Spacer stability and prostate position variability during radiotherapy for prostate cancer applying a hydrogel to protect the rectal wall

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ABSTRACT

Background and purpose: The aim was to evaluate the spacer dimensions and prostate position variability during the course of radiotherapy for prostate cancer.

Materials and methods: CT scans were performed in a group of 15 patients (G1) after the 10 ml injection of a hydrogel spacer (SpaceOAR™) and 30 patients without a spacer (G2) before the beginning of treatment (CT1) and in the last treatment week, 10–12 weeks following spacer implantation (CT2). Spacer dimensions and displacements were determined and prostate displacements compared.

Results: Mean volume of the hydrogel increased slightly (17%; p < 0.01), in 4 of 15 patients >2 cm³. The average displacement of the hydrogel center of mass was 0.6 mm (87% < 2.2 mm), −0.6 mm (100% < 2.2 mm) and 1.4 mm (87% < 4.3 mm) in the x-, y- and z-axes (not significant). The average distance between prostate and anterior rectal wall before/at the end of radiotherapy was 1.6 cm/1.5 cm, 1.2 cm/1.3 cm and 1.0 cm/1.1 cm at the level of the base, middle and apex (G1). Prostate position variations were similar comparing G1 and G2, but significant systematic posterior displacements were only found in G2.

Conclusions: A stable distance between the prostate and anterior rectal wall results during the radiotherapy course after injection of the spacer before treatment planning. Larger posterior prostate displacements could be reduced.

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External beam radiation (EBRT) is a well established curative treatment for prostate cancer [1–4]. Increasing doses are known to improve biochemical control [5], but rectal toxicity is dose-limiting [6]. Rectal bleeding rates have been frequently evaluated in the literature [7–9]. Additionally, symptoms like pain, incontinence, frequency and urgency can potentially reduce quality of life [10,11]. Major technical advances, as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), are increasingly adopted to allow accurate targeting with the best possible protection of normal tissues [12–17].

The application of a spacer to increase the distance between the prostate and the anterior rectal wall is an innovative technique helping to protect effectively the rectal wall [18–21]. Studies applying a hydrogel spacer have shown that the rectal wall volume inside the 70 Gy isodose can be decreased by >50% [20,21]. As rectal toxicity is known to be associated with both total dose to a specific volume and the volume inside a specific isodose [5–9,22], a considerable reduction of toxicity can be expected.

A consistent protection of the rectal wall throughout a fractionated treatment is essential for a successful outcome. An ideal spacer is required to remain at the injected position and maintain the distance between the prostate and the rectum that has been calculated in the initial treatment planning computed tomography (CT) scan.

The aim of this study was to analyze changes throughout the treatment by comparing planning CT scans with CT scans performed in the last week of treatment. Spacer dimensions, spacer displacements, prostate displacements and changes of the distance between the prostate and anterior rectal wall were determined. Additionally, a group of conventionally treated patients was used as a reference for the displacements and distances without a spacer (CT scans performed at the same intervals).

Materials and methods

Hydrogel implant

The injection of a spacer gel (SpaceOAR™ System, Augmenix Inc., Waltham, MA) was performed in 18 patients with prostate cancer (PSA < 20 ng/ml, Gleason score < 3 + 4) in our department after local ethics committee approval. These patients have been in-
cluded in a multi-institutional phase II clinical trial (study sponsor: Augmenix Inc.). All patients have signed informed consent before being included in this study.

The SpaceOAR™ System is a polyethylene glycol gel (PEG) that polymerizes in seconds, creating a hydrogel space. In use, a 18 gauge needle is advanced via the transperineal approach to the space between the prostate and the rectum under transrectal ultrasound guidance. Following confirmation of proper needle location, the liquid hydrogel precursors are injected where they expand the perirectal space and then polymerize, or solidify without measurable temperature rise. The hydrogel amount was limited to 10 ml (15 ml for first patient). The hydrogel must maintain space for approximately three months during the complete duration of EBRT. It is absorbed in about six months with the degradation products cleared via renal filtration.

A total dose of 78 Gy was prescribed to the PTV in 2 Gy fractions with 15 MeV photons for an Elekta SLi linear accelerator (multileaf collimator with leaves projecting to 1 cm at isocenter) using a five-field intensity-modulated radiotherapy (IMRT) technique and daily ultrasound-based image-guided radiotherapy (IGRT).

Imaging

CT scans were performed before treatment (CT1) and in the last treatment week (CT2) in the group of patients after spacer gel injection (G1) to determine organ volumes and spacer volumes/dimensions, distances between the prostate and anterior rectal wall, as well as prostate (clinical target volume) displacements. CT scans were performed with a slice thickness of 5 mm from the anal canal up to the sacral promontory with a full bladder and a supine patient position. No bowel or intravenous contrast injection (G1) to determine organ volumes and spacer volumes. CT2) in the group of patients after spacer gel injection (G2). Comparing the subgroups G1 and G2, the only significant difference resulted for the bladder volume in the last treatment week. It was significantly smaller in the G2 subgroup (p < 0.01). No significant differences were found comparing the percentages of patients with a PSA > 20 ng/ml. Concerning volume changes of different patient groups, the Mann–Whitney U-test was applied. A homogeneity of variance test (Levene’s test) and the chi-square test (for the frequency of a displacement within certain distances) served to compare displacements for the subgroups with or without the spacer gel. All p-values reported are two-sided, p < 0.05 is considered significant.

Results

Prostate, rectum and bladder volumes in both subgroups at the specific intervals are presented in Table 1. Mean bladder and rectum volumes decreased in both groups (G1: 49 cm³ and 9 cm³; G2: 69 cm³ and 13 cm³, statistically significant only in G2). Comparing the subgroups G1 and G2, the only significant difference resulted for the bladder volume in the last treatment week. It was significantly smaller in the G2 subgroup (p < 0.01). No significant differences were found comparing the percentages of patients with a PSA < 10 ng/ml. Mean bladder and rectum volumes decreased in both groups (G1: 49 cm³ and 9 cm³; G2: 69 cm³ and 13 cm³, statistically significant only in G2). Comparing the subgroups G1 and G2, the only significant difference resulted for the bladder volume in the last treatment week. It was significantly smaller in the G2 subgroup (p < 0.01). No significant differences were found comparing the percentages of patients with a PSA < 10 ng/ml. 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![Fig. 1. Sagittal CT reconstruction demonstrating the definition of the levels of the base, middle and apex, as well as the points P1 (superior prostate/semenal vesicle), P2 (level of the bladder neck) and P3 (inferior prostate).](image)
was 17%. Spacer dimensions increased accordingly, predominantly at the base level, though the difference was found to be only small (Table 2). Examples of a patient with a constant spacer volume and a second patient with increasing spacer volume, particularly visible at the level of the prostate base, are shown in Fig. 2.

The mean (standard deviation) distance between prostate and anterior rectal wall before/at the end of radiotherapy was 1.6 cm (0.6 cm)/1.5 cm (0.6 cm), 1.2 cm (0.2 cm)/1.3 cm (0.3 cm) and 1.0 cm (0.4 cm)/1.1 cm (0.4 cm) at the level of the base, middle and apex. The corresponding distances in the G2 subgroup without a spacer were considerably smaller ($p < 0.01$ for all comparisons between G1 and G2): 0.9 cm (1.1 cm)/1.1 cm (1.0 cm), 0.3 cm (0.3 cm)/0.3 cm (0.3 cm) and 0.2 cm (0.1 cm)/0.2 cm (0.1 cm) at the level of the base, middle and apex. Differences between the respective distances in CT1 and CT2 have not been found to differ significantly.

Center of mass displacements of the prostate and displacements of points P1 (superior prostate/semenal vesicle), P2 (bladder neck) and P3 (inferior prostate) along the $y$-axis are presented in Table 3. No significant differences have been found in the homogeneity of variance test and chi-square test comparing the percentage of displacements $> 5$ mm. However, in contrast to the G1 group with a spacer, significant systematic posterior displacements have been found in the conventional G2 group ($>6.5$ mm in 27% vs. 0% in G2 vs. G1; $p = 0.03$).

**Discussion**

The application of a hydrogel spacer has been shown to be a very effective technique to reduce the dose to the rectal wall, potentially allowing a safe dose escalation to the prostate or hypofractionated treatments without detrimental bowel effects for the patient. Effects on dose distribution have been demonstrated recently in a cadaver study [20] and a clinical study evaluating

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**Table 1**

Mean volumes (standard deviation) before treatment (CT1) and in the last treatment week (CT2) ($p$-values refer to comparison between CT1 and CT2 within G1 or G2).

<table>
<thead>
<tr>
<th></th>
<th>G1 (spacer)</th>
<th>G2 (conventional)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT1 (cm$^3$)</td>
<td>CT2 (cm$^3$)</td>
</tr>
<tr>
<td>Prostate</td>
<td>56 (28)</td>
<td>56 (26)</td>
</tr>
<tr>
<td>Rectum</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Bladder</td>
<td>73 (36)</td>
<td>64 (22)</td>
</tr>
</tbody>
</table>

**Table 2**

Mean spacer gel volumes and dimensions (standard deviation) before treatment (CT1) and in the last treatment week (CT2).

<table>
<thead>
<tr>
<th></th>
<th>CT1 (cm$^3$)</th>
<th>CT2 (cm$^3$)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spacer volume</td>
<td>9.9 (1.6)</td>
<td>11.5 (2.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$x$-axis (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>2.3 (1.6)</td>
<td>2.5 (1.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Middle</td>
<td>3.3 (0.6)</td>
<td>3.4 (0.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Apex</td>
<td>2.5 (1.1)</td>
<td>2.5 (1.0)</td>
<td>0.94</td>
</tr>
<tr>
<td>$y$-axis (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>0.7 (0.5)</td>
<td>1.0 (0.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Middle</td>
<td>1.0 (0.2)</td>
<td>1.2 (0.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Apex</td>
<td>0.8 (0.3)</td>
<td>0.9 (0.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>$z$-axis (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>3.7 (0.6)</td>
<td>3.9 (0.7)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

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**Fig. 2.** Examples demonstrating a patient with a constant spacer volume (patient A) and a patient with increasing spacer volume during the treatment (patient B).
three-dimensional conformal and IMRT techniques before and after spacer injection [21].

This study demonstrates a stable protection of the rectum throughout the treatment. Distances between the prostate and anterior rectal wall were maintained at all analyzed levels. Mean distances were found to be at least 1 cm, in contrast to a usually direct adherence of the prostate and rectum over several cm in a normal anatomy. These results are encouraging for continuing to apply this method during radiotherapy for prostate cancer.

During the course of radiotherapy, bladder and rectum volumes decreased in the group with and without a spacer. These effects can be explained by to some extent increasing urinary and bowel urgency in the acute phase of the treatment [23,24]. Larger mean decreases and a statistical significance were only found without a spacer. The differences respecting the bladder volume can hardly be explained by the spacer. The most probable explanation is a difference between the treatments of the groups with and without the spacer. Patients without the spacer have been treated without IGRT. Patients treated with daily IGRT receive a daily feedback concerning the bladder volume. Ultrasound based imaging is relying on a satisfactory bladder volume, so that an intensive patient education results. A larger bladder volume is known to decrease the dose–volume-load to the bladder and to decrease radiotherapy associated toxicity [25,26].

Comparing CT scans before and after spacer injection in a recently published analysis [21], rectum volumes have been found to decrease as a result of the spacer injection in patients with initially larger rectum volumes, indicating a possibly improved bowel emptying. A smaller mean difference between CT scans before and in the last week of treatment might potentially indicate less bowel urgency in the group of patients with the spacer.

The hydrogel spacer could be identified at all analyzed levels with the exception of patients with larger prostates of at least 70 cm³ with no spacer at the level of the base. The injected volume of 10 ml might be inadequate for patients with larger prostates. However, the distance at the level of the base is frequently sufficient even without a spacer (mean of approximately 1 cm). Patients with larger prostate volumes sometimes present with large middle lobes that are invading the interior of the bladder. Furthermore, the rectum is frequently positioned more posteriorly with increasing distance from the anus (see also Fig. 1).

The spacer volume remained rather stable throughout the treatment for the majority of patients. It increased slightly in some patients, so that a statistically significant difference in comparison to the baseline volume resulted. This difference is predominantly the consequence of the changes at the level of the prostate base. A potential explanation is a tissue edema that is known to develop in the acute phase of radiotherapy and might have an effect on the spacer dimensions. Anatomically, the largest room for expansion is available at the base of the prostate. The measured displacements of the spacer center of mass displacements were only minimal and statistically not significant. The only mean displacement > 1 mm was found in the superior direction, which is the consequence of a slightly increasing volume at the base.

Prostate position variations as, for example, represented by the standard deviation, were similar in the patient groups with and without the spacer. The prostate position is known to be predominantly determined by the rectum filling (and only to a lower extent by the bladder filling) [23,24], so that the prostate and the spacer can be displaced to some extent. As a consequence of a decreasing rectum volume during the treatment, a systematic posterior displacement of the prostate usually results. It has been found to be statistically significant in the group without a spacer.

In the patient group with a spacer, larger posterior displacements were reduced significantly. Mean posterior displacements of the analyzed posterior points P1, P2 and P3 in relation to the planning CT scans before treatment were only small (<1 mm). Even a slight anterior mean displacement resulted at the level of the superior prostate/seminal vesicles, which again resulted from increasing spacer dimensions at this level.

Taking into account similar prostate position variations with or without hydrogel spacer, image guidance methods need still to be recommended urgently for position verification and a safe reduction of treatment margins around the prostate.

Conclusions

A stable distance between the prostate and anterior rectal wall results during the radiotherapy course after injection of the hydrogel spacer before treatment planning. Prostate position variations are comparable to patients who are treated conventionally without a spacer, but larger posterior prostate displacements could be reduced.

References


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