Evaluation of seminal vesicle volume variability in patients receiving radiotherapy to the prostate.

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Abstract

Introduction

Prostate positional variability has been widely explored with seminal vesicle (SV) variability only coming into the forefront in recent years. While PTV margins and preparation protocols ameliorate the effects of bladder and rectum volume changes on prostate, studies on SV variation have looked at position only and not volume variability.

Aim

The aim of this study was to investigate whether interfraction volume variability of the seminal vesicles can exist in patients receiving radiotherapy to the prostate.

Method

SV variability was investigated by comparing 4 on-treatment Cone Beam Computer Tomography (CBCT) scans to a planning Computer Tomography (CT) image for two patients receiving prostate radiotherapy. Variation in volumes (cm^3) were compared with intraobserver variation for each case.

Results

SV volume variability was seen in both patients with the largest change in volume being 78.38%. This variance was considerably (between 2 and 10 times) larger than the measured intraobserver variance

Conclusion

This study identified potential for daily SV volume variability in patients receiving prostate radiotherapy. Future large scale studies are warranted to identify the extent of this motion and potential clinical impact. Evidence-informed PTV margins and possible SV volume control protocols may need to be adopted.

Introduction

The seminal vesicles (SV) sit posterior and inferior to the bladder and laterally to the ductus deferens. They are blind-ended tubes containing multiple pockets that are encased within connective tissue and are approximately 5-7cm in length.[1] The SVs are always included within the Clinical Target Volume (CTV) for intermediate and high-risk prostate cancers due to the higher risk of spread.[2]

Movement of the prostate and SVs has been documented in several studies with a 2005 paper[3] first identifying a large distal SV displacement. It was the distal SVs which were also noted to have contributed to a greater variability in a 2012 study[4] which compared the dosimetric impact of displacement of the prostate and SVs in two groups; full SV (FSV) and proximal SV (PSV). They concluded that the SVs move independently of the prostate and that their displacement was greatest in the distal region of the SVs; meaning variability increases with distance from the prostate. Even after correcting for changes in prostate position, the position of the SVs can still vary throughout treatment, compared to the position on the planning computed tomography (CT) scans. This poor correlation between SV and prostate position was confirmed by a 2008 fiducial marker study[5] which found variations in SV position to be independent of prostate fiducial markers. Despite these findings, it is common to prioritise prostate coverage over SV coverage because the prostate contains the largest portion of the Gross Tumour Volume (GTV). Since SV variation has a small impact on GTV match results, this can increase the simplicity and speed of on-line image matching.[3]

Organ-at-risk (OAR) motion of bladder and rectum has been shown to exceed that of prostate and SV variability[3] meaning that prostate and SV deformation have long been considered to be second order effects behind OAR motion.[6-8] The evidence underpinning this, however, largely predates the introduction of image-guided radiotherapy (IGRT) and the resulting change in Planning Target Volume (PTV) margins.[9,10] A 2018 paper[11] concluded that OAR motion is not the main cause of prostate and SV motion although it can contribute. There is an element of compromise inherent in consideration of OAR motion with the PTV margin commonly being reduced posteriorly as per the widely accepted “conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer” (CHHIP) trial protocol[9] to minimise rectal toxicity. Tumours often reside in the posterior peripheral region of the prostate; some authors have suggested that this factor along with reduction of margin size in this area can lead to tumour underdosage.[12]

Apart from the posterior margin, traditionally, an equal PTV margin is placed around the prostate and SVs. However several authors[3-5] confirm that SV motion and deformation is independent of prostate motion and suggest that a separate PTV margin should be considered for the SVs to prevent underdosage. Evidence from a 2012 study[4] found that a 5mm margin was adequate for setup of PSV prostate patients and capable of achieving target V_{95} coverage in 90% of the patients (mean V_{95}= 99.6+/-0.8%). For "full" FSV patients this margin was insufficient leading to satisfactory V_{95} coverage in only 45% of patients (mean V_{95}=97.9+/-2.4%). The study clearly identified the need for a separate margin for the prostate and seminal vesicles.

Guidance from 2007[13] states that in patients with one or more risk factors, (Prostate Specific Antigen (PSA) >10, Gleason ≥ 7, > T2a, or percentage of positive biopsy > 50%) the risk of SV invasion is at least 15% and the seminal vesicles should be included in the target volume. Despite this, in clinical image-guided radiotherapy (IGRT) matching, the SV match is secondary to the prostate due to their reduced significance in terms of tumour control. Although the evidence suggests that only the proximal SVs should be included in the target volume, some authors[13] have suggested that this evidence is contradictory and an insufficient basis for applying this practice to all patients. Currently there is little data that has considered SV position throughout prostate treatment, and in particular, no evidence related to SV volume variability. Accordingly, the aim of this preliminary investigation was to investigate whether interfraction volume variability of the seminal vesicles could be present in patients receiving radiotherapy to the prostate.

Methods

Patient data sets

This pilot study aimed to measure SV volumes on planning CT and IGRT conebeam (CBCT) images from 10 patients treated with radical prostate radiotherapy. Patients were chosen at random from those who had at least 4 on-treatment images taken between March and July 2018; at the centre in question this included patients enrolled in the PIVOTAL boost study.[14] Planning CT images were used as a reference, along with 4 other subsequent CBCT on-treatment images obtained using an on-board imager (OBI) immediately after patient set-up. Prior to all scans, patients followed a preparation protocol including a full bladder and rectal enema. They were scanned in a head first supine position and immobilisation included omniboard, foot stocks, and headboard for each treatment.

SV delineation

Delineation of the SVs was carried out using treatment planning software by two users; a third-year radiotherapy student (user 1), and an experienced outliner (user 2). Credentialing was performed through repeat contouring of twelve training datasets to ensure intra-observer variability was minimised. Three repeats of SV contours (OL1, OL2, OL3) were performed for every acceptable data set; this enabled intra-observer variability to be calculated as well as average daily image variability for each patient. The inferior border of the SVs was difficult to distinguish on the CBCT images; therefore, in order to reduce variability due to unclear borders, the inferior border for all fractions was equalised. This was not necessary for the superior borders of the SVs as these were clearer to see and any subsequent variability would be due to volume variation above the defined level.

Data analysis

In this study the volume of each SV contour on each image was calculated; variance and standard deviation (SD) for intra-observer volume variability (IOVV) and interfraction volume variability (IFVV) were then calculated. Comparing these values allowed the impact of intra-observer variability[15] in outlining to be assessed. If IFVV was much greater than IOVV then it would indicate a true variation of volume.

Ethical issues

This study was classified as a "service evaluation" by the hospital Audit Committee; since retrospective anonymised patient data was utilised, consent was not mandated.

Results

Not all the gathered data had sufficient CBCT image quality to allow confidence in delineation of seminal vesicle volumes. The aim of this preliminary study was to identify if volume variation occurred in any prostate patients rather than to objectively quantify any potential effect. Accordingly the following two cases illustrate results confirming that this is a potential issue worthy of further quantitative study. Tables 1-4 present measured SV volumes per case (Case One and Two), user (User One and Two), fraction (a-e) and outlining (OL1-3).

Noteworthy examples from this data are depicted in Figure 1 with overlaid contours highlighting volumetric and positional variation in Case One. In particular, a large volume variation can be seen in the bottom left image. In contrast, the bottom right image demonstrates an identical volume but clear positional variation. Variability of the mean outlined volumes is depicted graphically for each

case and user in Figure 2. The data anonymisation process removed date stamps from the datasets so the chronological order of fractions is unknown.

Summary of results

It can be seen that for these selected cases there was considerable variation on SV volume which was much higher than intraobserver outlining variability, as seen in Table 5. The smallest and largest volumes for each patient and each user were used to calculate the maximum percentage increase in volume as seen in Table 6.

Discussion

Limitations

There were several key limitations to this study. CBCT image quality for many of the sampled datasets was insufficient to outline SV volumes with confidence. The cases presented here were the exception and future work will need to draw on alternative imaging modalities to quantify variation with confidence. In addition, neither outliner in this study was a clinician; this was ameliorated to some extent through use of training, credentialing and repeat outlining. Expertise and confidence in outlining was felt to be more valuable than clinical interpretation for this phase of the study. Intraobserver variability was measured in order to eliminate this as an explanation for the findings. The accuracy of intraobserver variation has been estimated to be around 11% compared to accuracy of shape variation which was around 5%.[3] Time between intraobserver delineation seems to affect variability with short term intra-observer variability demonstrated to have no significant effect on treatment planning.[16] In this study, outlining was all performed within three days to minimise this potential impact. The small number of cases, while normally a limitation, in this case was a strength as the aim of the work was to identify the potential for this variation and not to measure it. The detection of two cases of volume variation within such a small sample strongly suggests a high overall incidence in the wider population.

Causes of variability

It is clear from the findings of this pilot study that in at least some cases, there is potential for interfractional SV variability in prostate patients. Future work intends to quantify the magnitude and frequency of these changes as well as identify impacting variables. The shrinking effect of hormone therapy on the prostate, for example, is well documented.[11] yet none of the reported data includes SV volumes so it may be useful to study the effects of these in SV variability in future studies.

Frequency of ejaculation has certainly been demonstrated to impact on SV volume in a number of studies on healthy individuals. [17,18] A 2017 magnetic-resonance image (MRI)-based study identified significant changes in 13 out of the 15 participants with mean volumes decreasing from 6.45 to 4.80cm^3.[17] This variation compares well with the variation identified in this study and would suggest that ejaculation whilst on radiotherapy treatment could be a factor impacting on SV volume and position. It is unknown how relevant these findings would be when applied to the more challenging prostate radiotherapy cohort and their well-documented sexual function issues.[19] Recent findings, however, indicate the therapeutic value of both medication and regular sexual activity in penile rehabilition and long-term preservation of sexual function.[20]

Clinical implications of variability

It is unknown what the true incidence and extent of SV volume is amongst radiotherapy patients or, indeed, whether the variability is associated with clinical outcomes. It is already clear that SV motion independent of prostate position is a problem[4] and that existing PTV margins may not be appropriate in all cases with distal SV involvement. This preliminary work compounds these findings by detecting volume variation and, if significant, this may warrant individual derivation of PTV margins according to measured variability. Variability may impact on dosimetry and local control rates and future studies using daily MR imaging alongside monitoring and control of potential variables will aim to identify the true clinical implications of this study's suggested variability.

Conclusion

This study concluded that there is potential for daily SV volume variability in patients receiving prostate radiotherapy, with up to 78.38% variation identified. More research is needed to determine how many and which patients this could impact on as well as to quantify the magnitude of variation and potential clinical impact. Future studies using MRI data, monitoring of variables and a larger number of patients are planned.

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Tables

Table 1: IFVV for Case One and User One

Fraction	OL1	OL2	OL3	Mean	Variance	S.D
a	4.4	4.4	3.7	4.17	0.11	0.33
b	5.6	5.2	5.3	5.37	0.03	0.17
c	5.3	5.6	5.7	5.53	0.03	0.17
d	6.6	6.2	6.3	6.37	0.03	0.17
e	5.6	5.2	5.5	5.43	0.03	0.17
Mean	5.5	5.32	5.3	-	-	-
Variance	0.50	0.35	0.75	-	-	-
S.D.	0.70	0.59	0.87	-	-	-

Table 2: IFVV for Case One and User Two

Fraction	OL1	OL2	OL3	Mean	Variance	S.D
a	4.1	4.7	4.6	4.47	0.07	0.26
b	4.8	4.9	4.5	4.73	0.03	0.17
c	4.5	4.9	4.9	4.77	0.04	0.19
d	6.4	4.9	5.3	5.53	0.40	0.63
e	5.5	4.9	5.7	5.37	0.12	0.34
Mean	5.06	4.86	5.0	-	-	-
Variance	0.66	0.01	0.20	-	-	-
S.D.	0.81	0.08	0.45	-	-	-

234 **Table 3: IFVV for Case Two and User One**

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Fraction	OL1	OL2	OL3	Mean	Variance	S.D
a	9.3	8.5	9.5	9.10	0.19	0.43
b	8.8	8.6	8.4	8.60	0.03	0.16
c	8.1	7.4	8.1	7.87	0.11	0.33
d	7.6	8.5	8.0	8.03	0.14	0.37
e	8.6	8.7	9.0	8.77	0.03	0.17
Mean	8.48	8.34	8.60	-	-	-
Variance	0.34	0.23	0.32	-	-	-
S.D.	0.58	0.48	0.57	-	-	-

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238 **Table 4: IFVV for Case Two and User Two**
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Fraction	SV1	SV2	SV3	Mean	Variance	S.D
a	9.60	9.10	8.70	9.13	0.14	0.37
b	9.40	9.40	10.20	9.67	0.14	0.38
c	6.10	6.10	6.80	6.33	0.11	0.33
d	6.70	6.80	7.40	6.97	0.10	0.31
e	7.50	8.50	8.50	8.17	0.22	0.47
Mean	7.86	7.98	8.32	-	-	-
Variance	1.99	1.69	1.37	-	-	-
S.D.	1.41	1.30	1.17	-	-	-

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Table 5: Summary of SV volume variation.

		Case One		Case Two	
		User One	User Two	User One	User Two
IOVV	Mean variance	0.04	0.13	0.10	0.14
	Mean SD	0.20	0.32	0.29	0.37
IFVV	Mean variance	0.53	0.29	0.30	1.69
	Mean SD	0.72	0.45	0.54	1.30

247 **Table 6: Smallest and largest volumes recorded and percentage increases**

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	Minimum	Maximum	% increase
SVOL5, User 1	3.7cm-^{3}	6.6cm^{3}	78.38%
SVOL5, User 2	4.1cm^{3}	6.4cm^{3}	56.10%
SVOL6, User 1	7.4cm^{3}	9.5cm^{3}	27.03%
SVOL6, User 2	6.1cm^{3}	10.2cm^{3}	67.21%

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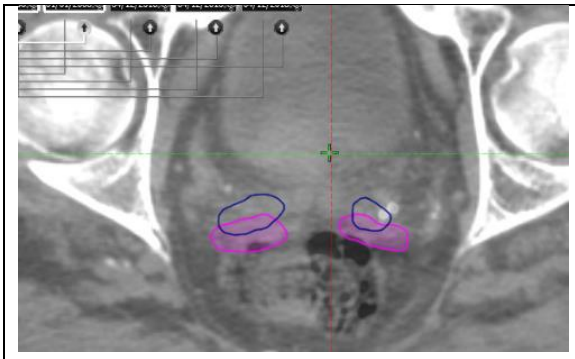
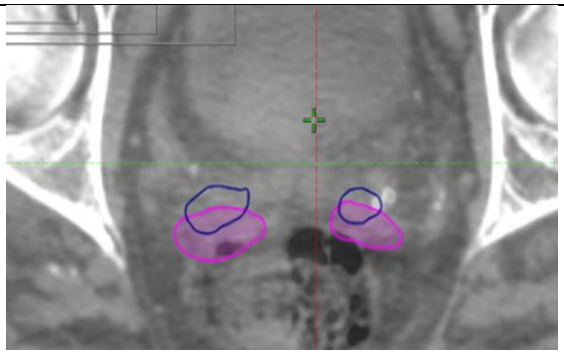
Figure 1: Example variation in Case One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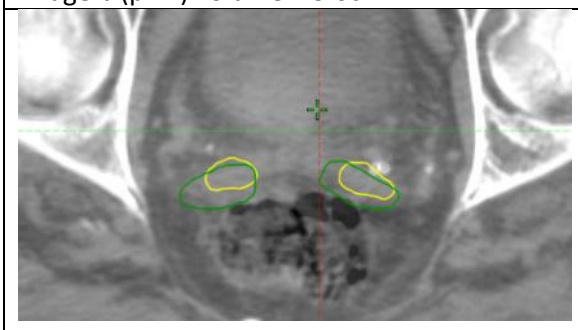
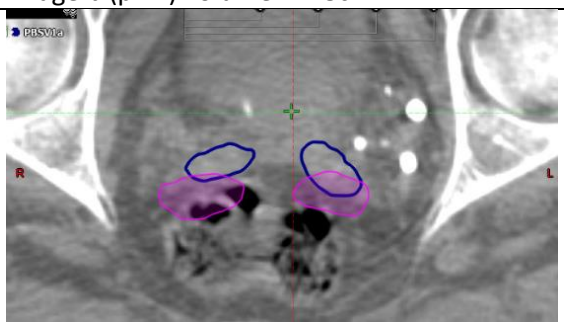
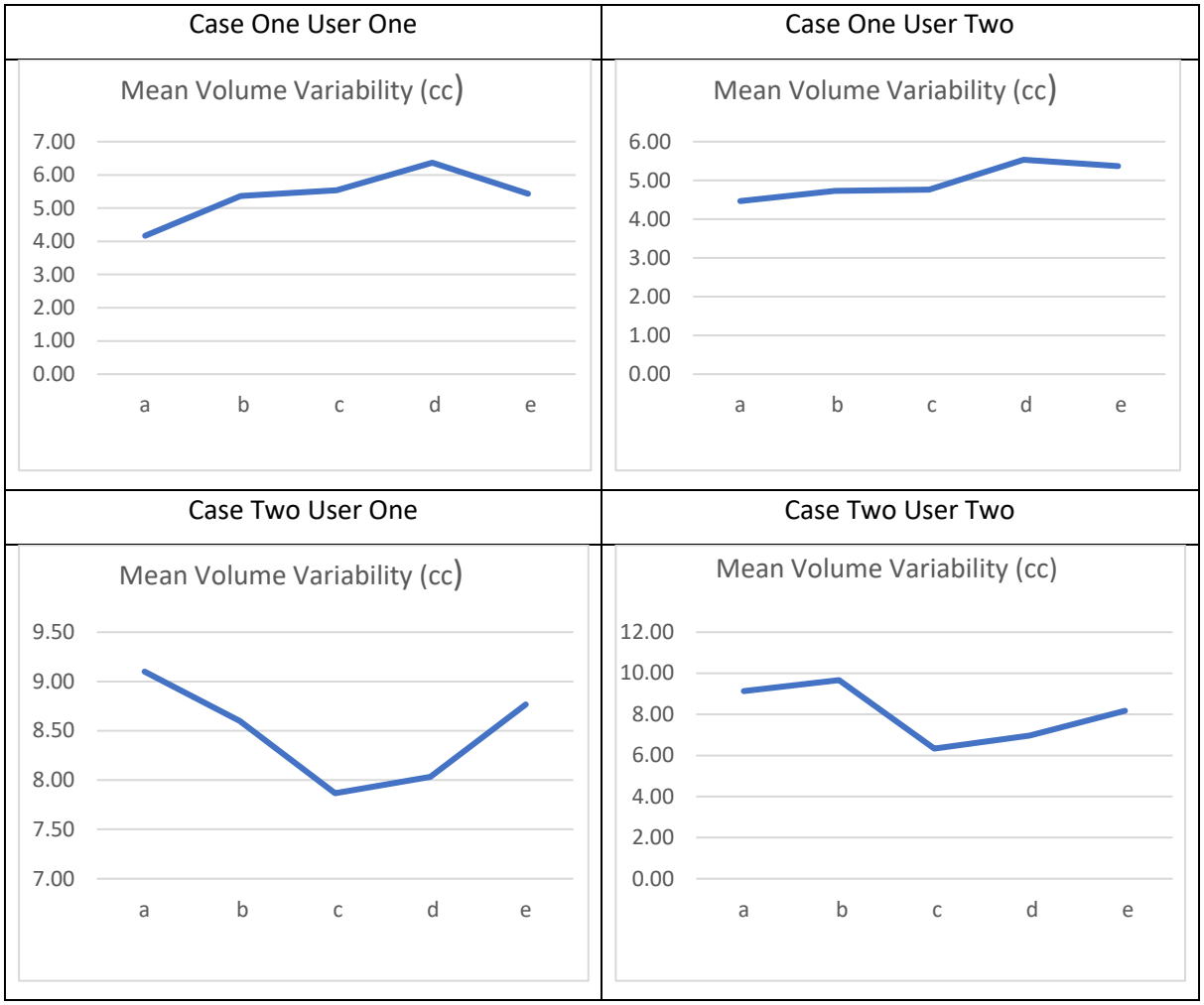
	

Image a (yellow) volume = 3.7cm^3 Image d (green) volume = 6.6cm^3	Image a (blue) volume = 4.7cm^3 Image e (pink) volume = 4.9cm^3

Figure 2: Mean volume variability (in cm^3)



Captions for illustrations

Figure 1: Example variation in Case One

Figure 2: Mean volume variability (in cm^3)