Radiological evaluation of an iodised hydrogel for prostate radiotherapy applications

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\textbf{A B S T R A C T}

\textbf{Purpose:} Physical separation of healthy tissue and target volumes in prostate radiotherapy through the insertion of hydrogel can improve patient toxicity rates. An iodised hydrogel may provide anatomical separation of prostate and rectum while being easily visualised through radio-opacity. The aim of this study was to characterise SpaceOAR Vue\textsuperscript{\textregistered} in kilovoltage (kV) images and megavoltage (MV) radiotherapy treatment planning.

\textbf{Methods:} Two cassettes were 3D-printed, one filled with water and the other with SpaceOAR Vue\textsuperscript{\textregistered}. Transmission dose through each cassette was measured in slab phantom geometry and compared for 6MV and 10MV photon energies. The SpaceOAR Vue\textsuperscript{\textregistered} slab phantom setup was simulated using computed tomography (CT) and a treatment plan created. The plan was calculated with the hydrogel segmented and material assignment set to water, and the resultant dose compared to corresponding measurement doses. The first 5 patients treated with SpaceOAR Vue\textsuperscript{\textregistered} were assessed with the volume and Hounsfield units (HU) of the hydrogel evaluated in CT and cone beam computed tomography (CBCT) imaging.

\textbf{Results:} Transmission through Water and SpaceOAR Vue\textsuperscript{\textregistered} agreed to within 0.5\% for both photon energies. Furthermore, the segmentation of SpaceOAR Vue\textsuperscript{\textregistered} and material assignment to water, resulted in a plan dose that agreed to measurement to within 0.5\%. Clinically, the SpaceOAR Vue\textsuperscript{\textregistered} volume and HU did not vary over patient treatment course, however was found to display differently on different kV imaging modalities.

\textbf{Conclusions:} SpaceOAR Vue\textsuperscript{\textregistered} was found to be radio-opaque on kV images, but dosimetrically behaved similarly to water in MV treatment beams, making it suitable for clinical use.

1. Introduction

Definitive prostate radiotherapy has been shown to support favourable survival outcomes for the majority of nonmetastatic patients, with most alive 10 years post-intervention [1]. As a result, a number of techniques have been implemented to reduce late toxicity rates, primarily of the rectum and bladder [2].

Image-guided Radiotherapy (IGRT) combined with volumetric kilovoltage (kV) imaging such as cone beam computed tomography (CBCT), has improved the geometric accuracy of treatment by visualising anatomy-of-the-day and enabled patient setup adjustment where necessary. This improvement in geometric accuracy complimented the use of complex treatment delivery such as intensity modulated radiotherapy (IMRT) [34], which in turn has been used for dose escalation and hypofractionation [56].

A common method of reducing organ at risk (OAR) dose was to introduce a physical separation of the healthy tissue from the target volume [7]. This can be achieved using a rectal retractor [8], or trans-perineal insertion of peri-rectal hydrogel [9]. SpaceOAR\textsuperscript{\textregistered} (Augmenix, Waltham, USA) is one such hydrogel currently available [10]. SpaceOAR Vue\textsuperscript{\textregistered} is a hydrogel with the addition of trace amounts of iodine (~1\%), aiming to separate the prostate and anterior rectal wall, and to improve delineation of the boundary between both organs [11]. This product utilises iodine’s radio-opacity on kV images, while still approximating tissue in a therapeutic megavoltage (MV) photon beam.

Radiotherapy treatment plans utilise kV computed tomography (CT) images to capture patient spatial anatomy and tissue radiodensity measured as Hounsfield Units (HU), where the latter is used for MV dose calculation. However, some substances such as iodine are visualised with high radiodensity or HU at kV energies, but do not have a correspondingly high megavoltage beam radiodensity. This can result in erroneous MV dose calculation without user intervention. This study aimed to characterise SpaceOAR Vue\textsuperscript{\textregistered} for both kV imaging and MV photon dosimetry, and to determine an appropriate voxel HU override to

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enable accurate treatment planning.

2. Method and materials

Two identical 25 cc cassettes were 3D-printed from thermoplastic monomer (PLA) to create a 5 cm $\times$ 5 cm $\times$ 1 cm volume, with 2 mm wall thickness, as seen in Fig. 1. The external dimensions were 5.4 cm $\times$ 5.4 cm $\times$ 1.4 cm. One was filled with 25 cc of SpaceOAR Vue™, the other with 25 cc of water.

2.1. MV photon dosimetry

The attenuation properties of SpaceOAR Vue™ were measured relative to water for both 6MV and 10MV photon beam energies in a slab phantom geometry using a Varian Truebeam linear accelerator (Varian Medical Systems, Inc., Palo Alto, CA). The slab phantom configuration comprised of 5 cm CIRS Plastic Water® build-up and 10 cm as backscatter, with the water-filled cassette placed along the central axis (CAX) and packed with gel bolus to a thickness of 14 mm. The phantom was oriented such that the centre of the cassette was positioned at source to axis distance (SAD) of 100 cm, as seen in Fig. 2.

The PTW Advanced Markus® parallel plate chamber was used to acquire transmission readings at 5 points positioned at 1 cm increments along CAX, starting at the distal surface of the cassette. A 4 cm $\times$ 4 cm field size was used to deliver 100 monitor units (MU). This process was repeated for the SpaceOAR Vue™-filled cassette. Each measurement was repeated to ensure the reading was not monotonically increasing or decreasing, and to ensure the coefficient of variation was no more than 0.5%.

A reference reading was taken using the PTW Advanced Markus® parallel plate chamber for both 6MV and 10MV beams by delivering 100 MU to the CIRS Plastic Water® slab phantom. The linear accelerator was calibrated traceable to the primary standard following the IAEA TRS-398 international code of practice [12], such that 100 MU delivered 100 cGy to depth of dose maximum for each energy under those conditions. The source to surface distance (SSD) was 100 cm and the field size set to 10 cm $\times$ 10 cm with the chamber positioned at 5 cm physical depth along CAX. The water-equivalent depth of the chamber position was determined using the product of the physical depth and mass density of the plastic water material as per TRS-398 [12]. A percentage depth dose correction was applied to calculate the chamber reading representing 100 cGy for each energy.

The ratio of transmission readings to PDD-corrected reference reading was used to determine the relative transmission dose for each measurement position and for both energies. The temperature and pressure of the chamber was monitored, and all chamber readings corrected as per TRS-398 [12].

2.2. TPS override determination

The experimental setup outlined above was replicated with the SpaceOAR Vue™ cassette and scanned using the Phillips Brilliance CT using a 120 kV fan-beam. A treatment plan replicating the experimental dose delivery was created in the Varian Eclipse treatment planning system (TPS) with the Acuros External Beam (AXB) algorithm v15.606 (Varian Medical Systems, Inc., Palo Alto, CA), utilising a 1 mm dose grid, reporting dose to medium ($D_m$). The plan was calculated with fixed monitor units for both 6MV and 10MV beams, and the dose corresponding to chamber measurement positions recorded. The SpaceOAR Vue™ was then segmented and the mean HU and TPS material composition of the material recorded. The structure was then overridden to 0 HU, and the material assignment set to water as per the vendor’s treatment planning guide and based on the conversion of HU to mass density [13]. The plan was then recalculated, and doses were compared to the corresponding doses obtained from chamber measurements.

2.3. Clinical opacity of space OAR Vue

The opacity of SpaceOAR Vue™ with respect to clinical kV imaging was characterised through assessment of the first 5 patients in our department to receive SpaceOAR Vue™. The hydrogel was delineated on the simulation CT dataset for each patient and the mean CT number and structure volume recorded. Patients were treated with either 5 or 20
fractions and received daily kV CBCT imaging on a Varian Truebeam, or Varian Halcyon (Varian Medical Systems, Inc., Palo Alto, CA). The process of delineating the hydrogel was repeated on 5 CBCT datasets and the same parameters recorded. Patients receiving long course treatment sampled fractions 1, 5, 10, 15 and 20, while CBCT images were assessed every fraction in the 5-fraction cohort. Consent for the use of patient data was obtained with ethics approval (ref LNR/15/HAWKE/355).

3. Results

3.1. MV photon dosimetry

Table 1 displays the measured dose for both the water-filled and SpaceOAR Vue™-filled cassette configurations at each measurement depth.

<table>
<thead>
<tr>
<th>Position no.</th>
<th>6MV</th>
<th>10MV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (cGy)</td>
<td>Hydrogel (cGy)</td>
<td>Diff (%)</td>
</tr>
<tr>
<td>1</td>
<td>80.65</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2</td>
<td>75.58</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3</td>
<td>71.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>4</td>
<td>67.33</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>5</td>
<td>63.31</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Table 2 displays the TPS-calculated dose for both scenarios; the SpaceOAR Vue™ being overridden to water and 0 HU as per vendor recommendations. Calculation conducted with fixed MU (100 MU) for both 6 MV and 10 MV beam energies.

<table>
<thead>
<tr>
<th>Position no.</th>
<th>6MV</th>
<th>10MV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogel (cGy)</td>
<td>%Diff from measured</td>
<td>Override (cGy)</td>
</tr>
<tr>
<td>1</td>
<td>79.8</td>
<td>-0.6</td>
</tr>
<tr>
<td>2</td>
<td>75.4</td>
<td>-0.1</td>
</tr>
<tr>
<td>3</td>
<td>71.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>4</td>
<td>66.9</td>
<td>-0.7</td>
</tr>
<tr>
<td>5</td>
<td>63.0</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

Fig. 3. The volume of SpaceOAR Vue™ delineated on both clinical planning CT and 5 CBCT datasets per patient. For the CBCT images the interquartile range, median (line), and mean (circle) volume contoured for each patient is shown.

Fig. 4. The mean HU of SpaceOAR Vue™ delineated on both clinical planning CT and corresponding CBCT datasets per patient. For the CBCT images the interquartile range, median (line), and mean (circle) Hounsfield Units contoured for each patient is shown.

All measurement points were found to have excellent agreement, with dosimetric variation less than 0.5 % when comparing the transmission dose through the water-filled and SpaceOAR Vue™-filled cassettes.

3.2. TPS override determination

Table 2 displays the dose to the 5 measurement points calculated in the TPS for both scenarios: the SpaceOAR Vue™ and the water override, compared to the corresponding chamber measurements.

The mean HU of the SpaceOAR™ Vue structure was 212, with a TPS material composition of 90 % cartilage and 10 % bone. With this material composition the TPS transmission dose calculation agreed with measurement to within 1.0 %. When using the recommended material...
4. Discussion

This study determined that the low concentration of iodine present in the hydrogel did not exclude the product from behaving approximately equivalent to water in the MV energies tested. This was shown through the close agreement of transmission measured through equivalent volumes of liquid water and SpaceOAR Vue™.

The largest variation in chamber dose measurements were seen closer to the distal surface of the cassette (position #1). This may be a result of small phantom setup variation. Furthermore, this may be a result of real dosimetric variation in the ‘rebuild-up region’ [14] due to MV photon transmission through hydrogel/water and PLA. In this case the reported dose variation was ≤0.5 % and deposited within approximately 0.3 mm of the plastic distal surface according to the effective point of measurement of the Advanced Markus chamber. The magnitude of dose variation is in line with uncertainties expected from phantom dosimetry [15], thus the overall dose variation may be seen as insignificant to overall plan quality and would not impact dosimetric plan objectives.

This study determined that the vendor-recommended material assignment of the hydrogel as water, was appropriate as the overridden SpaceOAR Vue™ matched dosimetric measurements to within 0.5 %. This data suggests that TPS modelling uncertainties, such as geometric set up variation between chamber measurement and CT image acquisition may account for variation, rather than the impact of the material assignment. The resolution of both CT datasets was 1.17 mm within each slice, and therefore the limit of geometric precision. According to local TPS data, variation in the TPS plan SSD of 1 mm could result in dosimetric difference of approximately 0.2 %, while variation in the phantom slab thickness of 1 mm would result in approximately 0.5 % dosimetric difference.

Furthermore, a calculation of the experimental setup without a material override was performed to characterise the impact of SpaceOAR Vue™ on a clinical plan. The impact was subtle and resulted in average doses of 0.5 % and 0.4 % less than the overridden hydrogel for 6MV and 10MV, respectively, and up to 1 % less than measurement.

The opacity of SpaceOAR Vue™ in 5 clinical cases was assessed in planning CT and CBCT images. Firstly, even the low concentration of iodine (~1%) within the product was radio-opaque when viewing a kV image, with the mean CT numbers reported ranging between 139 and 168 HU when viewed on a planning CT acquired at 120 kVp. This is distinguishable from muscle and adipose tissue, which are represented by approximately +50 and −50 HU, respectively.

A lower volume of SpaceOAR Vue™ was seen when viewed on a clinical CBCT. While this may represent a real loss of hydrogel volume, it more likely is a result of a poorer soft tissue resolution and image quality typical of CBCT images. Furthermore, the volume of SpaceOAR Vue™ delineated on the CBCT was consistent between fractions for each patient and did not appear to change over the time periods assessed. This is corroborated by Saito et al, where a reduction in conventional SpaceOAR volume between simulation to the end of treatment was less than 1 cm³ [16], however this study was conducted over a short time-period. It was also observed qualitatively that the geometric distribution or shape of the hydrogel could vary between fractions, as seen in Fig. 5, however this was likely a result of variation in rectal distention.

No relationship between mean HU of SpaceOAR Vue™ delineated on planning CT and CBCT datasets per patient was seen, however the HUs were consistent within repeated CBCT images for each patient. This was not an unexpected result due to the difference in the calibration curve of attenuation to HU, for CBCT compared with CT [17]. Rather, the main takeaway was that the iodised hydrogel was still visible using on-board imaging. Furthermore, the CBCT datasets from patients 3 and 5 were acquired with 140 kVp, as compared to 125 kVp, and contained significant photon starvation artefacts due to large separation of the patient. The increased mean HU seen in the hydrogel volumes were likely due to a combination of the beam energy change and low imaging signal, as the hydrogel was present in the region of affected voxels.

Fig. 5. A) axial ct slice of patient 4 with spaceoar vue™ in place contoured in green, b)-f) Axial CBCT slice of the same patient in the treatment position on fractions 1–5. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
SpaceOAR Vue™ has the potential to improve both planning and treatment visualisation of the rectum and prostate, as shown in Fig. 5. It is expected that the time and expertise required to register Magnetic Resonance (MR) images to a planning CT, as well as a treatment CBCT to planning CT, will be reduced due to the clear visualisation of opaque hydrogel. For patients who are unable to tolerate MR imaging, it can be used to aid organ delineation on CT images [11].

Furthermore, a significant benefit may be seen for patients undergoing CBCT-guided online adaptive radiotherapy. This on-couch adaptation utilises anatomy-of-the-day contours segmented on the session CBCT to optimise a new treatment plan [18]. Soft-tissue resolution of CBCT images can be poor in comparison to CT images, which during an adaptive fraction can increase the time taken to segment anatomy, as well as reduce the accuracy of the final contours [1920]. Improved visualisation of the prostate and rectum border could result in improved accuracy of the final adaptive plan, which in turn could improve local control and minimise toxicity.

A limitation of this study was that the MV characteristics of SpaceOAR Vue™, while modern proton therapy is delivered over 360° (such as with IMRT). However, further evaluation at oblique angles of incidence would introduce additional geometric uncertainty in the experimental setup.

5. Conclusion
SpaceOAR Vue™ was found to be radio-opaque on kV images, with a HU distinguishable from soft tissue such as muscle and adipose, aiding in the visualisation of the prostate and rectum. The measured MV dosimetric difference between SpaceOAR Vue™, containing a low concentration of iodine, and liquid water was found to be clinically negligible. The process of contouring the hydrogel and assigning the material to water, was found to accurately represent the MV dosimetry when using kV images for treatment planning.

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.

References