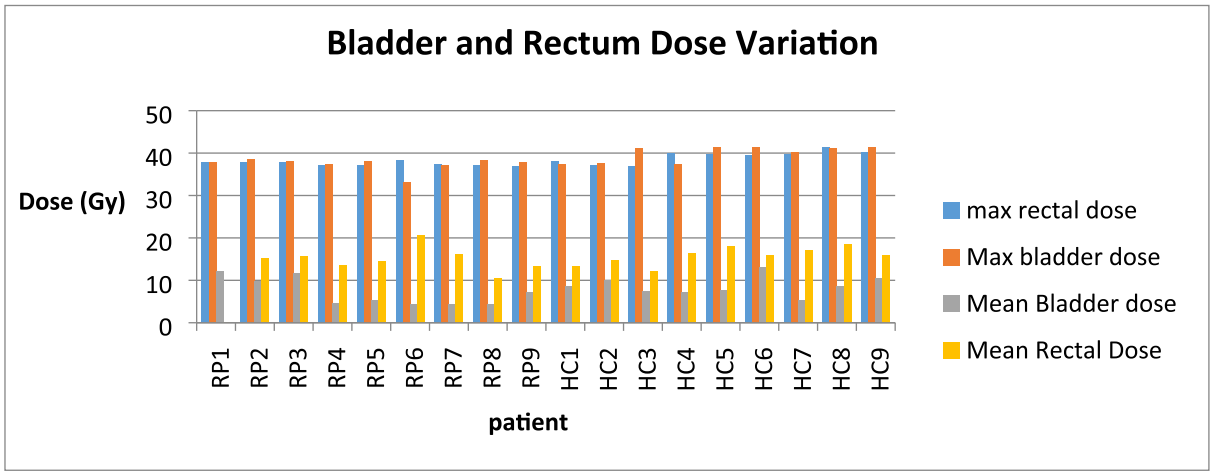


Fig. 5. Percentage of total overall session time motion was detected > 2 mm.



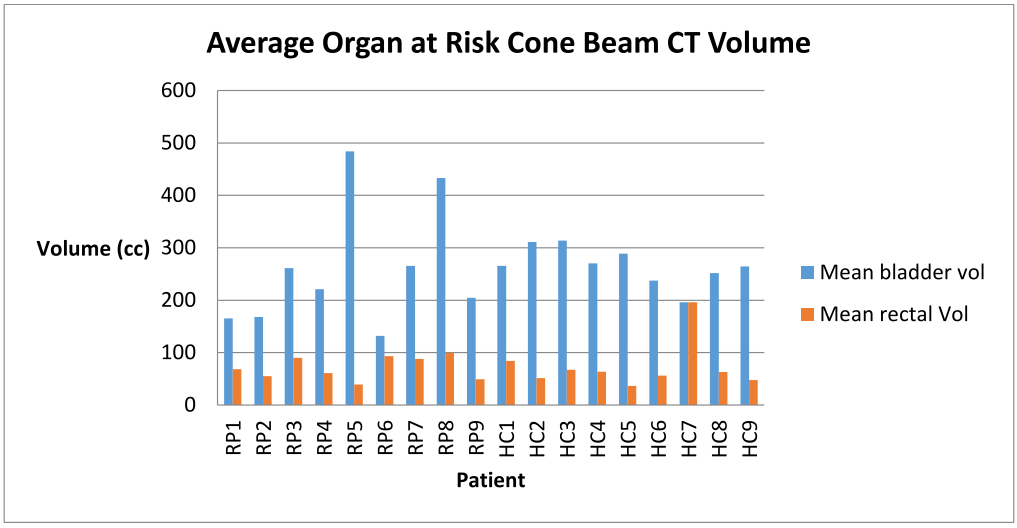


Fig. 6. A: Maximum and Mean dose data, for the rectum and bladder, for all Raypilot and Hypocath patients as per CBCT. B: Rectum and Bladder Volume Variation as per CBCT data.

Table 2
Toxicity values and frequency.

Raypilot				*Hypocath*			
TOX REPORTED	TC	6 WK FU	12 WK FU	TOX REPORTED	TC	6 W FU	12 WK FU
G0 GU	1	0	3	G0 GU	1	1	4
G1 GU	4	7	6	G1 GU	4	3	3
G2 GU	4	2	0	G2 GU	4	3	1
G0 GI	3	1	5	G3 GU	0	2	0
G1 GI	4	7	4	G0 GI	4	4	6
G2 GI	2	0	0	G1 GI	5	2	1
G3 GI	0	1	0	G2 GI	0	2	0
				G3 GI	0	1	0

Table 3
Toxicity and average on-treatment shift comparison.

Test Condition	P Value	Test Condition	P Value
G0GULONGTP3	0.8469	G1GULATTP3	0.1337
G0GULATTP3	0.152	G1GULONGTP3	1
G0GUVRTP3	0.3307	G1GUVRTTP3	0.9718
G1GULONGTP1	0.9235	G2GULATTP1	0.0294
G1GUVRTTP1	0.3962	G2GULONGTP1	0.4857
G1GULATTP1	0.1039	G2GUVRTTP1	0.9183
G1GULATTP2	0.234	G0GILATTP3	0.01329
G1GULONGTP2	0.3278	G0GILONGTP3	0.9307
G1GUVRTTP2	0.2996	G0GIVRTTP3	0.7837

recorded in a patient fitted with the RP device (−1.71 mm). Correspondingly the largest displacement from the reference position in the HC cohort, during treatment delivery, was also a posterior shift of 1.11 mm. Treatment Lng displacements ranged from 1.08 mm inferiorly to 0.13 mm superiorly, with those patients fitted with the RP device reporting greater deviations than those in the HC cohort (−1.08 mm to + 0.02 mm RP, −0.31 mm to + 0.13 mm HC). With Vrt and Lng prostate organ motion predominantly influenced by rectum and bladder fluctuations [14–19] the observations in these organs on CBCT analysis could account for these displacements in this study. Standardising bladder volumes, as a result of the use of a urinary catheter in the HC cohort, could account for the smaller displacements recorded in the Lng plane in this patient group. However, both devices reported approximately the same amount of displacements exceeding 2 mm in this plane which would contradict this assumption and indicate bladder volume possibly may not have a strong correlation to motion in this direction. The smallest on-treatment displacements were recorded in the Lat position, again in line with observations demonstrated in previous studies [19,25,27], with motion in this plane less likely to be influenced by fluctuations in size of the bladder and rectum. Lat transmitter displacements were in the range of −0.3 mm to + 0.23 mm across both cohorts. Although the Lat displacement proved to be the smallest it was the only one that proved to be statistically significantly different

between the two devices (P=0.003). Lateral motion > 2 mm accounted for a treatment interruption in 14 (N=6 RP, N=8 HC) of the 18 patients involved in this study. Motion in this plane, although not directly impacting the dose delivered to the OARs, could account for an under dose to the PTV, and therefore should be an important consideration for the treating RTT. Overall, there was no statistically significant difference in frequency of treatment interruptions between the RP and HC groups. Graphical interpretation demonstrated that those patients who reported the largest on-treatment displacements also reported the most treatment interruptions, with motion exceeding the 2 mm tolerance occurring in the highest percentage of session time. Reassuringly no on-treatment displacements > 2 mm were detected, indicating that both the RP and HC systems were effective in notifying the treating RTT of a change requiring action.

CBCT analysis

Examination of all pre and post CBCTs, and the associated OAR contours, allowed for a more detailed analysis of the dose and volume variation to the bladder and rectum over the course of treatment. The results show a smaller range in the variation of the on-treatment bladder volumes observed in those patients fitted with the HC device (132.05 cc to 483.70 cc RP v 196.11 cc to 313.85 cc HC), however this was not found to be statistically significant between the groups. Using a system incorporating a urinary catheter, and thus more control of bladder filling and emptying, did allow for bladder volumes to be of a more standardised volume during the treatment session in this cohort of patients. It is known that smaller bladder volumes do not result in smaller bladder doses due to a larger proportion of the bladder being irradiated [31,32]. The HC group did report a larger range in mean dose overall, however, these results were not found to be statistically significant. The study indicated that the urinary catheter device did provide the treating RTTs with more control of achieving a suitable bladder volume. This contributed to a more efficient clinical pathway, benefitting both the on-treatment workflow and the patient. Rectum volumes varied over the duration of treatment in both patient groups with a smaller range in volumes observed in the RP group (38.80 cc to 99.45 cc RP v 36.56 cc to 196.11 cc HC). Although on initial observation of calculated DVH's, dose variation appeared to be similar between the RP and HC groups, statistical analysis did highlight a significant difference in the maximum rectum dose (P=0.009) with seven of the nine patients in the HC cohort reporting a higher dose max overall. However, no significance was demonstrated in rectal volumes or mean dose between the groups.

Toxicity

Both groups experienced toxicity similar to toxicity reported in previous studies [9,10]. There was more grade 2 and higher GU toxicity reported in the HC group with eight patients reporting grade 2 acute toxicity over the three time points and two patients reporting grade 3 toxicity at the 6 week follow up visit. In comparison grade 2 GU toxicity was reported on six occasions in the RP group with no reports of grade 3. Reassuringly grade 3 toxicity was not reported at the 12-week post treatment follow up with only one patient still reporting grade 2 GU toxicity at this time point. Although the HC device was very well tolerated, some patients reported initial mild urethral irritation which may have contributed to some of the outcomes reported. Patient reported GI toxicity was similar between the groups with two occasions of grade 2 toxicity reported in both groups and grade 3 toxicity being reported on one occasion. No grade 2 or above GI toxicity was reported at the 12-week post treatment time point (TP3).

Statistical analysis comparing the patient reported toxicities and the on-treatment displacements recorded returned two significant differences between the RP and HC groups. P values of 0.029 and 0.013 were returned when displacements in the Lat direction were compared for those patients reporting grade 2 GU toxicity at treatment completion (TP1) and those reporting no GI toxicity at the 12 week follow up (TP3). This may be a further indication that, although small, lateral prostatic motion needs to be an important consideration at time of treatment delivery. No significant results were observed between the groups when the recorded average displacements in the Vrt or Lng direction were tested against any of the patient reported toxicities or time points.

Clinical use and the role of the RTT

Both devices were well tolerated by all the patients in the study, although HC patients did report minor urethral irritation, which was minimised with supportive intervention of further catheter advice. RTTs involved in the study found that the ability to control bladder filling simplified treatment. This has led to further work incorporating this more formally into a planned patient experience survey at 2 years follow-up.

Both of the devices discussed in this paper have, in our experience, allowed the RTT to take a lead role in a technique which provides real time data to support crucial treatment decisions. Initial device insertion, on-treatment monitoring, image interpretation and device removal have all been undertaken by suitably trained RTTs, allowing a smooth clinical workflow which works well with the daily workload of a busy linear accelerator. Furthermore, as a result of being integral to the whole procedure, this has helped to raise awareness of prostatic motion and increased confidence when hypofractionated radiation doses are being delivered.

Study limitations

It should be noted that this study is not without its limitations. The data presented here is based on a small sample of patients and average on-treatment values. A further investigation, using a much larger sample size and with a more detailed examination of both the individual patient and each individual treatment session is currently ongoing.

Conclusion

Real time motion monitoring of the prostate gland has been shown to be possible with both of the implantable devices reported in this preliminary study and has proven to be beneficial in the accurate delivery of dose during prostate SBRT. The pattern of prostate shift and the acute toxicity observed using these devices is in line with previous studies. Both devices have been well tolerated by patients. Being able to insert the transmitter during a normal catheterisation procedure, eliminating a surgical appointment, has not only proven to be beneficial to the scheduling of treatment sessions but has allowed RTTs to be involved throughout the whole pathway. Reassuringly monitoring prostatic motion, via the urethra, has not proven to be detrimental to the dose delivered to the bladder and rectum when compared to the original device. Acceptable, acute, patient reported toxicities are reported for both groups. At the time of treatment delivery having the ability to control bladder volume, by way of the catheter, has helped with a more efficient workflow.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors gratefully acknowledge the support of the staff in the Edinburgh Cancer Centre, the Institute of Genetics and Cancer, College of Medicine and Veterinary Medicine at the University of Edinburgh and the Institute for Imaging, Data and Communications, College of Science

and Engineering at the University of Edinburgh. The study was supported by the NHS Lothian Charity, Jamie King Uro-oncology Fund. The PRINTOUT Study (AC18048) received ethical approval in May 2018, study number NCT04081428.

References

[1] Katz A, Kang J. Stereotactic body radiotherapy with or without external beam radiation as treatment for organ confined high-risk prostate carcinoma: a six year study. Radiat Oncol 2014;9:1. https://doi.org/10.1186/1748-717X-9-1.

[2] Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: $\alpha/\beta = 1.4$ (0.9-2.2) Gy. Int J Radiat Oncol Biol Phys 2012;82(1):e17–24. https://doi.org/10.1016/j.ijrobp.2010.10.075.

[3] Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet 2019;394(10196):385–95. https://doi.org/10.1016/S0140-6736(19)31131-6.

[4] Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiother Oncol 2014;110(1):104–9. https://doi.org/10.1016/j.radonc.2013.09.026.

[5] Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol 2019;20(11):1531–43. https://doi.org/10.1016/S1470-2045(19)30569-8.

[6] Tree AC, Ostler P, van der Voet H, Chu W, Loblaw A, Ford D, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2022;23(10):1308–20. https://doi.org/10.1016/S1470-2045(23)00177-8.

[7] Van As N., Tree A., Patel J., Ostler P., Van Der Voet H., Loblaw D.A., Chu W., Ford D., Tolan S., Jain S., Armstrong J.G., Camilleri P., Kancherla K., Frew J., Chan A., Naismith O., Manning G., Brown S., Griffin C., Hall E. 5-Year Outcomes from PACE B: An International Phase III Randomized Controlled Trial Comparing Stereotactic Body Radiotherapy (SBRT) vs. Conventionally Fractionated or Moderately Hypo Fractionated External Beam Radiotherapy for Localized Prostate Cancer.Int J Radiat Oncol Biol Phys. Volume 117, Issue 4, 15 November 2023, Pages e2-e3 Doi: 10.1016/j.ijrobp.2023.08.027.

[8] Houben J, McColl G, Ham Kaanders J, Smeenk RJ. Patient reported toxicity and quality of life after hypofractionated high-dose intensity-modulated radiotherapy for intermediate- and high risk prostate cancer. Clin TranslRadiatOncol 2021;29:40–6. https://doi.org/10.1016/j.ctro.2021.05.005.

[9] Heemsbergen WD, Incrocci L, Pos FJ, Heijmen BJM, Witte MG. Local Dose Effects for Late Gastrointestinal Toxicity After Hypofractionated and Conventionally Fractionated Modern Radiotherapy for Prostate Cancer in the HYPRO Trial. Front Oncol 2020;10:469. https://doi.org/10.3389/fonc.2020.00469.

[10] Wilkins A, Mossop H, Syndikus I, Khoo V, Bloomfield D, Parker C, et al. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2015;16(16):1605–16. https://doi.org/10.1016/S1470-2045(15)00280-6.

[11] Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, Pei X, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 2012;84(1):125–9. https://doi.org/10.1016/j.ijrobp.2011.11.047.

[12] Macdougall ND, Dean C, Muirhead R. Stereotactic body radiotherapy in prostate cancer: is rapidarc a better solution than cyberknife? Clin Oncol (R Coll Radiol) 2014;26(1):4–9. https://doi.org/10.1016/j.clon.2013.08.008.

[13] Bauman G, Rumble RB, Chen J, Loblaw A, Warde P. Expert Panel MotII. Intensity-modulated radiotherapy in the treatment of prostate cancer. Clin Oncol (R Coll Radiol) 2012;24(7):461–73. https://doi.org/10.1016/j.clon.2012.05.002.

[14] Byrne TE. A review of prostate motion with considerations for the treatment of prostate cancer. Med Dosim 2005;30(3):155–61. https://doi.org/10.1016/j.meddos.2005.03.005.

[15] Lovelock DM, Messineo AP, Cox BW, Kollmeier MA, Zelefsky MJ. Continuous monitoring and intrafraction target position correction during treatment improves target coverage for patients undergoing SBRT prostate therapy. Int J Radiat Oncol Biol Phys 2015;91(3):588–94. https://doi.org/10.1016/j.ijrobp.2014.10.049.

[16] Ballhausen H, Reiner M, Kantz S, Belka C, Söhn M. The random walk model of intrafraction movement. Phys Med Biol 2013;58(7):2413–27. https://doi.org/10.1088/0031-9155/58/7/2413.

[17] Ten Haken RK, Forman JD, Heimburger DK, Gerhardsson A, McShan DL, Perez-Tamayo C, et al. Treatment planning issues related to prostate movement in response to differential filling of the rectum and bladder. Int J Radiat Oncol Biol Phys 1991;20(6):1317–24. https://doi.org/10.1016/0360-3016(91)90244-x.

[18] Sengupta C, Skouboe S, Ravkilde T, Poulsen PR, Nguyen DT, Greer PB, et al. The dosimetric error due to uncorrected tumor rotation during real-time adaptive prostate stereotactic body radiation therapy. Med Phys 2023;50(1):20–9. https://doi.org/10.1002/mp.16094.

[19] Sihono DSK, Ehmann M, Heitmann S, von Swietochowski S, Grimm M, Boda-Heggemann J, et al. Determination of Intrafraction Prostate Motion During External Beam Radiation Therapy With a Transperineal 4-Dimensional Ultrasound Real-Time Tracking System. Int J Radiat Oncol Biol Phys 2018;101(1):136–43. https://doi.org/10.1016/j.ijrobp.2018.01.040.

[20] Brennan VS, Burleson S, Kostrzewa C, Godoy Scripes P, Subashi E, Zhang Z, et al. SBRT focal dose intensification using an MR-Linac adaptive planning for intermediate-risk prostate cancer: An analysis of the dosimetric impact of intra-fractional organ changes. Radiother Oncol 2023;179:109441. https://doi.org/10.1016/j.radonc.2022.109441.

[21] Rose C, Ebert MA, Mukwada G, Skorska M, Gill S. Intrafraction motion during CyberKnife® prostate SBRT: impact of imaging frequency and patient factors. Phys Eng Sci Med 2023. https://doi.org/10.1007/s13246-023-01242-7.

[22] Kron T, Thomas J, Fox C, Thompson A, Owen R, Herschtal A, et al. Intra-fraction prostate displacement in radiotherapy estimated from pre- and post-treatment imaging of patients with implanted fiducial markers. Radiother Oncol 2010;95(2):191–7. https://doi.org/10.1016/j.radonc.2010.01.010.

[23] Gladwish A, Pang G, Cheung P, D'Alimonte L, Deabreu A, Loblaw A. Prostatic displacement during extreme hypofractionated radiotherapy using volumetric modulated arc therapy (VMAT). Radiat Oncol 2014;9:262. https://doi.org/10.1186/s13014-014-0262-y.

[24] de Muinck Keizer DM, Kerkmeijer LGW, Willigenburg T, van Lier ALHM, Hartogh MDD, van der Voort van Zyp JRN, et al. Prostate intrafraction motion during the preparation and delivery of MR-guided radiotherapy sessions on a 1.5T MR-Linac. Radiother Oncol 2020;151:88-94. DOI: 10.1016/j.radonc.2020.06.044.

[25] Falco MLaT. Intrafractional prostate motion management with the clarity autoscan system. Med Phys Int J 2013;vol.1, No.1.

[26] Langen KM, Willoughby TR, Meeks SL, Santhanam A, Cunningham A, Levine L, et al. Observations on real-time prostate gland motion using electromagnetic tracking. Int J Radiat Oncol Biol Phys. 2008;71(4):1084-90 DOI: 10.1016/j.ijrobp.2007.11.054.

[27] Kupelian P, Willoughby T, Mahadevan A, Djemil T, Weinstein G, Jani S, et al. Multi-institutional clinical experience with the Calypso System in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. Int J Radiat Oncol Biol Phys 2007;67(4):1088–98. https://doi.org/10.1016/j.ijrobp.2006.10.026.

[28] Langen KM, Chauhan B, Siebers JV, Moore J, Kupelian PA. The dosimetric effect of intrafraction prostate motion on step-and-shoot intensity-modulated radiation therapy plans: magnitude, correlation with motion parameters, and comparison with helical tomotherapy plans. Int J Radiat Oncol Biol Phys 2012;84(5):1220–5. https://doi.org/10.1016/j.ijrobp.2012.01.046.

[29] https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/study-using-breath-predict-what-happens-tissue-during-radiotherapy-prostate-cancer-PRINToUT.

[30] van Herk M, Bruce A, Kroes AP, Shouman T, Touw A, Lebesque JV. Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration. Int J Radiat Oncol Biol Phys. 1995;33(5):1311-20. DOI: 10.1016/0360-3016(95)00116-6.

[31] Pinkawa M, Asadpour B, Gagel B, Piroth MD, Holy R, Eble MJ. Prostate position variability and dose-volume histograms in radiotherapy for prostate cancer with full and empty bladder. Int J Radiat Oncol Biol Phys 2006;64(3):856–61. https://doi.org/10.1016/j.ijrobp.2005.08.016.

[32] Tsang YM, Hoskin P. The impact of bladder preparation protocols on post treatment toxicity in radiotherapy for localised prostate cancer patients. Tech Innov Patient Support Radiat Oncol 2017;3–4:37–40. https://doi.org/10.1016/j.tipsro.2017.10.001.