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Original Research Article

A study of the clinical, treatment planning and dosimetric feasibility of dose painting in external beam radiotherapy of prostate cancer

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ABSTRACT

Background and purpose: Radiotherapy dose painting is a promising technique which enables dose escalation to areas of higher tumour cell density within the prostate which are associated with radioresistance, known as dominant intraprostatic lesions (DILs). The aim of this study was to determine factors affecting the feasibility of radiotherapy dose painting in patients with high and intermediate risk prostate cancer.
Materials & Methods: Twenty patients were recruited into the study for imaging using a 3 T magnetic resonance imaging (MRI) scanner. Identified DILs were outlined and the scan registered with the planning computed tomography (CT) dataset. Intensity-modulated plans were produced and evaluated to determine the effect of the organ-at-risk constraints on the dose that could be delivered to the DILs. Measurements were made to verify that the distribution could be safely delivered.
Results: MRI scans were obtained for nineteen patients. Fourteen patients had one to two DILs with ten overlapping the urethra and/or rectum. The target boost of 86 Gy was achieved in seven plans but was limited to 80 Gy for five patients whose boost volume overlapped or abutted the urethra. Dosimetric measurements gave a satisfactory gamma pass rate at 3%/3 mm.
Conclusions: It was feasible to produce dose-painted plans for a boost of 86 Gy for approximately half the patients with DILs. The main limiting factor was the proximity of the urethra to the boost volumes. For a small proportion of patients, rigid registration between CT and MRI images was not adequate for planning purposes.

1. Introduction

Prostate tumours often take the form of dominant intraprostatic lesions (DILs) for which there is evidence of radioresistance [1,2]. Dose painting [3] may improve local control without increasing toxicity [4] by boosting DILs while keeping the dose to organs-at-risk (OAR) within constraints. To achieve this, DILs must be localised using the appropriate scanning technique; planned using the localisation scan registered with a computed tomography (CT) image, verified dosimetrically then delivered to the patient. Treatment is accompanied by image guidance to minimise positioning uncertainties.

Previous studies have shown the potential of molecular imaging and functional MRI techniques to delineate the gross target volume (GTV) for dose painting, and some have used a dose painting by numbers (DPBN) approach to adjust the dose as a function of uptake/signal [5]. Other studies [4] have shown the value of radiobiological optimisation of the dose distribution to maximise tumour control probability (TCP), while normal tissue complication probability (NTCP) was maintained at values corresponding to dose constraints.

Clinical trials have included the phase III FLAME (Focal Lesion Ablative Microboost in prostatE cancer) [6] and PIVOTALboost (a phase III randomised controlled trial of prostate and pelvis versus prostate alone radiotherapy with or without prostate boost) [7] trials, plus the phase II DELINEATE (Dose EscaLation to Intraprostatic tumour Nodules in localisEd prostATE cancer) study [8].

One of the key issues regarding dose painting is to understand how far DILs can be boosted *without* significantly increasing toxicities. The FLAME trial reported no significant differences in gastrointestinal (GI)

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Table 1
Dose-Painting Structures.

Structure	Method
GTV	DILs identified by radiologist.
CTV1	Prostate and seminal vesicles
CTV2	Prostate and involved seminal vesicles
CTV3 (boost)	GTV expanded by 3mm but edited to avoid overlap with OAR and to avoid extending outside CTV2.
PTV1 (planning target volume) (61Gy in 37#)	CTV1 with uniform margin of 10mm
PTV2 (74Gy in 37#)	CTV2 with uniform margin of 5mm
PTV3 (boost up to 86Gy)	CTV3 expanded with uniform margin of 2mm
OARs	Bladder, urethra, rectum, other bowel and femoral heads

or genitourinary (GU) toxicities between the boost and standard arms of the trial at two years post-treatment. However, the urethra was not delineated, and no dose constraints were set.

The DELINEATE study included standard and hypofractionated arms, with the standard fractionation (74 Gy in 37 fractions) the same as this study but, with a lower boost dose and higher urethra tolerance.

Consequently, in this study the urethra was outlined and a dose constraint set, together with the rectum and bladder. Image guidance for FLAME, PIVOTALboost and DELINEATE was achieved using fiducial markers with daily cone beam CT (CBCT). However, since prostate motion can take place following imaging [9] the performance of a trans-perineal ultrasound system for real time image guided radiotherapy (IGRT) [10] in relation to DIL margins was evaluated. In view of the high dose gradients, small size of the DILs and their proximity to OARs, measurement was used to verify that the planned dose distributions could be accurately delivered. This was a feasibility-only study and no patients were treated with the new technique.

The primary aim for this study was to determine how OAR dose constraints limited the boost dose to the DILs when they were in close proximity.

2. Methods and materials

2.1. Patient selection

Patients were identified by a clinical oncologist, given a patient information sheet, and then formally consented. Patients eligible for this study had intermediate or high risk prostate cancer, no evidence of nodal or distant metastases, no previous pelvic radiotherapy and a recent satisfactory glomerular filtration rate (GFR). See supplemental table S1 for details. The study had Research Ethics Committee approval. Twenty patients were consented into the study with a median age of 72 years and a mean PSA on diagnosis of 20 ng/mL. There were ten intermediate and ten high risk patients. Full details are shown in supplemental table S2. Of the twenty patients, one was claustrophobic in the scanner and had to be withdrawn.

2.2. Scanning

Planning CT and MRI scans were performed the same day, with as short a time as possible between scans. Patients were positioned within the scanners on a couch with a flat insert to mimic a radiotherapy couch top. CT scans were performed with patients supine with knee and footstock immobilisation on a Big Bore 16 slice scanner (Philips, Amsterdam, Netherlands), 30 min after drinking 500 mL of water and emptying their rectum (using micro-enema). Scans 2 mm wide were acquired with the Clarity TPUS probe (Elekta, Stockholm, Sweden) [11–13] in position. To replicate this on the MRI scanner, patients were scanned in the same position with a 'dummy' probe constructed of compatible materials in position. At this stage patients had received three to four months of Luteinizing hormone-releasing hormone (LHRH) agonist therapy.

A Siemens 3 T Magnetom Skyra (Siemens Healthineers, Erlangen, Germany) was used for the MRI scans. Multi-parametric sequences were used to determine the location/presence of DILs within the prostate (a combination of anatomical and functional MRI sequences) as recommended in the ESUR prostate MRI guidelines 2012 [14] and elsewhere including the FLAME study [6].

2.3. Reporting and outlining

The MRI scans were reported by an experienced radiologist. Prostate and seminal vesicles were reviewed with the peripheral and transition zones assessed separately. The peripheral zone, where 65–70% of cancers occur, was imaged using DWI (diffusion weighted imaging) as the dominant sequence. DCE (Dynamic Contrast Enhanced) imaging was used to further assess the lesions for malignancy. Gadolinium-based contrast agent was used. In the transition zone, T2 Weighted imaging was the dominant sequence. Axial T2 images were used for treatment planning. Full details are given in supplemental table S3.

As expected, some patients did not have dominant tumour foci but instead had diffuse disease without a definable edge [3]. The scans were reviewed by a clinical oncologist experienced in treatment planning prior to rigid registration with the CT using a mutual information match on the Oncentra TPS, in use at the start of the study. An automatic match was used for most plans, but where results were poor, other approaches were used. The clinical target volume (CTV) and OARs were delineated based on CT images with the help of the MRI scan, and the urethra position was based solely on the MRI scan. The use of MRI in addition to CT slightly changed the CTV volume but there were no observable trends. Structures were outlined as in table 1.

Marked structures were 'grown' to produce the CTV/ PTV using an isotropic margin expansion tool. The boost volume was formed by firstly growing the GTV (DIL) by 3 mm to give CTV3, then growing this by 2 mm to give PTV3, giving 5 mm overall. Overlap of the CTV with OARs was avoided by cropping to the edge of the organ. PTV2 (prostate high dose volume) was grown from the CTV2 by 5 mm to give both PTVs the same combined margin. A similar approach was used by Uzan et al [4]. Where the initial structure margins fell between CT slices in the superior/inferior direction, the planned dose distribution was reviewed on a sagittal plane to ensure adequate coverage.

2.4. Treatment planning and constraints

For the dose-painted plans there was no consensus on the appropriate dose level for DILs, so the value from Uzan et al [4] was used. The aim was to deliver 74 Gy in 37 fractions to the prostate median isodose level with a concurrent boost of 86 Gy to the DILs. The rectum and bladder tolerances were taken from the CHHiP [10,15–17] protocol. In the CHHiP constraints, the max (1 cm^3) rectum dose was limited to 77 Gy and max (1 cm^3) bladder dose to 80 Gy as per the FLAME [6] study. The FLAME study did not specify a urethra tolerance and Uzan et al [4] limited this to 74 Gy. Our standard protocol did not require the urethra to be outlined, resulting in maximum doses for our standard plans of 74 Gy to 77 Gy. As a conservative measure, it was decided to

Table 2
Treatment plan dose statistics and measurement results.

Patient No.	Plan type	Treatment Plan Dose Statistics							% difference between measured and planned doses			% points failing Gamma at 3 %/3 mm
		Boost Dose [Gy]	Rectum Mean [Gy]	Rectum D_{1cc} [Gy]	Bladder Mean [Gy]	Bladder D_{1cc} [Gy]	Urethra $D_{0.1\%}$ [Gy]	Boost PTV3 vol [cm^3]	PTV 1	PTV2	PTV3	
DP02	Clinical Plan		36.9	74.1	31	74.7	75.9					
	VMAT No Boost		32.1	74.2	28.9	75.1	73.8		1.1	0.9	N/A	0
	Boost Plan	86	34.3	74.8*	30.7	75.3	73.3	8.5	0.4	0.2	0.5	0
DP04	Clinical Plan		39.9	74.2	26.8	74.3	76.4					
	VMAT No Boost		34.6	74.2	22.9	75	74		0.8	0.8	N/A	0
	Boost Plan	86	37.2	75.8*	23.8	74.7	74	2.5	0.1	0.1	0.9	0
DP06	Clinical Plan		44.6	74.1	21.9	75.3	77					
	VMAT No Boost		43.2	74.4	21.3	75.3	73.8		0.5	0.4	N/A	0
	Boost Plan	86	41.6	76.2*	21.7	75.7	73.7	6.9	0.9	1.0	0.5	0.02
DP07	Clinical Plan		36.9	73.7	22.4	75	75.7					
	VMAT No Boost		29.6	74.1	19	74.9	73.6		0.3	0.2	N/A	0
	Boost Plan	86	31.1	74.6*	20.3	76.4	73.1	2.6	0.1	0.3	0.1	0
DP08	Clinical Plan		37.7	74.3	32.4	75.3	75					
	VMAT No Boost		32.1	74.4	29.1	74.9	73.7		0.7	0.6	N/A	0
	Boost Plan	80	37.2	73.9	32.2	74.8	76.5*	5.4	0.0	0.2	0.4	0
DP12	Clinical Plan		43.2	74	30.6	75.6	76.2					
	VMAT No Boost		39.4	74.2	29.5	74.9	73.9		0.3	0.2	N/A	0.01
	Boost Plan	80	39.1	74.0	30.8	74.9	77.9*	4.3	0.7	0.8	0.9	0
DP13	Clinical Plan		40.1	74.2	32.8	75.0	76.2					
	VMAT No Boost		36.2	74.3	28.2	75.6	73.3		0.1	0.0	N/A	0.08
	Boost Plan	80	35.4	73.9	28.7	76.1	78*	2.2	0.2	0.3	0.4	0
DP14	Clinical Plan		39.4	73.7	36.3	75.5	75.6					
	VMAT No Boost		28.9	74.2	32.5	75.2	73.8		0.8	0.7	N/A	0
	Boost Plan	86	33.4	74.7	37.6	74.5	73	6.3	0.4	0.6	0.6	0.01
DP15	Clinical Plan		40.9	73.6	38.6	75	76.9					
	VMAT No Boost		35.5	73.7	33	74.3	73.3		0.0	0.1	N/A	0.03
	Boost Plan	80	36.5	73.7	33	74.1	77.3*	8.7	0.1	0.1	0.2	0.03
DP16	Clinical Plan		39.7	73.3	27.3	75.3	76.4					
	VMAT No Boost		37.4	73.6	24.1	75.3	73.6		0.3	0.3	N/A	0.14
	Boost Plan	80	37	74.6*	24.7	75.8	76.8*	20.1	0.2	0.3	0.4	0
DP17	Clinical Plan		40.3	73.6	30.1	75.1	75.2					
	VMAT No Boost		33.5	74.2	26.2	74.9	73.9		0.2	0.1	N/A	0
	Boost Plan	86	41.4	76.8*	27.4	76.3	76.8	2.8	1.0	1.0	0.5	0
DP19	Clinical Plan		41.2	73.5	42.8	75.1	76.3					
	VMAT No Boost		27.1	74.1	30.7	75	73.5		0.4	0.4	N/A	0
	Boost Plan	86	30.7	74.1	30.5	73.3	76	13	0.7	0.8	0.1	0

(*continued on next page*)

Table 2 (*continued*)

Patient No.	Plan type	Treatment Plan Dose Statistics							% difference between measured and planned doses			% points failing Gamma at 3 %/3 mm
		Boost Dose [Gy]	Rectum Mean [Gy]	Rectum D_{1cc} [Gy]	Bladder Mean [Gy]	Bladder D_{1cc} [Gy]	Urethra $D_{0.1\%}$ [Gy]	Boost PTV3 vol [cm^3]	PTV 1	PTV2	PTV3	
Median over all boosted	Clinical Plan		40.1	73.9	30.8	75.1	76.2		N/A	N/A	N/A	N/A
	VMAT No Boost		34.1	74.2	8.6	75.0	73.8		N/A	N/A	N/A	N/A
	Boost Plan		36.8	74.6	29.6	75.1	76.3	5.9	N/A	N/A	N/A	N/A

For each patient the clinical, unboosted and boosted plan data is shown. For each plan the mean and maximum OAR doses are shown and for the boost plans, the boost dose and PTV3 volume are shown. The percentage differences between the measured and planned doses are shown for the unboosted and boosted plans, together with the percentage of points failing the gamma factor test using criteria of 3% and 3 mm. NB * against an OAR dose value indicates the presence of a DIL overlapping/ abutting the OAR.

limit the point max urethra dose to 74 Gy for no overlap with PTV3, or 78 Gy where overlap occurs. Where dose tolerances for OARs were exceeded, the median boost dose to the whole DIL *without* exceeding the tolerance was recorded.

Oncentra Master Plan (OMP), (Elekta, Stockholm, Sweden) and Raystation (RaySearch Laboratories, Stockholm, Sweden) were used to produce boost and standard plans. To carry out a full comparison, three treatment plans were produced per patient. The clinical plan used to treat patients was created using OMP (TPS1), using five field IMRT at 6 MV and a 10 mm leaf size multileaf collimator (MLC) and included for comparison as our then current technique. Research plans with and without a boost were created using Raystation (TPS2) with full volumetric modulated arc therapy (VMAT) arcs using 3 degree control point spacing and a collimator angle of 15 degrees. 10 MV and 5 mm leaf MLCs were used for these plans. Dual arcs were required for the boost plan.

2.5. Dosimetry

The accuracy of plan delivery was assessed using a MatriXX (IBA Dosimetry, Schwarzenbruck, Germany) ionisation chamber array system mounted on an Agility linac (Elekta, Stockholm, Sweden). Delivered dose distributions were reconstructed on the planning CT using COMPASS software (IBA Dosimetry, Schwarzenbruck, Germany) and the measured and planned distributions compared using gamma analysis [18]. The percentage difference between the measured and planned doses to PTV1, PTV2 and PTV3 (DILs) were also determined. Raystation plans alone were assessed as the distributions clearly showed a superior dose fall-off outside the PTV, and would be in use going forward.

3. Results

Fourteen patients had identifiable DILs, of which two could not be planned due to internal motion between the CT and MR scan. The twelve patients planned (table 2) had one to two DILs and of these, ten plans had boost volumes overlapping or abutting OARs. Of these ten plans, five had boost volumes overlapping or abutting the urethra which could not be planned for more than 80 Gy without exceeding the urethra constraint. Six plans had boost volumes overlapping or abutting the rectum including one plan with a large DIL close to both the rectum and urethra. For the five plans with boost volumes overlapping or abutting the rectum only, all could be planned for the target dose of 86 Gy. The two cases with no OARs compromised were also planned to the target dose giving seven cases altogether able to be planned to the full boost dose. None of the boost volumes compromised the bladder constraints. A sample MRI scan and planning image for a patient with two DILs adjacent to the rectum are shown in Fig. 1.

Table 2 shows the gamma analysis and comparison of DVH statistics carried out between the planned and reconstructed doses. The percentage of points within the 15% isodose failing gamma analysis at 3%/3 mm, and the differences in mean PTV doses between planned and reconstructed dose were all within local tolerances.

4. Discussion

In this study patients were scanned using CT and MRI, and, where DILs were identified, planned for external beam radiotherapy. DILs close to OARs limited the boost for the dose painted plans. Of the 19 patients scanned, 14 had identifiable DILs. The use of LHRH agonist therapy may have made the DILs more difficult to identify due to the effect of the hormone therapy. The CT/MRI registration issues for two patients were due to internal motion between the scans and more consistent bladder and bowel prep between scans may have helped avoid this. Rigid registration was used, so deformable registration may have a role in this area despite its current limitations [19]. ‘MRI only’

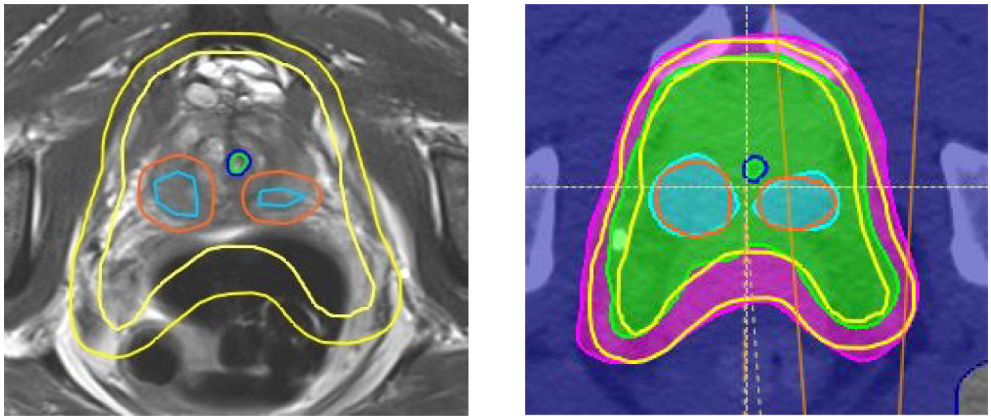

Fig. 1. Patient images from the study showing (a) MRI scan with CTV and PTV marked (b) CT image of same patient with colourwash of dose levels during treatment planning.

planning is a promising technique which may avoid this issue by generation of a 'synthetic CT' scan from the MRI, but this is at an early stage of adoption [20–22].

For the patients where the boost PTV3 overlapped or abutted the OARs (table 2), the maximum (D1 cm^3/D 0.1%) OAR dose was generally higher on the boosted than the non-boosted plans. Where there was no abutment/overlap, there was little difference in maximum dose. Of the twelve patients planned, five had boost doses limited to 80 Gy due to proximity of the DILs to the urethra. Although some plans had boost volumes abutting or overlapping the rectum, this did not limit the boost dose. For the urethra, the median difference was 4 Gy (range 2.8–4.7 Gy) for the boosted plans and 0.0 Gy (range −0.5–2.9 Gy) for the non-boosted plans. For the rectum, the median difference was 1.3 Gy (range 0.5–2.6 Gy) and 0.1 Gy (range −0.5–0.5 Gy) on the non-boosted plans. Over all twelve patients, the median dose to the rectum was 34.1 Gy for the TPS2 non-boosted plans and 40.0 Gy on TPS1 non-boosted plans. This difference was due to the improved dose fall-off with TPS2 VMAT. There was no suggestion that larger PTV3 volumes had a detrimental effect on plan quality. The median PTV3 volume was 5.9 cm^3 (range 2.2–20.1 cm^3).

A key issue was uncertainty regarding the optimal TD5/5 (5% risk at 5 years) for the urethra. The whole length of the urethra and DILs were delineated with the help of an experienced radiologist without any urethral catheter insertion. Within the FLAME study [6] the urethra was not delineated and no constraints were set, so boosted patients may have received a high urethral dose. As a consequence, increased fibrosis of the urethra may take place, eventually leading to strictures. This may emerge as a late toxicity (greater than 2 yrs), but at the two year FLAME study follow-up point, no significant differences in urethral toxicity were noted. Interestingly, the group limited the urethral dose to 42 Gy/5 # in the hypo-FLAME study [23]. Similarly, within the PIVOTALboost study [24] the urethra was highlighted as an OAR but while a dose constraint is cited for brachytherapy, there is not one for EBRT dose painting. The protocol recommended [7], however, that hot spots in the urethra should be avoided, although it was marked only if visible on planning scans. In the DELINEATE report for the 37 fraction cohort [8], a higher tolerance was allowed for the urethra (77 Gy optimal and 83 Gy mandatory) vs 74 Gy optimal and 78 Gy mandatory in our study. The boost dose was also *lower* in DELINEATE (82 Gy) than this study (86 Gy) which may explain the fulfilment of all the dose objectives the DELINEATE series. Longer term, if clinical evidence emerges that a higher dose to the urethra could be tolerated, it may be possible to boost a larger proportion of patients.

The results of comparison between the planned and measured doses showed good agreement for both the PTV dose and gamma factor. This was consistent for all the measured plans despite the challenges of small field dosimetry [22], confirming the deliverability of the boosted plans.

Image-guided techniques have become increasingly important for inter- and intra-fractional monitoring particularly for escalated doses and the move to hypofractionation in prostate radiotherapy. This Centre used a TPUS which had the advantage of being less invasive; used non-ionising radiation and could be utilised for inter- and intra-fractional motion. However, the uncertainty in the TPUS derived position needs to be smaller than the setup uncertainty, otherwise part of the target volume could be underdosed. The CTV-PTV margin size is related to the uncertainty in prostate position via the van Herk methodology [25]. There have been a number of studies concerning monitoring accuracy using the TPUS system. It has been compared with fiducial markers imaged with cone beam computed tomography (CBCT), as well as electromagnetic transponders [26]. Yu et al [27] reported that 'tracking accuracy is within a millimetre when target motion is less than 3 mm' using a phantom system. Grimwood et al [11] used intraprostatic fiducials which were identified on portal image scans for comparison with TPUS- based estimates. Mean differences between the TPUS and electronic portal imaging device (EPID) based positions were 0.6 mm, but the 95% limit of agreement was 2.5 mm. It was proposed that for prostate SBRT, CBCT was used for daily inter-fraction adaption, while the TPUS was used for intra-fraction motion. They stated that the 'recommendations for margin reduction using the Calypso electromagnetic transponder may be applied to Clarity®' [26]. In this department, audits have shown 95% agreement between offline 'experts' and online matching by radiographers to within less than 3 mm [28]. Results were broadly in agreement with the study by Grimwood [11] and Pang [9] suggesting margins of 2–3 mm are appropriate. As this is essentially a manual method, automated matching, when available, may reduce this further.

A different approach using an MRI linac [29] could provide non-invasive online three-dimensional (3D) imaging and possibly beam tracking of the target volume. Combined with an MRI based planning approach, this would result in an MRI-only treatment pathway [20–22] avoiding CT/MRI registration issues. However, such modalities are costly. Alternatively, the dosimetric properties of proton radiotherapy suggest advantages for dose-painting [30]. Pedersen et al [31] found that both intensity modulated proton therapy (IMPT) and photon based VMAT increased the TCP for focal prostate boosted treatment plans, although the small benefit of IMPT was lost when inter-fractional motion was included, as *inter* (rather *intra*-) fractional IGRT was used. Potentially, for OARs close to the PTV the steeper distal and lateral dose gradients could allow for further focal dose escalation [32].

The extra resources required for external beam dose painting are a consideration; an extra MRI scan was used in our study and the time of an experienced radiologist was required. A weakness of this study was that as it concerned the feasibility of the technique, no patients received the escalated dose, so we have no toxicity data.

In conclusion, the feasibility of using external beam dose painting has been demonstrated for a subset of the group of patients in the study. The majority of patients (14/19) had discrete DILs identifiable using MRI and for a small proportion of patients, rigid registration between CT and MRI was insufficient. Half the remaining patients could be boosted to the target dose of 86 Gy, but the other half could only be boosted to 80 Gy due to proximity of the DILs to the urethra, requiring further information regarding late toxicities at boost doses. Image guidance with the TPUS system was demonstrated to be compatible with the margins used in this study.

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.

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Appendix A. Supplementary data

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