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FULL PAPER

Safety and feasibility of prostate stereotactic ablative radiotherapy using multimodality imaging and flattening filter free

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Objective: To investigate feasibility and safety of stereotactic ablative radiotherapy in the management of prostate cancer while employing MR/CT fusion for delineation, fiducial marker seeds for positioning and Varian RapidArc with flattening filter free (FFF) delivery.

Methods: 41 patients were treated for low-intermediate risk prostate cancer with initial prostate-specific antigen of ≤20 ng ml^{-1}, Gleason score 6–7. Patients had MR/CT fusion for delineation of prostate ±seminal vesicles. CT/MR fusion images were used for delineation and planned using flattening filter free modality. Verification on treatment was cone beam CT imaging with fiducial markers for matching. Patients had Radiation Therapy Oncology Group scoring for genitourinary and gastointestinal symptoms at baseline, week 4, 10 and 18.

Results: Clinically acceptable plans were achieved for all patients, all plans achieved the objective clinical target volume D99% ≥ 95%, and for planning target volume D95% ≥ 95%. Rectum dose constraints were met for 95.1% for V18 Gy ≤ 35%, 80% V28 Gy ≤ 10%. A total of 32 (78.0%) plans achieved all rectum dose constraints.Grade 1 acute genitourinary symptoms were 53.7% of patients at baseline, 90.2% [95% CI (76.8–97.3%)] (p = 0.0005) at treatment 5, falling to 78.0% (62.4–89.4%) at week 4, and 75.0% (58.8–87.3%) by week 10 and 52.5% (36.1–68.5%) (p = 1.00) at week 18.Acute gastrointestinal symptoms were 5% at baseline, 46.3% [95% CI (30.7–62.6%)] at treatment 5, week 4 43.9% [95% CI (28.5–60.3%)], week 10 25.0% (11.1–42.3%), and declined slightly by week 18 [–20.095% CI (12.7–41.2)] p = 0.039. Overall 75.6% (31/41) of patients experienced Grade 1–2 toxicity during or after treatment.

Conclusion: This planning and delivery technique is feasible, safe and efficient. A homogeneous dose can be delivered to prostate with confidence, whilst limiting high dose to nearby structures. The use of this technology can be applied safely within further randomized study protocols.

Advances in knowledge: Multimodality imaging for delineation and linac-based image-guided RT with FFF for the treatment of prostate stereotactic ablative radiotherapy.

INTRODUCTION

Prostate cancer is the second most common cancer among males in Western Europe.[1] In the UK around 47,000 males are currently diagnosed each year.[2]

There are several treatment options for early stage organ confined disease including active surveillance, prostatectomy, external beam radiotherapy (EBRT) and brachytherapy.[3]

EBRT is a non-invasive treatment which delivers potentially curative doses of RT to the target. Conventionally, fractionated RT for prostate cancer typically involves doses of 74–78 Gy delivered in 37–39 fractions.[4–6] A recent trial of conventional *vs* hypofractionated high-dose intensity modulated RT for prostate cancer (CHHIP) demonstrated that a moderate hypofractionated schedule of 60 Gy in 20 fractions was non-inferior to commonly used 74 Gy in 37 fractions. This regime has been recommended as the new

standard of care, in which patients can have equivalent treatment in fewer hospital visits.[7]

EBRT is a complex medical intervention with elements of uncertainty resulting from: delineation, inter- and intrafraction motion. It is not possible to irradiate the prostate alone, nearby organs are at risk of exposure to a high dose. Advances in RT planning and delivery have increased the efficiency of the procedure, reducing exposure to the nearby organs and surrounding healthy tissues. In the UK and Europe, standard gantry-based linear accelerators which can deliver intensity modulated RT, image-guided RT and rotational therapy are more readily available.[8,9]

There is evidence to suggest that prostate cancer has a low α/β ratio (1.5 Gy), lower than that of late responding normal tissues. Such evidence can be utilized in one of two ways; to deliver larger doses to the prostate in fewer fractions, thus improving tumour control rates without increasing the risk of late normal tissue complications or to deliver isoeffective doses in fewer fractions, aiming to reduce late toxicity.[10,11]

Internationally, hypofractionated stereotactic ablative radiotherapy (SABR) has become accepted as a therapeutic modality in the treatment of organ-confined prostate cancer, not currently recommended in the UK.[12,13] SABR delivers a higher dose of radiation over a smaller number of fractions. These hypofractionated regimens typically involve a dose of around 35–40 Gy delivered in five fractions either daily or on alternate days.[14] Current evidence on toxicity comes from a number of case series with some mature data demonstrating outcomes up to 7 years.[15,16]

This study aims to contribute to the body of evidence regarding the feasibility of using SABR in the management of prostate cancer, employing MR/CT fusion for delineation, fiducial markers for positioning and Varian RapidArc with flattening filter free (FFF) delivery. Primary end points for this study were:

(1) Can clinically acceptable plans be achieved in 90% of study patients using prostate SABR protocol by assessing planning target volume (PTV) coverage and specified dose constraints for rectum and bladder.
(2) Safety will be demonstrated, if incidence of Radiation Therapy Oncology Group (RTOG) grade toxicity of rade ≥3 occurs in less than 10% of patients.

METHODS AND MATERIALS

This prospective study was approved by the Research Ethics Committee on 21 May 2013. Patients in this study provided written informed consent.

Patient selection and characteristics

Patients in the study had low- to intermediate-risk prostate cancer, *i.e.* organ-confined disease, initial prostate-specific antigen (iPSA) of ≤20 ng ml^{-1}, Gleason score 6–7. All patients had histologically proven adenocarcinoma of the prostate. Biopsy was obtained using a transrectal approach. All patients underwent a staging MRI. Only patients with a PSA ≥10 had a bone scan, as per local guidelines. Patients with intermediate-risk disease received androgen deprivation therapy (ADT) in the form of luteinizing hormone-releasing hormone analogues, for a period of 6–9 months. RT started 3 months after initiation of ADT.

Protocol treatment planning

2 weeks before planning, patients attended seed clinic. A urine sample was checked for infection and an enema administered. Three gold markers measuring 5 mm (BEBIG gold fiduciary markers, Riverpoint Medical, Portland, OR) were inserted into the prostate transrectally using transrectal ultrasound guidance. Intended positions of the seeds were the left superior lobe, left apex and right midgland. Ultrasound images were acquired and a 5 day course of ciprofloxacin antibiotics was given to reduce the risk of infection.

Patients received a microlax enema before the CT simulation appointment. Once this had taken effect, patients emptied their bladders and drank 450 ml of water 30 min before scanning. Patients were scanned using a GE MultisliceLightSpeed™ 16 helical CT scanner (GE Medical Systems, Waukesha, WI).

Scans were acquired in a supine position, with head support and Prostep immobilization device (ProSTEP™ ABS, MEDIZINTECHNIK GMBH). Slices were reconstructed at 2.5 mm width. Orthogonal and anterior tattoos were aligned to the origin of the scan to aid daily treatment setup.

MRI scans were acquired on the same day as the planning CT on a GE Signa HDxt1.5T (HD23.0_VOL_1210a) (GE Medical Systems). Setup was achieved using the immobilization employed at CT following the same bladder and bowel preparation. A flat couch top was used with a 4-channel cardiac coil. Sequences included: Ax 3DGRE*2.5 SEED, axial T_2 HiRes −2.5 mm (small field of view) 50 slices, check field of view includes the heads of femurs and prostate, interleaved, zero spacing. MR and CT scans were registered in Eclipse using a mutual information match and adjusted manually to ensure the seeds were in alignment.

Delineation

Delineation was performed using the fused MRI/CT image set.

The CTV was taken as the prostate only (or in some circumstances prostate + seminal vesicles) as outlined by the clinical oncologist (CO). The PTV was taken as CTV with 5 mm margins added in all directions except posteriorly (3 mm, to spare as much rectum as possible). The organs at risk (OAR), in accordance with the SABR Consortium UK guidelines[13] were the rectum (from the anus to the rectosigmoid junction), the bladder (including wall and lumen) and left and right femoral heads.

Planning

Treatments were planned and delivered using volumetric-modulated arc therapy (VMAT) (RapidArc™) on a VarianTruebeamSTx linear accelerator using FFF mode.

Treatment planning was performed in Eclipse External Beam Planning system V10.0.39 (Varian Medical Systems, Palo Alto, CA).

Plans were optimized using the inverse planning Progressive Resolution Optimiser (PRO3) and the final dose calculation was performed using Anisotropic Analytical Algorithm AAA 10.0.28 with a calculation grid size of 1.25 mm.

Intended planning criteria was V95% > 99% for the CTV and V95% > 95% for PTV.[17] Constraints placed on the OARs were rectum; V18 Gy < 35%, V28 Gy < 10%, V32 Gy < 5% and D1% < 35 Gy and bladder; D1% < 35 Gy. These constraints were based on those used by Alongi et al[18].

Each plan used two full arcs with a collimator separation between the two arcs of 90° degrees. This separation ensures that any effect of multileaf collimators (MLCs) leakage is not summed throughout both arcs and also gives a greater variety of beam orientations around the target volume.

Quality assurance

Verification plans were produced within Eclipse, delivered to the SunNuclearMapCHECK 2 phantom. A sagittal plane of interest was analysed and agreement criterion was set to 3% dose difference, 3 mm distance to agreement, threshold of 10%. Agreement in at least 95% of dose points is deemed acceptable. All plans passed pre-treatment QA checks.

Treatment

Patients were prepared and immobilized as described previously. Each fraction was administered with two full arcs on a Truebeam STX using 10X FFF and a dose rate of 2400 MUmin^{-1}.

Verification

Verification was performed to allow online correction prior to treatment delivery. A CBCT image was acquired on the Truebeam STX (VarianMedicalSystems, Palo Alto, CA). An automatic match was performed using PTV as volume of interest. Manual adjustments were made to the registration by radiographers to ensure seeds aligned correctly. The CO then checked through transverse slices to visualize organs at risk, CTV coverage before online correction applied.

Follow up

Baseline data was recorded before the first treatment. Patients were reviewed before each treatment fraction, then by telephone 4 weeks after starting treatment. Subsequently, patients were reviewed at clinic week 10, 18, 26 and 6 monthly, thereafter. The RTOG acute and late toxicity scoring criteria used to record skin, gastrointestinal (GI), genitourinary (GU) toxicity.[19] Erectile dysfunction was recorded from week 18 onwards. Routine follow up after 18 weeks, collected late toxicity data and assessed PSA levels.

Statistical analysis

Grouped dose volume histograms (DVH) were produced for prostate and OAR. We report both the number and the proportion of patients who reported each grade of toxicity at: baseline, each treatment and each follow up. Median and IQRs were used to summarize continuous variables. McNemars test and exact 95% confidence intervals were used to compare the proportion of patients with acute toxicity. Statistical analyses performed using StataCorpStata Statistical Software: v. 14.0.

Table 1. Patient characteristics

Baseline characteristics (n = 41)		Median (IQR) or % (n)
Age (years)		68 (65–71)
initial PSA (ng ml^{-1})		10.5 (8.0–13.3)
T stage[a]	1	14.6 (6)
	2	82.9 (34)
Gleason score	6	41.5 (17)
	7	58.5 (24)
Androgen deprivation therapy	No	24.4 (10)
	Yes	75.6 (31)

[a]T-stage not recorded for one patient. IQR, interquartile range; PSA, prostate-specific antigen.

RESULTS

Patient characteristics

41 patients were recruited between 22 November 2013 and 30 March 2016. Median PSA was 10.5 ng ml^{-1} (range 4.3–29.9) (Table 1). Three patients recruited had iPSA greater than 20 due to initial uncertainty over iPSA measurements, these patients were retained in our analysis. The median age was 68 [interquartile range (IQR) 65–71] years. A total of 24 (58.5%) patients had a Gleason score of 7, all other patients [17 (41.5%)] were Gleason score 6. Six patients had Stage 1 disease, all others were Stage 2 (35 85.4%). Over three quarters of patients (31/41) had received ADT. The median initial PSA was 10.5 (IQR 8.0–13.3) ng ml^{-1}.

Planning characteristics are shown in Table 2. The median CTV and PTV was 36.0 cm^3 (IQR 29.9–45.1) and 76.4 cm^3 (IQR

Table 2. Clinical and planning treatment volume (cm^3) and volume of organs at risk

Planning characteristics (n = 41)	Median volume (IQR) (cm3)
CTV	36.0 (29.9–45.1)
PTV	76.4 (64.8–90.1)
Organs at risk	
Rectum	67.1 (56.4–78.2)
Bladder	164.4 (120.3–229.2)
Right femoral head	62.5 (55.1–68.3)
Left femoral head	61.9 (54.2–68.1)

IQR, interquartile range; CTV, clinical target volume; PTV, planning target volume.

Table 3. Planning objectives and number (%) of plans achieving these

Organ	Planning objective or constraint	Median volume (IQR) (%)	Range	Number of plans meeting objective (%)
CTV	V95% > 99%	100 (100.0–100.0)	99.8–100.0	41 (100)
PTV	V95% > 95%	96.3 (95.4–97.0)	95.0–99.6	41 (100)
	1 cm^3 < 107%			38 (92.7)
Rectum	V18 < 35%	26.9 (22.6–31.2)	11.9–42.0	39 (95.1)
	V28 < 10%	7.7 (6.2–9.3)	1.3–22.5	33 (80.5)
	V32 < 5%	3.7 (2.6–4.6)	0.2–14.8	34 (82.9)
	V35 < 1%	0.2 (0.0–0.6)	0.0–2.4	38 (92.7)
Bladder	V35 < 1%	0.1 (0.0–0.6)	0.0–3.0	34 (82.9)

64.8–90.1) respectively. The median PTV was approximately two times the median CTV.

Table 3 shows planning objectives and proportion of plans achieving these. All plans achieved the objective that 99% of the CTV should receive at least 95% dose, and that 95% of the PTV should receive at least 95% prescribed dose. The proportion of plans meeting rectum dose constraints ranged from 95.1% (39/41) for the relative volume receiving 18 Gy (V18) being less than 35%, to just over 80% (33/41) for the relative volume receiving 28 Gy (V28) being less than 10%. Overall a total of 32 (78.0%) plans achieved all rectum dose constraints. One plan failed to achieve all rectum dose constraints. Constraints on the dose received by the bladder were met by 34 plans, the proportion of bladder receiving >35% of the dose ranged from 0 to 3.0%.

Figure 1 shows the median cumulative DVH for all patients and each structure highlighting the IQR and minimum and maximum volume at each point dose. The figure shows very small variation between plans for doses received by CTV and PTV. The plots for rectum and bladder show large variation in the volume receiving each point dose. Femoral heads show rapid decline in the dose received.

Table 4 summaries the dose received by the CTV and PTV in more detail.

The proportion of patients who reported acute genitourinary (GU) and GI toxicity during and after treatment are shown in Figures 2 and 3. Grade 1 acute GU symptoms were prevalent among 53.7% of patients (22/41) at baseline. The percentage of patients who experienced any symptoms increased during treatment and peaked at 90.2% [95% CI (76.8–97.3%)] (37/41) (p = 0.0005) at treatment 5. The prevalence of symptoms declined slowly thereafter, falling to 78.0% (62.4–89.4%) at week 4, and 75.0% (58.8–87.3%) by week 10. At 18 weeks, two patients continued to experience Grade 2 symptoms, but the overall percentage of patients with symptoms had returned to baseline levels– 52.5% (36.1–68.5%) (p = 1.00). All patients reported Grade 1 or worse GU symptoms, of which 46.9 (18/41) did not report symptoms at baseline. The proportion of patients reporting Grade 2 or worse was 14 of 41 (34.1%). Only two patients experienced Grade 3 symptoms (4.9%).

Five percent (2/41) of patients reported acute GI symptoms at baseline. These increased during treatment, reported by 46.3% [95% CI (30.7–62.6%)] of patients at treatment 5. GI symptoms continued to be raised at week 4 in 43.9% (95% CI 28.5–60.3%). GI side effects were lower at week 10 [25.0% (11.1–42.3%)], and declined slightly by week 18 [–20.095% CI (12.7–41.2)] p = 0.039. Acute Grade 2 GI toxicity was experienced by three patients (7.3%). No patients experienced Grade 3 GI toxicity. Overall, 75.6% (31/41) of patients experienced Grade 1–2 toxicity during or after treatment.

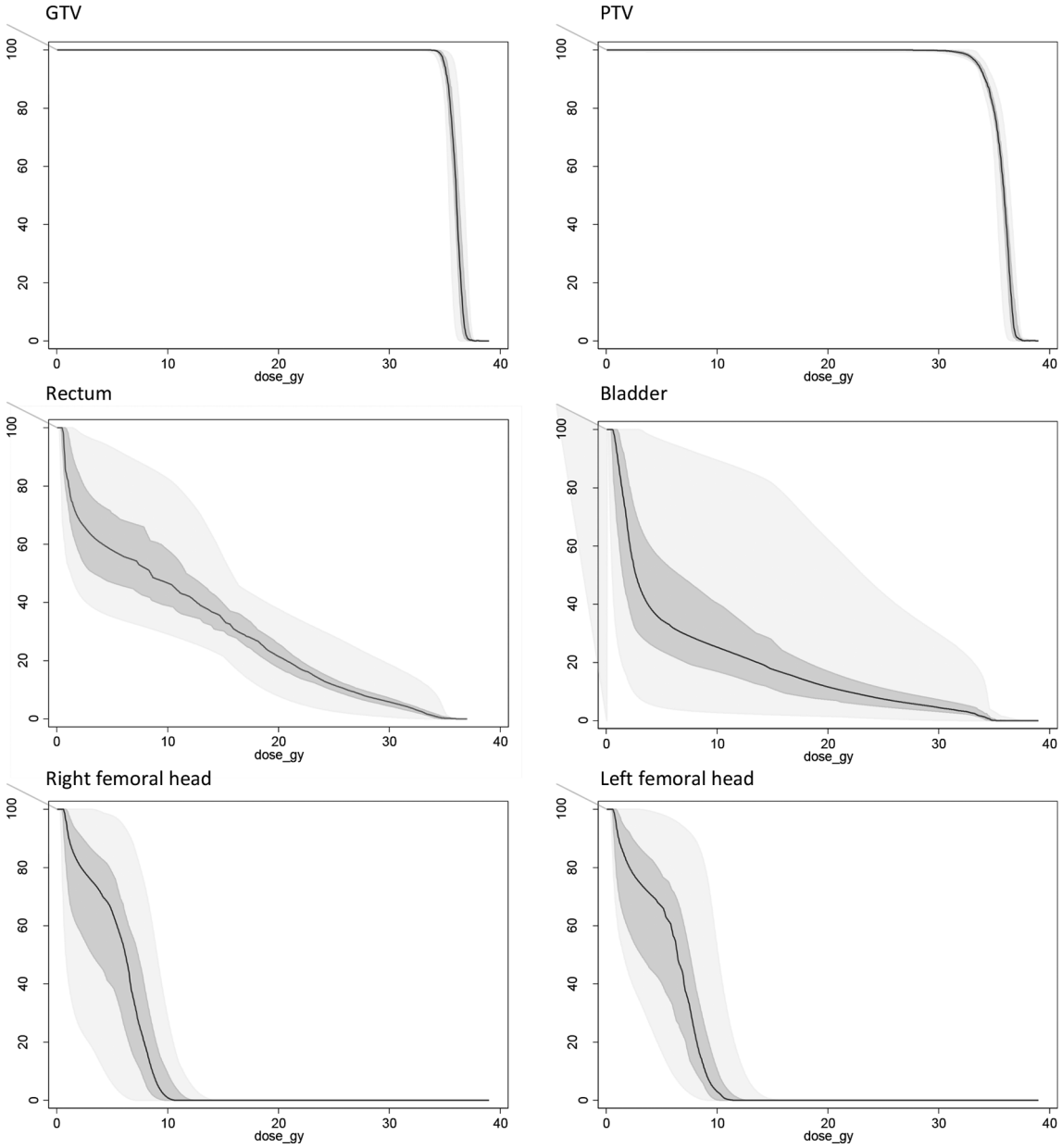
At baseline, the median PSA was 10.5 (IQR 8.0–13.3). By week 18, the median PSA was 0.6 (IQR 0.2–1.1). A total of 24 patients (68.6%) had a PSA <1, 17.1% had a PSA between 1 and ≤ 2, and 14.3% had PSA levels between 2 and ≤ 4 (Figure 4).

DISCUSSION

This is the first UK study to show SABR of low-intermediate risk prostate cancer with FFF is feasible and safe. It is also the first prospective study reporting on this method of planning and delivery using CT/MR fusion, fiducials and CBCT. While a number of studies have described patient outcomes for prostate cancer who received SABR, there is a lack of randomized study evidence to support its use as the standard of care. In this analysis, treatment plans were assessed as clinically acceptable for all patients. Assessment of acute side effects among patients receiving SABR for prostate cancer with a median follow-up of 18 weeks showed that this treatment is well-tolerated.

Reported outcomes were similar to those in the CHHIP trial, where GU toxicity in hypofractionated arm peaks at week 5 which is 1 week after end of treatment. Acute GU toxicity in our study peaked earlier than CHHIP trial with the highest incidence of toxicity being noted at fraction 5, *i.e.* at the end of treatment. This reduced slightly at week 4, dropping to near baseline at week 18. GI toxicity peaked at week 4, same as CHHIP and although Grade 2 returned to 0 by week 18, Grade 1 toxicity was still reported.[7] Acute side effects described were acceptable and are consistent with other studies.[15,16,18] PSA levels were reduced in all patients.

Figure 1. Median cumulative dose volume histograms for each organ highlighting the range and interquartile range at each dose.



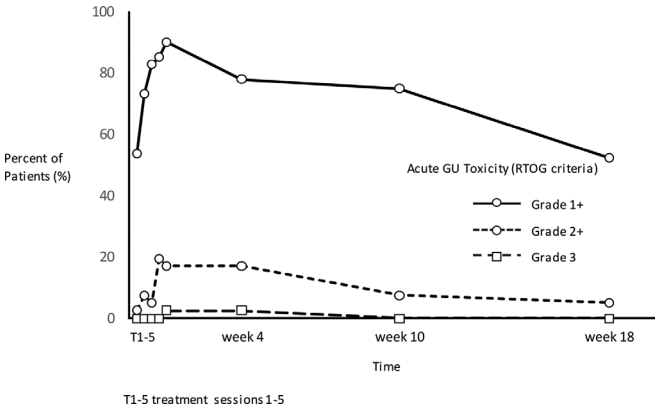
The dose used within this study was 35 Gy delivered in five fractions on alternate days. This has been reported elsewhere and results have shown good biochemical recurrence free survival (BRFS) in low-intermediate group. Katz et al[15] reported 7 years being 95.6% for low-risk and 89.6% for intermediate risk, also indicating there was no difference in biochemical disease free survival (bDFS) between delivering 35 and 36.25 Gy. Our patients were treated on alternate days, taking a total of 11 days to deliver the full course. This was selected to allow recovery of normal tissue between fractions.[20] Previous reports have suggested daily

Table 4. Summary of the dose received by clinical and planning treatment volumes

Planning characteristics (n = 41)	Dose (%) received by 99% of volume (D99%)	Dose (%) received by 1 cm^3	Volume (%) receiving ≥ 95% of dose (V95%)	Volume (%) receiving ≥ 105% of dose (V105%)	Volume (%) receiving ≥ 107% of dose (V107%)
CTV	98.6 (96.8–101.0)	105.2 (102.8–106.9)	100 (99.8–100.0)	4.4 (0–47.2)	0.0 (0.0–2.0)
PTV	91.5 (86.6–95.6)	105.7 (103.4–107.1)	96.3 (95.0–99.6)	4.5 (0–31.5)	0.0 (0.0–1.5)

Numbers are medians and range. CTV, clinical target volume; PTV, planning target volume.

Figure 2. Acute GU toxicity (RTOG criteria). GU, genitourinary; RTOG, Radiation Therapy Oncology Group.



treatment increased toxicity, however this has since been challenged, with dose being a more relevant predictor of late effects.[15] Disease control is not covered in this paper as those data are not mature enough to present.

The treatment modality used was 10X FFF. This is a relatively new modality which delivers the beam without the use of a flattening filter. Delivery using this technique allows a much higher dose delivery per pulse which results in an accelerated delivery of around 2400 MU min^{-1}, around four times faster than with filter. Thus, enabling a dose of 700 cGy to be delivered in around 2 min per fraction, limiting time intrafraction movement can occur. FFF technology also offers potential for a reduction in out of field dose due to reduced head scatter and reduced residual electron contamination.[20,21]

Equivalent dose of RT using Cyberknife would take around 45 min. Although tracking of the target volume is intermittent throughout, the patient has to lie in the treatment position for a significantly longer duration.[20,21] There are fewer publications using linac-based delivery systems, mostly reported using routine equipment with MV imaging.[22–24]

TruebeamSTx is Varian Medical Systems newest platform of linear accelerator. This model offers a new high-definition MLC

Figure 3. Acute GI toxicity (RTOG criteria). GI, genitourinary; RTOG, Radiation Therapy Oncology Group.

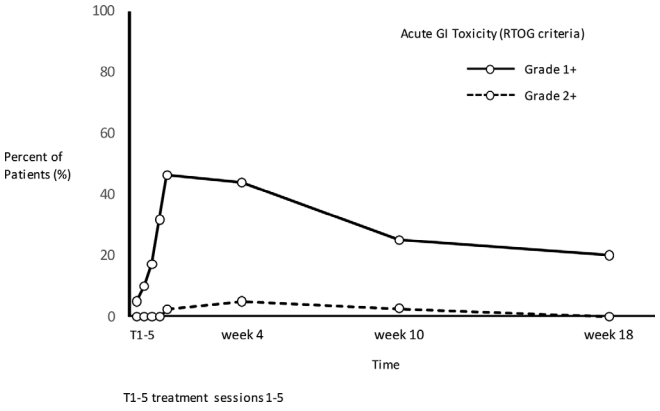
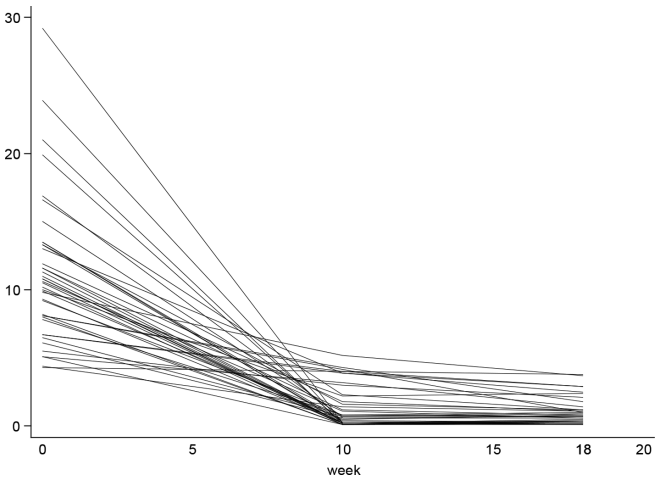


Figure 4. Distribution of PSA levels at baseline and at week 18. PSA, prostate-specific antigen.



system, which has a reduced individual leaf width of 2.5 mm. All plans developed for this study utilized this MLC system.

Cumulative DVHs demonstrate that prescribed planned dose to CTV and PTV was achieved for all patients. A homogeneous dose achieved, with little variation between patients. Rectum and bladder constraints show more interpatient variability. This is due to the variation in; organ volume, location and the limited number of constraints applied. Possibly, by applying further constraints, this variation could be reduced. Unlike other anatomical sites, where dose would be prescribed to an isodose line, it is beneficial for the prostate to receive a uniform dose, prescribed to the volume. Where patients failed to meet one or more rectal constraints, further investigation suggested overlap with PTV was the cause of this. In this study, PTV had priority over OAR.

Pre-treatment QA checks were performed on each study plan to ensure the planned treatment could be delivered accurately. Satisfactory results from this study have confirmed, it is not necessary to undertake any further, extensive testing for such plans. Future prostate SABR treatments will be verified in accordance with routine departmental protocol.

PACE international randomized study is ongoing and will compare laparoscopic prostatectomy, SABR and conventionally fractionated RT. This will address the current lack of randomized evidence by comparing SABR to conventional treatment or SABR to surgery.[25] This study previously mandated MR for improved delineation. However, PACE study data using MR/CT fusion to delineate the prostate gland has been presented to support the use of CT only delineation in recent versions of the protocol. This change will allow centres with limited MR resource to recruit to the study.[26] When CTV is compared to evidence, the volumes among our patients were on average approximately 30% smaller than those in the studies by Henderson and Alongi, suggesting the use of MR/CT fusion significantly reduces the size of the CTV.[14,18] It is known that soft tissue delineation of the prostate using MR is optimal due to the enhanced soft tissue contrast and

that volumes on MR are smaller than on CT.[27,28] Fiducial markers are essential to allow accurate fusion of the MR and CT, minimizing fusion error. A publication by D'Agostino reported on a similar planning methodology, however, no CT/MR fusion was described, only MR-assisted delineation.

Patients in our study had CBCT and fiducial markers before treatment allowing all setup corrections to be made. We found it necessary to use both methods to ensure the prostate was aligned to that of the planning CT at each session and visually assess rectum and bladder displacement/volume change. Three-dimensional information gave gross indication of the high dose region in relation to OAR and PTV. Online images were approved by a CO, with appropriate training, in our opinion this could become a radiographer led process. Alongi et al[18] described the use of three-dimensional CBCT prior to each treatment to aid setup. This was performed without complementary use of fiducial markers in the prostate. Following on from this, a subsequent publication by the same group included a further 50 patients. Again, fiducials were not mandated and no indication is given to how many patients had them inserted, meaning accurate fusion of MR/CT would not have been possible. They also described an alternative method of online verification, where no correction for a setup error within 3 mm was applied.[29]With reduced margins in SABR treatment, it is essential to correct for all errors. Study uptake was high, possibly due to a reduced number of treatment sessions and overall time. Attending a specialist centre daily for up to 8 weeks is challenging for patients with comorbidities, who are continuing to work or caring for others. This is especially true in our centre, where there is a large geographical catchment area. There are also potential opportunities to reduce burden on RT services where capacity issues exist.

CONCLUSION

This prospective prostate SABR study, using multimodality imaging for delineation and volumetric arc RT with FFF demonstrates safety and feasibility for this group of patients. This adds to the body of evidence on choosing the optimal RT technique, achieving a homogeneous dose to the prostate and margin, whilst limiting high dose to nearby structures. It also confirms, it is possible to implement a stereotactic setup with FFF beam to safely deliver a highly conformal dose to the prostate with confidence. The use of this new technology can be applied safely within further randomized study protocols.

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