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ORIGINAL ARTICLE

Absence of prostate oedema obviates the need for delay between fiducial marker insertion and radiotherapy simulation

Deepti Patel, BAppSc (MRT),[1] Alex Tan, MBBS, FRANZCR,[1,2] Amy Brown, MSc (Research), BAppSc (MRT), [1] & Tilley Pain, BSc, PhD[2,3]

[1]Townsville Cancer Centre, Townsville University Hospital, Townsville, Queensland, Australia
[2]James Cook University, Townsville, Queensland, Australia
[3]Townsville University Hospital, Townsville, Queensland, Australia

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Correspondence
Deepti Patel, Radiation Oncology, Townsville University Hospital, PO Box 670, Townsville, QLD 4810, Australia. Tel: +61 7 44331664; Fax: +61 7 44331661; E-mail: deepti.patel@health.qld.gov.au

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Abstract

Introduction: Fiducial markers (FMs) are commonly inserted into the prostate for image guided radiation therapy. This study aimed to quantify prostate oedema immediately following FM insertion compared to prostate volumes measured a week later, at the time of simulation for radiation therapy. **Methods:** Thirty patients underwent a verification computed tomography (VCT) scan in treatment position immediately after the fiducial insertion and their planning computed tomography scan (PCT) one week after. Patient data sets were retrospectively evaluated, comparing prostate volumes and planning target volumes (PTV). Volumes were delineated by a single radiation oncologist, blinded to whether the scan was VCT or PCT. Distances between the FMs were measured on both scans. Descriptive statistics described the data, DICE similarity co-efficient (DSC) calculated, and paired t-tests were used to compare paired data. **Results:** The median prostate volume was 35.09 cc and 36.31 cc for VCT and PCT data sets, respectively, and median PTV was 118.56 cc and 127.04 cc for VCT and PCT, respectively. There was no significant difference in prostate volumes ($P = 0.3037$) or PTV ($P = 0.1279$), with a DSC of 0.87 (range 0.76–0.91) and 0.91 (range 0.85 to 0.95), respectively. Similarly, there was no significant difference in distance between fiducial markers ($P > 0.05$). **Conclusion:** This study demonstrates no statistically significant difference in prostate or PTV volumes ($P > 0.05$) between the CT acquired at fiducial marker insertion compared with the CT acquired a week later. Therefore, oedema is not significant enough to justify a delay between FM insertion and simulation.

Introduction

Radiotherapy is one of the most common treatment options for prostate cancer, the most prevalent cancer and the second most common cause of death from cancer in Australian men.[1,2] There are two main methods of delivering radiation: brachytherapy or external beam radiation therapy (EBRT). Greater accuracy of EBRT has been achieved with the introduction of image guided radiotherapy using gold fiducial markers (FMs) to localise the prostate prior to treatment.[3,4] Fiducial marker use has improved tumour targeting and allowed dose escalation to safely improve treatment outcomes for prostate cancer patients.[4,5] Brachytherapy is considerably more invasive as it involves the insertion of approximately 80–100 radioactive seeds (low dose rate brachytherapy) or multiple hollow catheters (high dose rate brachytherapy) into the prostate via a transperineal route while the patient is under anaesthetic. The procedure causes haemorrhage and oedema, which may cause up to 50% increase in gland volume.[6]

Fiducial markers insertion to aid image guided EBRT is now considered gold-standard practice.[4] The procedure is often performed by urologists or radiologists, while at

Townsville Cancer Centre, a multidisciplinary radiation oncology team approach was implemented. The team comprises a radiation oncologist (RO) to perform the insertion, a trained radiation therapist to control the ultrasound machine and a nurse to assist the procedure. Three FMs are inserted into the prostate gland transrectally with a 17-gauge needle under ultrasound guidance and local anaesthetic requiring a minimum of five needle insertions. During the implementation of insertions by the ROs, patients underwent a verification computed tomography (VCT) scan within 30 min of the insertion procedure in the treatment position to confirm correct placement of the FMs. Patients had their radiation therapy planning computed tomography scan (PCT) one week later. Patients underwent the same CT protocol for both scans, and 2 mm slice thickness was acquired to allow for optimal visualisation of the fiducial markers which are 1 × 3 mm cylinders (CIVCO, Iowa, USA).

Fiducial markers insertion and brachytherapy procedures both cause prostate oedema. Mechanical trauma from the needle insertion, intra-prostatic bleeding and the general inflammatory response can cause the prostate to swell; this swelling and inflammation can give an inaccurate representation of true prostate size and shape.[7] Therefore, a delay of at least one week between FM insertion and treatment simulation is standard to allow oedema to resolve.[4] However, no previous studies have investigated the magnitude and clinical relevance of prostate oedema following FM insertion, and thus, the one week delay may not be required. This study measured FM-induced prostate swelling by measuring the distance between the FMs and the prostate volumes on CT scans both immediately after and one week following insertion.

Method

Design and data

This study was a retrospective audit of CT images to recalculate prostate volumes. The planning scans of 30 patients selected ad hoc between August 2013 and December 2014 were re-contoured by the RO. Participants were included if they had prostate cancer, were treated using EBRT and had no contraindications for treatment. Participants were excluded if there were fewer than three FMs on either scan or if extensive CT artefacts such as those caused by hip prostheses made prostate delineation difficult.

Sample size

An initial sample size of 21 patients was calculated, for a level of significance of 0.05 and power of 80%, detecting a 5% difference in prostate volume size. To enable the possibility of parametric tests on potentially nonparametric data, the sample was increased to a total of 30.[8]

Volume and distance measures

The data sets from both the verification and planning CT scans were deidentified and renamed in the Monaco planning system (Elekta, Missouri, USA) so that the RO was blinded to which CT scan they were contouring. Additionally, the RO contoured each prostate contour separately on each relevant scan, without reference to any previous contour, with at least one week between contouring the previous volume to minimise any prior knowledge bias. The VCT and PCT were fused, using the fiducials as points of interest for the registration. To improve fusion of the two scans, rotational correction was also used. Where an acceptable fusion could not be achieved, a 'best-fit' fusion was performed and verified by another investigator. If consensus on an acceptable fusion could not be reached, the patient was excluded.

One RO contoured the prostate volume and generated the PTV volumes on both verification and planning scans for all patients. A conventional PTV expansion of 10 mm except 5 mm in the posterior direction was applied. The VCT volumes were then copied to the PCT data set. The intersect volume, that is the common volume, shared by both the VCT and PCT contours was generated utilising the contouring tools within the planning system (Figure 1). The prostate and PTV volumes, intersect prostate and intersect PTV volumes were recorded in cubic millimetres. Utilising these recorded volumes, the Concordance Index (CI), DICE Similarity Co-efficient (DSC; Equation 1) and Hausdorff distance were calculated. The CI is a ratio of the overlap presented as a percentage.[9] The DSC is a measurement of the spatial similarity of two volumes where 0 indicates no overlap between the two volumes and one indicates complete overlap between the two volumes, indicating agreement between both volume and space.[10,11] Both the DSC and Hausdorff distance were calculated using SlicerRT.[12]

DICE similarity co-efficient

$$\mathrm{DSC} = \frac{2 \times (A \cap B)}{(A + B)} \quad (1)$$

where A = volume from VCT, B = volume from PCT, $(A \cap B)$ = intersect of volumes A and B.

For the distance between markers, the coordinates of the centre of each fiducial marker contour were recorded for each scan, and the distance between each was recorded in centimetres.

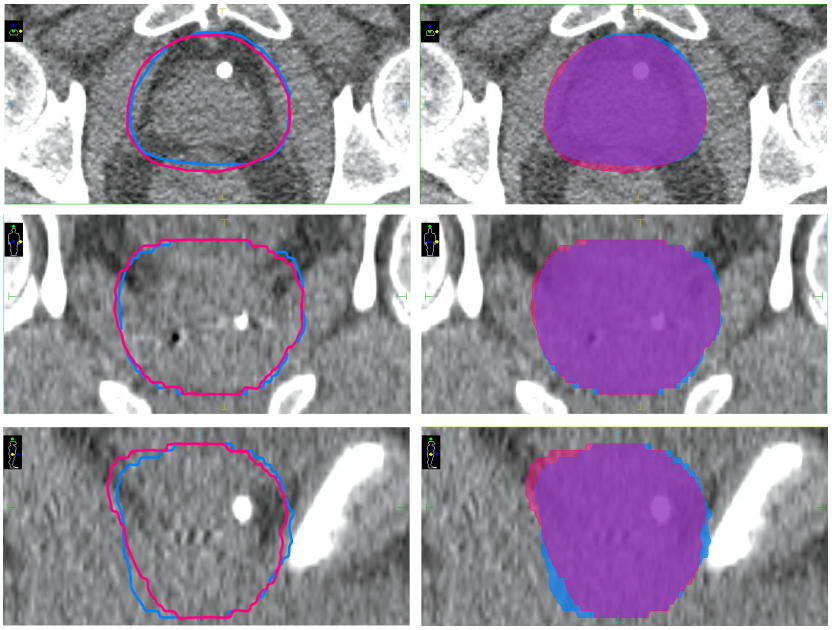

Figure 1. Example of PTV volumes assessed.VCT (blue) and PCT (magenta) PTV volumes as contoured by the RO, and volume intersect (purple) as generated by the planning system.

Statistical analysis

All data were recorded as numerical values. All data were collated in a spreadsheet (Microsoft Excel, Microsoft Corp., Washington, USA) and transferred to *R* statistical software version 3.6.1.[13] Data were paired and checked for normality assumptions. Median and interquartile ranges (IQ range) have been used to describe data, while paired t-tests were used to compare paired data.

Ethics

Ethics approval was obtained from The Townsville Hospital and Health Service Human Research Ethics Committee prior to data mining (HREC/13/QTHS/22). No patient contact was required for this study.

Results

Patient eligibility and demographics

During the study period, 36 patient data sets were screened. Five were excluded due to ineligibility. One patient had hip prosthesis. Three patients had fewer than three fiducials within the prostate on either scan; one with a seed placed outside of the prostate on the VCT. One further patient data set was excluded due to poor fusion quality, with large differences in pelvic tilt and surrounding bladder and bowel filling causing some potential prostate deformation.

Of the 30 patients, 23 (76%) were on hormone therapy for a median of 92 days prior to the VCT (range 0–353 days). Median age was 71 years (range: 57–81). No further demographics were collected on participants. Individual patient data are presented in Table 1.

Median planning verification and planning volumes

Median prostate and target volume measured at the verification scans were 35.09 cc (IQ range 27.77–50.07 cc) and 118.56 cc (IQ range 104.02–157.09 cc), respectively. A week later at the planning scan, the volumes for the prostate and target volumes were 36.31 cc (IQ range 27.34–55.12 cc) and 127.04 cc (IQ range 103.78–160.15 cc), respectively (Figure 2). Comparison between verification and planning scans show no significant difference for the prostate volumes ($P = 0.30$) or planning target volumes (0.13) (Table 2).

Median DICE similarity co-efficient

The median DSC between the verification and planning volumes for the prostate volumes was 0.87. The median DSC between the verification and planning volumes for the target volume was 0.91 (Table 2).

Table 1. Individual measurements for volume and distance measures.

	Prostate volumes (cc)								PTV volumes (cc)								Fiducial marker difference (cm)[2]		
							Hausdorff (mm)								Hausdorff (mm)				
Patient	VCT	PCT	Overlap	PCT/VCT	CI[1]	DSC	Avg	Max	VCT	PCT	Overlap	PCT/VCT	CI[1]	DSC	Avg	Max	FM1-FM2	FM2-FM3	FM3-FM1
1	52.58	51.86	47.93	0.99	92.42	0.88	1.67	7.12	161.95	160.23	151.94	0.99	94.83	0.92	1.81	6.31	−0.05	0.13	−0.03
2	29.69	32.75	27.12	1.10	82.81	0.82	1.96	8.30	115.92	119.28	108.26	1.03	90.76	0.89	1.98	7.87	0.07	0.10	−0.12
3	44.71	38.71	36.00	0.87	93.00	0.82	2.25	6.68	140.94	131.33	123.81	0.93	94.27	0.88	2.26	6.75	0.08	0.10	0.01
4	16.23	15.84	15.21	0.98	96.05	0.89	0.74	4.88	76.21	73.57	72.65	0.97	98.75	0.94	0.80	4.88	−0.16	−0.08	−0.11
5	28.76	26.57	24.19	0.92	91.04	0.83	1.94	6.27	107.14	101.99	96.81	0.95	94.92	0.90	2.00	5.68	0.02	0.15	0.13
6	29.76	29.65	25.74	1.00	86.81	0.81	1.78	7.42	114.09	111.90	104.70	0.98	93.57	0.89	1.89	7.79	-0.08	0.01	−0.19
7	26.53	27.66	25.76	1.04	93.13	0.90	0.95	5.28	101.26	103.31	98.88	1.02	95.71	0.94	1.06	5.28	0.03	0.02	0.18
8	24.13	27.23	23.39	1.13	85.90	0.85	1.35	5.59	105.25	107.70	100.94	1.02	93.72	0.92	1.41	5.69	−0.01	−0.05	−0.07
9	19.79	23.75	17.56	1.20	73.95	0.76	2.22	10.47	91.73	95.93	83.27	1.05	86.80	0.86	2.38	10.47	−0.07	−0.06	−0.06
10	25.19	26.94	23.97	1.07	88.98	0.87	1.36	5.76	95.11	100.98	93.08	1.06	92.18	0.92	1.39	5.33	0.01	0.11	−0.06
11	54.30	61.83	53.63	1.14	86.74	0.88	1.72	9.00	158.88	182.51	158.45	1.15	86.82	0.90	2.06	9.30	0.09	0.03	0.02
12	57.00	57.51	54.34	1.01	94.49	0.91	1.23	4.96	164.14	167.04	159.12	1.02	95.26	0.94	1.26	5.25	0.01	−0.17	0.04
13	35.73	37.33	34.85	1.04	93.36	0.91	1.05	5.73	118.43	129.58	118.19	1.09	91.21	0.92	1.38	6.26	−0.12	0.19	−0.10
14	33.77	36.60	33.18	1.08	90.66	0.89	1.24	7.88	118.69	131.34	119.00	1.11	90.60	0.92	1.50	7.88	−0.11	−0.06	−0.07
15	27.84	30.24	25.89	1.09	85.60	0.84	1.48	5.68	103.61	111.97	100.78	1.08	90.01	0.91	1.61	5.68	−0.02	−0.04	−0.01
16	37.42	40.20	34.33	1.07	85.39	0.84	1.84	9.80	127.59	133.90	120.15	1.05	89.73	0.89	2.00	9.64	0.04	0.23	0.05
17	29.24	22.57	21.16	0.77	93.78	0.78	2.24	10.33	114.46	92.25	89.17	0.81	96.66	0.85	2.46	9.48	0.01	−0.01	0.02
18	81.77	89.69	79.65	1.10	88.81	0.89	1.78	8.05	221.82	239.11	219.80	1.08	91.93	0.93	1.78	8.33	−0.07	−0.14	−0.05
19	27.74	28.51	26.26	1.03	92.10	0.88	1.27	8.87	100.47	105.21	96.90	1.05	92.10	0.91	1.53	9.06	−0.09	0.08	0.07
20	49.58	59.05	47.90	1.19	81.12	0.84	1.93	6.37	159.94	181.31	157.83	1.13	87.05	0.90	2.00	6.37	−0.19	0.05	−0.12
21	62.13	58.78	48.74	0.95	82.91	0.84	2.24	8.69	178.72	181.86	166.77	1.02	91.70	0.90	2.30	8.54	−0.10	0.07	−0.03
22	53.25	60.49	52.36	1.14	86.56	0.89	1.40	6.11	160.31	171.41	158.87	1.07	92.68	0.92	1.68	6.69	0.09	0.00	0.02
23	23.08	22.03	20.05	0.95	91.03	0.84	1.60	5.20	89.95	89.32	83.63	0.99	93.63	0.90	1.69	5.37	0.10	0.10	0.06
24	38.29	33.00	30.01	0.86	90.93	0.80	2.17	8.07	130.77	123.54	115.72	0.94	93.67	0.88	2.19	7.74	−0.11	−0.18	−0.20
25	50.23	57.97	48.91	1.15	84.38	0.86	1.92	7.12	151.70	168.43	148.41	1.11	88.12	0.90	2.07	6.91	−0.26	−0.15	−0.10
26	46.28	44.28	42.66	0.96	96.34	0.90	1.28	5.89	141.28	138.37	142.24	0.98	102.80	0.93	1.39	5.56	0.02	0.09	0.01
27	65.61	56.21	55.61	0.86	98.92	0.87	1.78	8.33	180.20	159.92	159.29	0.89	99.60	0.91	1.92	8.33	−0.22	−0.12	−0.14
28	23.11	24.11	22.55	1.04	93.52	0.90	1.05	4.14	88.44	90.37	87.61	1.02	96.94	0.95	0.99	3.79	−0.01	0.00	0.03
29	34.44	36.02	32.73	1.05	90.85	0.87	1.32	6.25	115.92	124.50	114.05	1.07	91.61	0.92	1.47	6.12	−0.01	0.22	0.09
30	44.27	39.00	37.47	0.88	96.09	0.86	1.83	4.36	141.89	130.45	128.59	0.92	98.58	0.92	1.75	4.98	0.00	0.00	0.02

[1]Concordance Index (CI) = (PCT volume/overlap) × 100.

[2]PCT fiducial marker position minus VCT fiducial marker position.

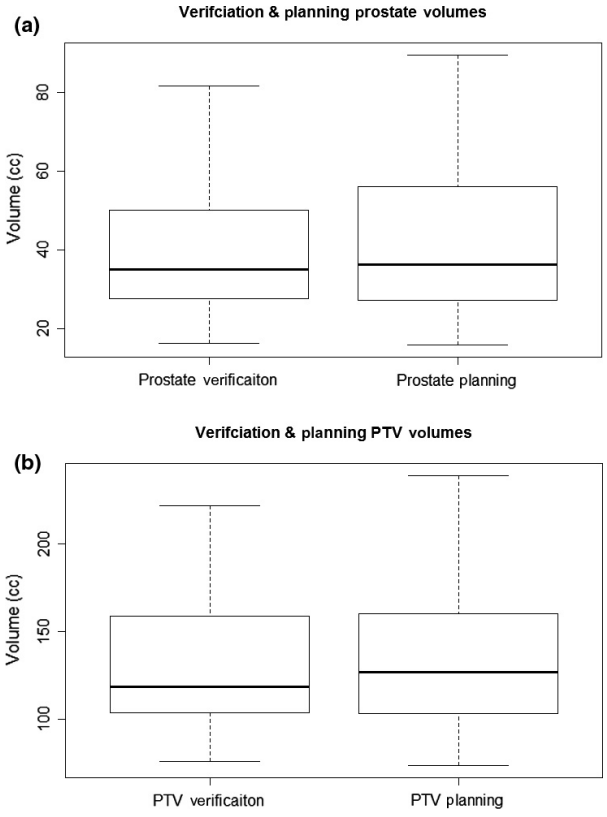

Figure 2. Boxplot of prostate (A) and PTV volumes (B), comparing verification and planning scans.

Hausdorff distance measures

The median Hausdorff distance between the verification and planning volumes for the prostate volumes was 1.69 mm. The median Hausdorff distance between the verification and planning volumes for the target volume was 1.76 mm (Table 2).

Median differences between fiducial markers

There was no significant difference in the distances between fiducial markers (Table 3). The median distance between fiducial markers 1 and 2 at verification was 2.45 cm, and at the planning scan, it was 2.39 cm. The median distance between fiducial markers 2 and 3 at verification was 1.39 cm, and at planning scan, it was 1.42 cm. The median distance between fiducial markers 1 and 3 at the verification was 2.38 cm, and at planning scan, it was 2.35 cm.

Discussion

This study demonstrates that there is no significant change in prostate size or shape between the VCT and PCT and confirms that the delay between FM insertion and CT simulation is unnecessary. Until this study, our departmental protocol of mandating a one-week delay between gold seed insertion and radiotherapy planning was consistent with the Royal Australian and New Zealand College of Radiologists' (RANZCR) recommendations.[4] A recent survey of 15 radiotherapy centres in the United Kingdom reported that all centres wait at least one week between insertion and CT simulation.[14] However, prostate oedema literature predominantly addresses oedema following brachytherapy, which is significantly more invasive than FM insertion, with no studies specifically investigating the degree or significance of oedema following FM insertion.

The magnitude of brachytherapy-induced prostate oedema is best determined by measuring the prostate volume pre- and post-insertion. A variety of prostate volume increases have been observed ranging from 10 to 43%.[6,15,16] However, the significant prostate volume changes seen after brachytherapy may not be seen after FM insertion because of the difference in the number of needle insertions and seeds. A limitation of our study is that there is no pre-implant scan to measure the direct magnitude of oedema caused by insertion.

Nichol *et al* compared prostate volumes by measuring pre-insertion prostate volumes calculated on ultrasound and comparing to MRI delineated volumes on the day of CT simulation, with a median of 6 days between the two.[17] The MRI volume was 3.5 mL larger than on US ($P = 0.006$); however, this is attributed to the different

Table 2. Comparison between VCT and PCT prostate and target volumes.

Volume measure	Median (cc)	Range	IQR	*P*-Value	DSC Median (Range)	Hausdorff (mm) Median (range) Average	Hausdorff (mm) Median (range) Max
Prostate VCT	35.09	16.23–81.77	27.77–50.07	0.3037	0.87 (0.76–0.91)	1.69 (0.74–2.25)	6.53 (4.14–10.47)
Prostate PCT	36.31	15.84–89.69	27.34–55.12				
Planning target VCT	118.56	76.21–221.82	104.02–157.09	0.1279	0.91 (0.85–0.95)	1.76 (0.80–2.46)	6.53 (3.79–10.47)
Planning target PCT	127.04	73.57–239.11	103.78–160.15				

Table 3. Fiducial marker distance between VCT and PCT scans.

Fiducial marker measurement[1]	Median (cm)	Range	IQR	*P*-Value
FM1-FM2 VCT	2.45	0.9–4.2	2.02–2.67	0.843
FM1-FM2 PCT	2.39	0.83–3.98	1.96–2.66	
FM1-FM2 difference	−0.01	−0.26–0.10	−0.09–0.02	
FM2-FM3 VCT	1.39	0.31–2.84	1.13–1.59	0.839
FM2-FM3 PCT	1.42	0.5–2.79	1.22–1.59	
FM2-FM3 difference	0.02	−0.18–0.23	−0.06–0.10	
FM3-FM1 VCT	2.38	1.28–4.21	2.11–2.82	0.895
FM3-FM1 PCT	2.35	1.23–4.25	2.03–2.79	
FM3-FM1 difference	−0.02	−0.2–0.18	−0.09–0.03	

[1]Difference: PCT fiducial marker position minus VCT fiducial marker position.

imaging modalities rather than insertion-induced oedema. Our study compares the prostate volumes and fiducial marker coordinates using the same imaging technique across both measurements.

This study demonstrated no difference in the clinically relevant measurements between verification and planning scans. The lack of significant difference between the prostate volumes, target volumes or the distances between fiducial markers demonstrates no significant oedema immediately after the procedure. Therefore, CT simulation could be performed on the same day as implantation.

Migration of fiducial markers has been a reported issue in the literature.[18] We noted that three patients lost a seed between VCT and PCT. While these were excluded for the purposes of this study, IGRT was still able to be performed with the remaining two seeds in conjunction with checking soft tissue on daily cone-beam CT (CBCT). Migration of FMs during the treatment course itself has not been noted within our institution, suggesting suboptimal FM insertion will have the greatest impact between simulation and treatment commencement. Therefore, departments should have a workflow to address this, such as using a combination of FMs and CBCT.

All but two patients who were on hormones were so for greater than 50 days prior to VCT; therefore, we assume the hormones had little further effect on prostate volume in the week between the two scans.

There was some contour edge variation evident in the Hausdorff distances recorded, upon visual inspection, these were largely at the base of the prostate, where differences particularly in bladder volumes impacted the prostate deformation and definition. Edge variability for the prostate has potential for clinical ramifications; however, this is largely mitigated by PTV margin expansions. The lowest prostate CI (73.95%) and DSC (0.76) and maximum prostate Hausdorff distances (10.47 mm) were observed in the same patient data set (Patient 9). We examined this patient's scans and noted that the prostate was particularly difficult to fuse and delineate in both scans. Of note is the PTV expansion DSC of 0.86 and CI of 86.8% demonstrated some expansion mitigation in this case. As noted, conventional CTV-PTV expansions of 10 mm except 5 mm in the posterior were used as per standard clinical practice; however, further consideration should be given to reduced margin expansion.

Difficulties in prostate delineation on CT alone are well recognised, with reported inter- and intra-observer differences.[19–21] These known difficulties in contouring on CT suggest this study could be repeated with other imaging modalities, such as MRI. However, MRI involves other considerations such as the local signal void of FMs on MR, introducing another potential limitation. [22] Additionally, timely access to MRI machines can be limited.

It is also recognised that individual patient factors may contribute to the rate of oedema, such as tissue perfusion and blood flow.[23,24] Taussky et al reported an association with smaller prostate sizes and greater oedema in the brachytherapy setting; however, this was not found in our cohort.[24]

In a simulated dosimetric study investigating the impact of prostate contouring variability, significant correlations were reported between volume similarity and PTV dosimetry.[25] Further study into dosimetric impacts and treatment outcomes following implementation of same-day FM implantation and CT simulation is recommended.

Radiation therapy CT simulation on the same day as fiducial marker insertion is of significant benefit to patients. Benefits include no additional CT appointment which saves the costs associated with travel, particularly for patients travelling from rural and regional centres, potential loss of wages, and is more convenient for the

patient and their family/carers. Similarly, the organisation benefits from an increased appointment capacity. It is recognised that other logistical issues may arise if insertion is being performed within another department or clinic, such as urology or radiology.

Conclusion

This study demonstrated no statistical difference in prostate or PTV volumes ($P > 0.05$) between a CT acquired at fiducial marker insertion compared with a CT acquired a week later and thus suggests there is no significant oedema to justify imposing a delay between FM insertion and CT simulation.

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Conflict of Interest

The authors declare no conflict of interest.

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