Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: Results of a multi-institutional phase II trial

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Purpose: To evaluate the safety and efficacy of an absorbable hydrogel when injected between the rectum and prostate to reduce rectal radiation toxicity in adult men undergoing Intensity Modulated Radiotherapy (IMRT) for treatment of low and intermediate risk prostate cancer.

Methods: This prospective, non-randomized, multi-center, single arm, open-label study included 52 men with a confirmed diagnosis of prostate cancer. They received transperineal injection of the hydrogel and 3–5 days after injection the simulation scans. All patients received IMRT (78 Gy delivered, 2 Gy per fraction). Space stability was evaluated by using MRI or CT. Gastrointestinal (GI) and genitourinary (GU) toxicity was assessed using RTOG/EORTC scoring system and proctoscopy after 12 months. The median follow up time was 12 months.

Results: Hydrogel application was straightforward using brachytherapy equipment and techniques, with minimal patient discomfort. Six patients (12%) experienced acute GI Grade 2 toxicity, with no patients experiencing Grade 3 or 4 toxicity. In addition, no patients had early late GI toxicity > Grade 2 after 12 months. The gel was stable during the course of radiotherapy and was not detectable in MRI after 9–12 months due to absorption in 42 of 43 patients.

Conclusion: These data demonstrated that the hydrogel is a safe method to displace the rectal wall away from the prostate therefore substantially reducing toxicity to the rectum.

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Prostate cancer is a serious threat to the health of men throughout the world. In the European Union (EU) over 345,000 cases of prostate cancer occurred in 2008 with over 87,000 of these resulting in death [1]. Furthermore, the incidence of new prostate cancer cases in 2010 was the highest of cancers among men in developed countries across the globe [2].

For cases of localized prostate cancer, external beam radiation therapy (RT) is a well-known curative alternative to surgery [3]. Increasingly, men choose radiotherapy for localized prostate cancer due to the perception that the risk of impotence and incontinence is lower than with surgery [4].

One of the risks associated with RT is the potential for rectal injury caused by direct mucosal damage from ionizing radiation. Unfortunately, most prostate cancers originate in the peripheral zone of the gland, the area adjacent to the rectum. Therefore, effective treatment of the tumor frequently exposes the rectum to high levels of radiation [5]. However, the success of primary radiation therapy of localized prostate cancer is correlated with the given dose [5–7].

Radiation oncologists must balance the treatment of cancerous tissue with sparing the radio-sensitive rectum from unacceptable high side effects. For this reason the rectum is the most dose-limiting structure in prostate cancer RT.

Absorbable in situ polymerizing polyethylene glycol (PEG) based hydrogels have been used as dural [8], vascular [9], and lung sealants [10]. This paper reports on the clinical outcome of high-dose radiation therapy used to treat adenocarcinoma of the prostate and the acute and 12 months side effects when using a PEG based spacer gel between rectum and prostate in a European multi-institutional phase II trial.

Patients and methods

This was a prospective, non-randomized, multi-center, single arm, open-label trial involving 52 men with a pathologically confirmed diagnosis of clinical stage T1 or T2 prostate cancer.

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who were indicated for a course of RT were enrolled in this study at four sites in Central Europe (University of Heidelberg (n = 21), University of Aachen (n = 20), NKI-AVL Nederlands Kanker Instituut Amsterdam (n = 7) and University of Geneva (n = 4)).

Most of the patients (96%) were Caucasian and the mean age of the group was 68.9 years (Table 1). The baseline characteristics were reflective of a low and intermediate risk prostate cancer population. The mean duration of the initial prostate cancer diagnosis was 110 days and half of the patients (50%) were classified in the T1c stage. There was an approximately even distribution of Gleason Scores 6 and 7. Patient mean PSA levels were 6.9 ± 4.5 ng/ml while mean prostate volume was 56.9 ± 20.4 cc (±SD).

Part way through the study it was appreciated that less hydrogel would be as effective in space creation, so the injected hydrogel volume was decreased from 15 ml to 10 ml. Additionally the routine use of stool softeners during radiation therapy was initiated to address the theoretical concern of rectal wall compression between the spacing gel and the compacted stool. Finally, changes to the application technique, including the use of side-fire transrectal ultrasound probe, a stepper for probe/image stabilization, and the use of a stand-off balloon improved needle control and spacer placement. Patients preceding these changes (Cohort 1, n = 23) had similar baseline characteristics to those enrolled after these changes (Cohort 2, n = 29) (Table 1).

About one-fourth (23%) of the patients had a history of gastrointestinal (GI) conditions. (i.e., history of polypectomy or polyps, diverticulitis, cholecystectomy, appendectomy, stomach resection, duodenal ulcer, gastric reflux, umbilical hernia, anal fissure, and hemorrhoids). Twenty-two patients (42.3%) had pre-existing genitourinary (GU) conditions, Grade 1 or Grade 2 GU toxicity was reported at baseline for 10 of the 22 patients with symptoms including hesitation, urgency, dysuria, nocturia, stricture, obstructive micturition, and irritable bladder.

**Patient eligibility**

Patients with pathologically confirmed clinical stage T1 or T2 invasive adenocarcinoma of the prostate; prostate size < 80 cc; PSA < 20 ng/ml; Gleason Score ≤ 6 or Gleason Score 7 with a grade 3 predominant pattern were eligible for participation. Androgen deprivation therapy was not an exclusion criterion. Informed consent was obtained from every patient. In accordance with institutional guidelines, all research was conducted under an institutional review board-approved prospective clinical protocol permitting collection and analysis of de-identified patient data at baseline and follow-up.

Patients with metastatic disease or planned pelvic lymph node radiotherapy, history of prostate surgery, prior radiation therapy to the prostate or pelvis, active bleeding disorder, or history of or active inflammatory bowel disease such as Crohn’s disease were excluded from participation. In addition, patients with a history of chronic prostatitis or any urogenital anatomic abnormality that would interfere with the ability to access the injection site were excluded from the study.

**Injection procedure**

The SpaceOAR System (Augmenix, Waltham, MA) and procedure is published elsewhere [11]. In brief, when injected into the perirectal fat, the liquid separates the prostate and the rectum and then polymerizes (solidifies) within 10 s into a soft hydrogel, by a reaction of PEG-ester and trilysine amine. The resulting hydrogel contains hydrolysable linkages at each PEG-trilysine junction whose kinetics is such that the gel remains solid for 3 months and thereafter liquefies, is absorbed and cleared via renal filtration.

**Treatment planning and treatment**

Within 3–5 days after hydrogel placement, a CT scan was taken for Intensity Modulated Radiation Therapy (IMRT) treatment planning. The gross tumor volume (GTV) was defined to be the prostate (as visualized on the simulation scan).

The clinical target volume (CTV) included the GTV and, per the treating physician’s discretion, the proximal 2/3 of the seminal vesicles. Primary tumor volume (PTV) included the CTV plus a non-isotropic 4–10 mm margin to compensate for daily setup variability and internal organ motion. Typically, less expansion was performed posteriorly than in other directions. The degree of PTV expansion was based on individual institutional experience and image guidance setup accuracy, and was generally 4–7 mm in the posterior direction.

A dose of 78 Gy (delivered in 39 fractions; 2 Gy per fraction) had to be delivered to an ICRU reference point within the PTV. At least 99% of the PTV had to receive at least 95% of the prescription dose. A maximum dose less than 107% of the prescription dose was required.

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**Table 1**

Patient baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Total no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.3 ± 6.0 (23)</td>
<td>67.0 ± 9.0 (29)</td>
<td>68.9 ± 8.0 (52)</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>12 (52%)</td>
<td>16 (54%)</td>
<td>28 (54%)</td>
</tr>
<tr>
<td>T2</td>
<td>11 (48%)</td>
<td>13 (44%)</td>
<td>24 (46%)</td>
</tr>
<tr>
<td>N Stage, radiologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nx</td>
<td>9 (39%)</td>
<td>2 (7%)</td>
<td>11 (21%)</td>
</tr>
<tr>
<td>Nm</td>
<td>14 (61%)</td>
<td>27 (93%)</td>
<td>41 (79%)</td>
</tr>
<tr>
<td>PSA level (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>5 (22%)</td>
<td>6 (21%)</td>
<td>11 (21%)</td>
</tr>
<tr>
<td>≥4–10</td>
<td>14 (61%)</td>
<td>17 (59%)</td>
<td>31 (60%)</td>
</tr>
<tr>
<td>≥10–20</td>
<td>4 (17%)</td>
<td>6 (21%)</td>
<td>10 (19%)</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>13 (57%)</td>
<td>14 (48%)</td>
<td>27 (52%)</td>
</tr>
<tr>
<td>7</td>
<td>10 (43%)</td>
<td>15 (52%)</td>
<td>25 (48%)</td>
</tr>
<tr>
<td>Prostate volume (cc)</td>
<td>55.5 ± 19.3 (22)</td>
<td>58.0 ± 21.4 (29)</td>
<td>56.9 ± 20.4 (51)</td>
</tr>
<tr>
<td>Prior/Current hormone therapy</td>
<td>9 (39.1%)</td>
<td>5 (17.2%)</td>
<td>14 (27%)</td>
</tr>
</tbody>
</table>

* Values are n (%) unless otherwise noted.
Endpoint stability of the space and radiation toxicity

Following the last fraction, subjects underwent another MRI or CT scan for evaluation of the maintenance of the created space between rectum and prostate. Another CT or MRI was performed 90 days after completion of the IMRT (or approximately 6 months following hydrogel injection), with a final MRI performed 6 months after completion of IMRT treatment.

Symptoms of radiation proctitis were assessed via the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) GI toxicity score (acute and late). Genitourinary (GU) toxicity was assessed using an adapted RTOG/EORTC scoring system [12]. Weekly and at the completion of IMRT, patients were evaluated for acute rectal and genitourinary toxicity. During follow-up toxicity assessments were performed 90 days, 6 and 12 months after end of radiation therapy (RTOG/EORTC).

All events (GI, GU, and otherwise) captured from the hydrogel injection through the 12 months follow-up visit were identified using CTCAE V. 4.0. The incidence of adverse events (AEs) was summarized by body system and preferred term in accordance with Medical Dictionary for Regulatory Activities (MedDRA) term as appropriate.

All patients were planned to have a proctoscopy at the end of the follow-up period (12 months after end of radiation therapy). This proctoscopy was performed to evaluate the rectal mucosa reactions (Vienna Rectoscopy Score). The median follow up time was 12 months.

Statistics

GI and GU Toxicity was evaluated using frequency distributions. Based on technical changes of the protocol (see section Patients and methods), the evaluation is separated into two cohorts (23 patients in Cohort 1 and 29 patients in Cohort 2).

Results

Patient disposition

A total of 52 patients were included within this study. As described previously, twenty-three (23) of these patients were included in Cohort 1 and 29 in Cohort 2. Four patients (all from Cohort 1) were excluded from the Per-Protocol Population. Reasons for exclusion include no hydrogel injection (n = 2), inadvertent rectal wall injection (n = 1) and improper polymer reconstitution (n = 1).

<table>
<thead>
<tr>
<th>Per-Protocol Population (n = 48)</th>
<th>GI toxicity scores (n%)</th>
<th>GU toxicity scores (n%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute (n = 48)</td>
<td>Late (n = 27)</td>
</tr>
<tr>
<td>0</td>
<td>23 (48%)</td>
<td>25 (93%)</td>
</tr>
<tr>
<td>1</td>
<td>19 (40%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>2</td>
<td>6 (12%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Grade 1 or more</td>
<td>25 (52%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Grade 2 or more</td>
<td>6 (12%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Acute GI/GU = Up to and including the end of acute study phase visit. Late GI/GU = 6 and 12 months follow-up visits. Toxicity score reported is the maximum score experienced by the subject across all intervals using the RTOG/EORTC scoring criteria.

The image guided radiotherapy modalities utilized included cone beam guidance (8 patients), ultrasound (21 patients) and megavoltage CT guidance (21 patients). All patients completed their course of IMRT. The Independent Medical Monitor (IMM) adjudicated 1 subject as experiencing a device-related event (GI proctitis) and 3 subjects as experiencing procedure-related events (focal rectal mucosal necrosis due to inadvertent injection of hydrogel into the rectal wall, bladder pierced during injection with hydrogel leak into bladder and urinary retention). All of these events resolved with no further sequelae. These events occurred early on in the study and were addressed with procedural and protocol modifications previously mentioned. With these modifications, no patients in Cohort 2 experienced a device or procedural related event. The IMM was unable to determine the procedure or device relatedness for 5 events in 5 subjects. Four of these events occurred in Cohort 1 (a G1 proctitis, a localized mucosal defect appearing 6 weeks post RT, a G1 constipation and one patient with a G2 dysuria/weak stream) with one event in Cohort 2 (G1 rectal urgency 3 weeks following start of RT). All of these events resolved with no further sequelae.

The radiation toxicity data are summarized in Table 2. Six patients experienced Grade 2 Acute GI toxicity. No patients experienced Grade 3 or 4 toxicity. In addition, no patients had early late GI or GU toxicity ≥ Grade 2.

Stability

After IMRT the created space for both cohorts was nearly unchanged in all patients, demonstrating that the perirectal space was maintained during the course of radiotherapy. At the end of the acute phase (6 months after implantation), the space remaining for Cohorts 1 and 2 was 5 mm and 2 mm, respectively, suggesting space reduction due to hydrogel absorption at the implant site (Fig. 1).

To date, T2w MR images for 43 patients approximately 9 months after gel injection have been evaluated. There was no hydrogel presence in 42 patients. Only one subject presented with a small amount of hydrogel after 9 months.

Proctoscopy

At present time there are proctoscopy data from 29 patients (19 from Cohort 1 and 10 from Cohort 2) at the end of the follow-up period (12 months after end of radiation therapy) available. The proctoscopy was evaluated by using the Vienna rectoscopy score...
In this trial, we demonstrated that a PEG based gel could successfully create a space between the prostate and the rectum which remained stable for the entire course of radiation therapy. The rate of acute Grade 1 and Grade 2 rectal toxicity in this study was only 40% and 12% (early late toxicity after 12 months 7% and 0%) with patients receiving a dose of 78 Gy. We believe this low toxicity rate can be ascribed to a reduction in rectal V70 due to spacer application. The corresponding data are evaluated separately. Since it is a multi-center study there is a possibility of PTV variability, which could influence the rectal toxicity data. However this risk exists in almost every clinical radiooncology trial even if the treatment is within the same department. We tried to reduce the variability by giving requirements for contouring.

Other groups used hyaluronic acid or collagen for creating space between the rectum and the prostate. In those studies, the number of patients was lower (1–27 patients) compared to our study and only the reduction of dose to the rectum was reported. Only Wilder et al. reported of a toxicity reduction in 10 patients [18]. While each technique reduces the volume of the rectum that is exposed to radiation, they also have characteristics that can prevent them from optimal performance. Hyaluronic acid can undergo partial degradation upon exposure to radiation, while human-based collagen can be challenging to use. In addition, the hyaluronic acid showed a stability of the volume and shape for close to one year, and showed only a slow regression thereafter [18]. The results of the current study demonstrated that the material was effective at displacing the rectal wall away from the prostate. The ~1 cm space created between the prostate (mid gland) and anterior rectum was maintained throughout the course of IMRT in all patients. In addition, at 6 months post implantation the space had decreased due to hydrogel absorption (Fig. 2). After 9 months there was no presence of hydrogel in 42 of 43 patients. Only in one patient there was a small amount of gel left.

The procedural modifications implemented for the patients in Cohort 2 provided a number of clinical benefits. Use of a TRUS probe improved visibility of the perirectal space. Use of the stepper increased TRUS probe stability and allowed both hands to be free to control the applicator. The optional stand-off balloon improved visibility of the perirectal space. Reducing the volume per kit from 15 mL to 10 mL decreased the total spacer volume and should result in decreased rectal wall stress. The implementation of stool softeners would also be expected to reduce stool-induced stress to the rectal wall by contents of the bowel.

The cohort analysis demonstrated that the procedural, product, and patient care enhancements implemented in Cohort 2 improved safety resulting in a marked reduction in device and procedure-related events.

The effectiveness of a temporary, absorbable spacer between rectum and the prostatic gland has important clinical implications.
for prostate RT, including dose escalation and hypofractionation. The advantages of these evolving radiation therapy treatments, including increased patient convenience and decreased overall costs, are potentially constrained by the potential increased rectal toxicity. Indeed, the report of the ASTRO Emerging Technology Committee (ETC) noted that most trials have studied modest increases in daily fraction size due to concerns of increased rectal toxicity and that the range of reported Grade 2 or higher gastrointestinal reactions was 14–52% [19]. At the University of Heidelberg, a randomized trial (hypofractionated proton or carbon ion radiation treatment of the prostate) was initiated in May 2012 using the SpaceOAR gel for the reduction of rectal toxicity (personal information by K. Herfarth).

**Conclusion**

These data suggest that creating a PEG based spacer between the prostate and the rectum results in a clinically meaningful reduction of rectal toxicity during and after IMRT of prostate cancer. The gel used in this study persists during the time of radiation therapy and was absorbed within one year. Given these important biochemical properties, Phase III studies are underway.

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Dr. De Weese served as medical monitor for this study and received compensation for this activity.

**Honoraria**

BrainLab (Dr. Weber).

**References**


[19] Buyyounouski MK, Price Jr RA, Harris EE, et al. Stereotactic body radiotherapy and was absorbed within one year. Given these important biochemical properties, Phase III studies are underway.