Hydrogel spacers in prostate radiotherapy: a promising approach to decrease rectal toxicity

Ranjani Padmanabhan¹, Michael Pinkawa² & Daniel Y Song^{*,3}

¹Department of Radiation Oncology, INOVA Health System Fairfax, 3300 Gallows Road, Falls Church, VA 22042, USA

²Department of Radiation Oncology, RWTH Aachen University, Pauwelsstrasse 30, 52057 Aachen, Germany

³Johns Hopkins Medicine, Department of Radiation Oncology & Molecular Radiation Sciences, Johns Hopkins University, 401 N Broadway, Baltimore, MD 21231, USA

* Author for correspondence: Tel.: +1 401 502 5875; Dsong2@jhmi.edu

High-dose radiation is a well-established method of treatment for prostate cancer. The main limiting structure for dose escalation is the rectum. The risk of rectal toxicity is related to dose received by the rectum. Several strategies for reducing dose to rectum have been explored; these include endorectal balloons as well as injection of rectal spacers like hydrogels. They create greater distance between rectal wall and prostate to confer a dosimetric advantage to the rectum. Early clinical studies with hydrogels have shown favorable outcomes. A low incidence of major procedural adverse effects with hydrogel use has been reported and it is well tolerated by patients. Hydrogel holds promise in establishing itself as an adjunct to standard of care in prostate radiation.

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Dose escalation for prostate cancer has been an accepted standard of practice over the last decade, based on several randomized trials demonstrating improved biochemical control with doses ≥ 70 –74 Gy. Introduction of technically advanced treatment methods like intensity-modulated radiotherapy (IMRT) and image guidance has made it possible to deliver high doses of radiation to the prostate while achieving considerable sparing of the surrounding tissues like rectum. Despite these advantages, a portion of the rectal wall remains exposed to high doses of radiation, which can result in acute and late rectal toxicities and proctitis [1].

The rectal wall has been established as an important dose limiting organ for the delivery of high-dose radiation to the prostate. The margins used around the prostate in 3D-CRT and IMRT plans are on the order of 4–10 mm, during which a part of the anterior rectal wall is included in the target volume. The volume of the rectal wall receiving more than 70 Gy has been well correlated with increased subsequent risk of rectal toxicity [2,3].

Introduction of a biologically inert material between the prostate and the rectum to create a 'space' is a logical solution to possibly reduce the volume of rectal tissue receiving undesirable doses. In the last few years, different spacer materials including cross-linked hyaluronan gel [4], human collagen [5], inflatable pillows/balloons [6] and hydrogel spacers [7–9] have been used to achieve improved rectal dose sparing, and have shown significant effects in reducing the rectal volume receiving high doses of radiation. Of the injectable materials, hydrogels have been approved by the US FDA for this purpose in the USA (with parallel medical device approvals in Europe and Australia) and are showing a trend toward wider acceptance in clinical practice.

Hydrogel spacers

Polyethylene glycol (PEG)-based materials have an established record for medical interventions having been used widely in neurosurgery and interventional procedures (e.g., DuraSeal Dural sealant, Mynx vascular closure device). A PEG-based hydrogel designed specifically for prostate has recently been introduced [7]. It contains precursor materials which, when injected simultaneously, polymerize *in situ* to form a firm gel after a few seconds. Following

Figure 1. T2 weighted magnetic resonance images of spacer post application. (A) Axial image, (B) Sagittal image.

polymerization, the gel remains stable for approximately 3 months and is completely resorbed by the end of 6 months.

Method of administration

Hydrogels are administered to patients under aseptic conditions. The procedure is carried out via a transperineal approach with transrectal ultrasound guidance, either using local anesthesia or under general anesthesia. First, hydrodissection is carried out using a needle introduced in the space posterior to Denonvilliers' fascia (rectoprostatic fascia) to create a potential space, followed by injection of the hydrogel (10–15 cm³) into the area. Early studies of these application procedures, mostly carried out by radiation oncologists and urologists, were reported to have a brief learning curve [10]. Eventually the procedures were reported to be 'easy' to 'very easy' [8] by clinicians. The injection is followed by a CT scan and MRI to confirm the position and distribution of the spacer material, as well as for radiation planning. MRI has advantages to delineate hydrogel from prostate as it can be difficult to precisely distinguish on CT alone, the hydrogel typically appears hyperintense (bright) on T2 sequences. (Figure 1A & B represent the MRI images of prostate with hydrogel in place. The hydrogel is seen to push the rectal wall away from the prostate).

Effects on rectal dosimetry

The volume of rectum receiving 70 Gy (V70) or more has been well correlated with the incidence of rectal toxicities. Preclinical data from cadaveric studies by Susil *et al.* [11] demonstrated histologic evidence of appropriate separation of rectum and prostate and a decrease of V70 in IMRT treatment plans from almost 20% without hydrogel to

4.5% with the use of hydrogel. This work established that the prostate could be separated from rectum in an anatomic fashion and laid the groundwork regarding the degree of rectal sparing that could be achieved using such an approach.

Song *et al.* subsequently reported on a multicentric Phase II study [9] involving 48 patients from four institutions where an IMRT-based plan was implemented to deliver 78 Gy in 2 Gy fractions with hydrogel *in situ*. The patients were scanned with CT/MRI prior to injection of hydrogel, followed by a repeat CT/MRI after the procedure. IMRT plans were created in both before/after CT/MRI scans and the dosimetric parameters were compared with one another.

The aims of the study were twofold:

- To demonstrate the ability to create a space of ≥ 7.5 mm between rectum and prostate at the level of mid-gland;
- To reduce the rectal V70 by 25% compared with the preinjection treatment plan.

Both end points were achieved successfully. A separation of 7.5 mm between the prostate and rectum at the level of mid-gland was achieved in 95.8% of patients and $>25\%$ reduction in V70 was achieved in 95.7% of patients. The mean reduction in rectal V70 was 8.0% (± 4.2). Statistically significant reductions were also shown for all other analyzed dose points as well (V10–V75). These end points were accomplished irrespective of inter-institutional variability in plan conformity, target definition, injected volume of gel, gel thickness mid-gland, mean gel thickness, gel symmetry and % length of planning target volume with gel contact, suggesting the benefit of hydrogel to be independent despite variation in technique among practices.

Following the initial report of dosimetric improvements in the 48 patients receiving hydrogel published by Song *et al.*, clinical toxicity results after IMRT in the same cohort were reported by Uhl *et al.* [12]. The patients were followed up to 12 months after completion of IMRT treatment and were assessed with prostate-specific antigen and proctoscopy. Proctoscopic observations of congested mucosa, telangiectasia, ulceration and necrosis were scored using Vienna rectoscopy scale. The results showed very low acute gastro-intestinal (GI) toxicities with 19 patients having grade 1, and six patients with grade 2 acute toxicities. No grade 3 and 4 acute effects were reported. A total of 20 patients experienced grade 1 acute genitourinary (GU) toxicity, 17 patients had grade 2, and one patient had grade 3 acute GU toxicities. The proctoscopic findings suggested that most patients (71%) had a Vienna rectoscopy scale score of 0. Telangiectasia was noted in 28% of patients, most of which were grade 1 and 2 (13% each) and few grade 3 (2%). Congested mucosa was seen in one subject. No ulceration, stricture or necrosis was noted at the end of the 12-month follow-up.

In a study by Whalley *et al.* [7], 30 patients with T1 and T2 prostate cancer were treated with an IMRT plan to deliver 80 Gy in 40 fractions with hydrogel in place. They were compared with a matched cohort of patients treated without hydrogel in place around the same time. The median follow-up was 28 months. The results of the study suggested that rectal doses for the group with hydrogel were distinctly lower than the patient group without hydrogel for all dose volume end points ranging from V30 to V80. The median V70s were 12.3% compared with 3.7% (no-hydrogel vs hydrogel). All these dosimetric differences were statistically significant.

Although there was no significant difference in acute grade 1 and 2 GI toxicity between the hydrogel and nonhydrogel groups, use of hydrogel did result in an impact on late rectal toxicities specifically grade 1. The incidence of late grade 1 rectal toxicities was significantly lower in the hydrogel group (16.6% hydrogel group, 41.8% nonhydrogel group; $p = 0.04$). The incidence of late grade 2 toxicity was similar in both the groups.

Interstitial brachytherapy has dosimetric advantages due to rapid falloff of dose at a distance away from the source; however, rectal toxicity remains a possibility. Rectal dose is a critical parameter to consider, as 2–10% of patients undergoing radiotherapy develop rectal complications ranging from mild proctitis to ulcer and fistula formation [13]. To curtail the adverse effects on the rectum the American Brachytherapy Society guidelines for I-125 interstitial implant [14] recommend the volume of rectum receiving greater than or equal to prescription dose (RV100) should not exceed 1 cm³ on day 1 and 1.3 cm³ on day 30.

In a study by Beydoun *et al.* [15], five patients received I-125 seed brachytherapy implant for T1 prostate adenocarcinoma. All the five patients had an RV100 at day 30 greater than 1.3 cm³. Hydrogel was inserted in these patients under transrectal ultrasound guidance. The prostate–rectum separation and the rectal dose were measured before and after hydrogel placement. The mean prostate–rectal separation was 15.1 mm (± 3.4). The mean difference in prostate–rectal separation with and without hydrogel was 12.5 mm (± 4.5). The mean RV100

decreased from 3.04 to 0.06 cm³ in the presence of hydrogel. Grade 1 adverse effects including perineal pain and rectal discomfort were noted in three patients. No grade 2 rectal toxicities were reported.

A single institutional study by Strom *et al.* [16] described their experience in 200 patients treated with high dose rate (HDR) brachytherapy and IMRT. Patients with National Comprehensive Cancer Network (NCCN) low- and favorable intermediate-risk cancers underwent HDR brachytherapy alone (2800 cGy in two fractions, 2–3 weeks apart). Patients with unfavorable intermediate-risk and high-risk disease received IMRT (4500 cGy in 25 fractions) plus two HDR brachytherapy sessions (1 week before IMRT and 2 weeks after the start of IMRT, respectively). A total of 100 out of 200 patients underwent insertion of PEG hydrogel, using a preparation marketed for neurosurgical use (DuraSeal Spinal Sealant System, Covidien, MA, USA). Patients received 10 ml of hydrogel for the first HDR fraction, and 5 ml for the second HDR fraction. Given that DuraSeal is commercially available in 5 ml quantities, two kits were utilized for the first injection; iodinated contrast, presumably to enhance visualization, was also mixed with the gel. The primary end point was to determine the rectal doses with and without hydrogel. Rectal doses were recorded as maximum dose received by 2 ml of rectum (D2), expressed as percentage of the prescription dose.

Hydrogel increased the mean rectal and prostate separation significantly (12 ± 4 mm with hydrogel and 4 ± 2 mm without hydrogel; $p < 0.001$). This increase in the distance between prostate and rectum was seen regardless of BMI of the patients. There was significant reduction in rectal D2 ($47 \pm 9\%$ with hydrogel and $60 \pm 8\%$ without hydrogel; $p < 0.001$).

Yeh *et al.* [17] reported toxicity outcomes of 326 patients with prostate cancer who underwent combined HDR brachytherapy (4 Gy twice daily implant for a total of 16 Gy) followed by IMRT (59.4 Gy in 33 fractions). PEG hydrogel was inserted during the second brachytherapy session to prevent ultrasound image distortion by the spacer during the first implant. The mean antero-posterior distance of the spacer achieved was 1.6 cm. The median follow-up was 16 months. The incidence rates of acute grade 1 and 2 radiotherapy-related toxicities were 37.4 and 2.8%, respectively, with the most common acute adverse effect being diarrhea. The incidence rates of late rectal grade 1 and 2 toxicities were 12.7 and 1.4%. However, grade 3 toxicities including severe proctitis and rectal fistula were reported in two individual patients (0.7%); unfortunately, no specific explanation was suggested as to the cause of these complications and whether the hydrogel effect on rectal sparing was present in these cases.

The only large multicentric randomized trial to date comparing patients with and without hydrogel spacer has been reported by Mariados *et al.* [8]. The study involved 222 patients with T1 or T2 prostate cancer (149 patients with hydrogel and 73 patients without hydrogel) treated with image guided-IMRT to deliver 79.2 Gy in 1.8 Gy fractions. The average perirectal space achieved after hydrogel insertion was 12.6 mm. On comparison of the dose-volume histograms prior and post procedure, the outcomes suggested a significant reduction of V50 through V80 Gy in the hydrogel group. Like the study by Song *et al.*, 97.3% of patients with hydrogel achieved >25% overall lower V70 following hydrogel. The use of spacer did not result in higher dose of radiation elsewhere in the surrounding tissues as evidenced by bladder dosimetry.

When adverse effects were analyzed over the first 3 months, no differences in the acute rectal or urinary toxicity were observed. However, there was significant reduction in late toxicities from 3 to 15 months of follow-up. Late grade 1 rectal toxicities were significantly lower in the hydrogel group (2% hydrogel group vs 7% for nonhydrogel group; $p = 0.044$); no grade 2 toxicities were reported in the hydrogel group, whereas there was a 1.4% incidence in the nonhydrogel patients at 15 months. In a recent update of the study, a 3-year median follow-up details were presented [18]. The benefit of hydrogel spacers on bowel toxicity was maintained as seen at 15 months. The grade 1+ rectal toxicities were reduced by 75% in the hydrogel group compared with the nonhydrogel group (hydrogel 2% vs nonhydrogel 9%; $p < 0.03$). No grade 2+ rectal toxicities were reported in the spacer group at 3 years (hydrogel 0% vs nonhydrogel 6%; $p < 0.015$). There was one case of grade 3 rectal toxicity in the nonhydrogel group. There was also a reduction in cumulative grade 1+ urinary incontinence at 3 years in the hydrogel group (hydrogel 4% vs nonhydrogel 15%; $p = 0.046$). There were no differences in other grade 1+ or grade 2+ urinary toxicities in the two arms of the study.

Together, these studies have shown consistent and significant dosimetric rectal sparing effects with the use of hydrogel with gel insertion resulting in prostate-to-rectum spacing of 12–16 mm versus 4–6 mm at baseline, as well as >95% of patients having rectal V70 reductions of at least 25% on IMRT treatment plans. Benefits of hydrogel when utilized with brachytherapy have also been demonstrated. These effects are associated with observed relative decreases in rectal toxicity. Tables 1, 2 and 3 show the summary of studies which have reported the acute GI, acute

Table 1. Acute gastro-intestinal toxicity reports with hydrogel.

Study	Treatment technique	Dose delivered	Patients (n)	Median follow (M)	Acute grade 0 GI toxicity	Acute grade 1 GI toxicity	Acute grade 2 GI toxicity	Acute grade 3 GI toxicity	Ref.
Uhl <i>et al.</i>	IMRT	78 Gy in 1.8–2 Gy fractions	48	12	23 (48%)	19 (39.6%)	6 (12.5%)	None	[12]
Whalley <i>et al.</i>	IMRT	80 Gy in 40 fractions	30	28	None	13 (43%)	None	None	[7]
Yeh <i>et al.</i>	HDR + IMRT	16 Gy brachytherapy and 59.4 in 33 fractions IMRT	326	16	None	37.40%	2.80%	None	[17]
Mariados <i>et al.</i>	IMRT	79.2 Gy in 1.8–2 Gy fractions	149/222 spacer group	15	108 (73%)	34 (23%)	6 (4.1%)	None	[8]

GI: Gastro-intestinal; HDR: High-dose rate; IMRT: Intensity-modulated radiotherapy; M: Month.

Table 2. Acute genitourinary toxicity reports with hydrogel.

Study	Treatment technique	Dose delivered	Patients (n)	Median follow (M)	Acute grade 0 GU toxicity	Acute grade 1 GU toxicity	Acute grade 2 GU toxicity	Acute grade 3 GU toxicity	Ref.
Uhl <i>et al.</i>	IMRT	78 Gy in 1.8–2 Gy fractions	48	12	10 (21%)	20 (41.7%)	17 (35.4%)	1 (2.1%)	[12]
Whalley <i>et al.</i>	IMRT	80 Gy in 40 fractions	30	28	None	None	None	None	[7]
Yeh <i>et al.</i>	HDR + IMRT	16 Gy brachytherapy and 59.4 in 33 fractions IMRT	326	16	None	None	None	None	[17]
Mariados <i>et al.</i>	IMRT	79.2 Gy in 1.8–2 Gy fractions	149/222 spacer group	15	14 (9.5%)	78 (52.7%)	56 (37.8%)	None	[8]

GU: Genitourinary; HDR: High-dose rate; IMRT: Intensity-modulated radiotherapy; M: Month.

Table 3. Late gastro-intestinal toxicity reports with hydrogel.

Study	Treatment technique	Dose delivered	Patients (n)	Median follow (M)	Late grade 0 GI toxicity	Late grade 1 GI toxicity	Late grade 2 GI toxicity	Late grade 3 GI toxicity	Ref.
Uhl <i>et al.</i>	IMRT	78 Gy in 1.8–2 Gy fractions	48	12	45 (95.7%)	2 (4.3%)	None	None	[12]
Whalley <i>et al.</i>	IMRT	80 Gy in 40 fractions	30	28	None	5 (16.6%)	1 (3.3%)	None	[7]
Yeh <i>et al.</i>	HDR + IMRT	16 Gy brachytherapy and 59.4 in 33 fractions IMRT	326	16	None	12.70%	1.40%	0.70%	[17]
Mariados <i>et al.</i>	IMRT	79.2 Gy in 1.8–2 Gy fractions	149/222 spacer group	15	145 (98%)	3 (2%)	None at 3 years	None at 3 years	[8]

GI: Gastro-intestinal; IMRT: Intensity-modulated radiotherapy; M: Month.

GU and late GI toxicities respectively, in patients who had hydrogel insertion.

Use of hydrogels for salvage radiotherapy or brachytherapy

In patients with history of previous radiation or surgery there is a theoretical concern of developing scar tissue which can impede the possibility of space creation for hydrogel insertion. Early studies with few patients have shown positive outcomes for the insertion of hydrogel in patients previously treated with radiation or surgery.

Mahal *et al.* described their experience in 11 patients undergoing salvage brachytherapy after having undergone prior radiotherapy (either prior brachytherapy or external beam). Spacing was achieved in eight patients, whereas three patients could not be successfully injected due to fibrosis and adhesions. Patients who were successfully

injected achieved median spacing of 7.7–10.9 mm (prior brachytherapy vs prior external beam radiotherapy). Late grade 3 or 4 GI or GU toxicity was 26%. One patient developed a prostate–rectal fistula requiring diverting colostomy [19].

Yeh *et al.* also recently reported in abstract form on 32 patients who underwent hydrogel injection followed by 72 Gy salvage radiotherapy to the prostatic fossa using image-guided IMRT. Nine patients (28%) developed grade 1 GI toxicity, and no patients had grade 2 or higher GI toxicity [20].

These reports although intriguing suggest that further study is warranted regarding utilization of hydrogel prior to salvage brachytherapy or prior to salvage radiotherapy after radical prostatectomy.

Use of hydrogels for stereotactic body radiotherapy prostate

Given the relative novelty of stereotactic body radiotherapy (SBRT), there have been fewer studies with limited patient numbers evaluating the role of SBRT for prostate cancer with concurrent use of hydrogels. In a recent study by Alongi *et al.*, 40 patients with low-risk and intermediate-risk prostate cancer were recruited for an accelerated SBRT treatment of 35 Gy in five fractions [21]. Hydrogel was inserted in eight patients, for whom the plan dosimetry was found to be improved after gel insertion. Within a median follow-up of 11 months, among all patients grade 0 acute rectal toxicities were noted in 30/40 (75%) patients, grade 1 in 6/40 (15%) and 4/40 (10%) with grade 2 toxicities. Genitourinary toxicities were noted in 16/40 (40%) patients having grade 0, 8/40 (20%) with grade 1, 16/34 (40%) with grade 2 toxicities. No acute grade 3 toxicities were noted. They did not report on the rates of radiotherapy toxicity within the subset of patients who received hydrogel, but there was one case of rectal fascia infection after hydrogel insertion which resolved with antibiotics.

Ruggieri *et al.* studied the dosimetric impact on near maximum target dose ($D_{2\%}$) along with the use of spacer [22]. SBRT was used to deliver 35 Gy in five fractions in 11 patients with prostate adenocarcinoma. The plans used to deliver radiation with this technique were typically associated with 33.2 Gy to $\geq 95\%$ planning target volume ($V_{33.2}^{PTV} \geq 95\%$). The aim of this study was to identify if the use of spacer improved the target dose coverage ($V_{33.2}^{PTV}$) with increased near maximum target dose ($D_{2\%}$), while maintaining the same $D1\text{ cm}^3 < 35\text{ Gy}$ constraint on the rectum. Each of the patients had two volumetric arc (VMAT) plans with necessary dose-volume constraints for planning approval ($D_{2\%}$ homogenous plan $\leq 37.5\text{ Gy}$, and $D_{2\%}$ heterogenous plan $\leq 40.2\text{ Gy}$) created before and after spacer insertion. By hypothesis testing, the target volume coverage and rectal sparing was compared across all the four plans. The effect of rectal sparing by spacer was tested by linear correlation analysis on the fractions of rectum receiving more than 18, 28 and 32 Gy (V_x^r). The results suggested that with the slightly increased $D_{2\%}$ in both the plans, along with the use of spacer assured a $V_{33.2}^{PTV} \geq 98\%$ to all patients. Significant rectal sparing was noted in both the plans. By linear correlation analysis there was a reduction in rectal V_x^r for $x \geq 28\text{ Gy}$, indicating that use of spacer in prostate SBRT was beneficial in rectal sparing. The early findings in these studies suggest that SBRT with spacer treatment for prostate cancer is a well-tolerated procedure. Further studies with larger patient groups are required to identify the acute and long term toxicities with SBRT and spacer.

Impact on patient-reported quality of life

The reduction in late rectal toxicities with the use of hydrogel spacers has had a measurable impact on quality of life (QOL) of patients. The Mariados trial followed patients up to 15 months using the Expanded Prostate Cancer Index Composite health-related quality of life questionnaire to assess for a 5–10-point decline from baseline over time [8,18]. At up to 3 months of follow-up, the patterns in reduction of QOL were similar in the hydrogel and the nonhydrogel groups. However, between 6 and 15 months there was less decline in bowel QOL scores among hydrogel-treated patients (11.6 vs 21.4%; $p = 0.87$). From 6 months to 3 years the hydrogel arm bowel score was near or above the baseline compared with that of nonhydrogel group ($p = 0.002$). There were similar declines in urinary QOL at 3 months with return to baseline by 6 months. At 3 years, there was a significant difference in urinary QOL favoring the hydrogel group (hydrogel +0.6 points vs nonhydrogel -3.3 points; $p = 0.04$). There were no significant differences in sexual QOL or vitality/hormonal QOL between the two arms at 3 years.

In a single institutional study by Pinkawa *et al.*, 167 patients receiving prostate radiation between the years 2010 and 2013 were followed up to 2 years following treatment. There were 66 patients treated without hydrogel and received up to 76 Gy in 2-Gy fractions. The 101 patients who were treated with hydrogel received up to 76–80 Gy. Both the patient groups were similar in baseline patient characteristics. The patients were surveyed using an expanded prostate cancer index composite (EPIC) questionnaire before radiation, at the last day of radiation, median time 2 months after radiation, and a median of 17 months (12–24 months) after radiation. The occurrences

of bowel problems and interventions done were compared between the two groups. The QOL changes due to acute toxicities at the end of radiation and after 2 months were not significantly different between the groups. The bowel score decrease by 10 points (29 vs 11%; $p < 0.01$) or 20 points (7 vs 1%; $p = 0.04$) after 1 year of radiation was significantly higher for the nonspacer group. More number of patients experienced bowel symptoms like loose stools, painful bowel movements and bloody stools after >1 year in the group without spacer. Patients without spacer also received medical intervention for management of bowel symptoms compared with those with spacer. More endoscopic procedures were performed in the nonspacer group for the bowel symptoms (19 vs 3%; $p < 0.01$). Application of spacer therefore had considerable advantages in improving the bowel quality of life scores in patients [23].

Impact of hydrogels on prostate motion

Prostate motion during radiation has been a point of concern, particularly to deliver more modern hypofractionated regimens which are often associated with longer treatment duration and greater potential for intrafractional movement. The use of an endorectal balloon [24] was found to compress the prostate against pubic symphysis and considered to be a stabilizing device for prostate motion.

The spacer material demonstrated consistent protection of rectum through treatment as evidenced by a study by Pinkawa *et al.* [25]. The changes in the spacer dimensions and displacements, changes in the distance between prostate and anterior rectal wall were determined in two groups, one with 15 patients with 10 ml of spacer injected and the other group with 30 patients without spacer. The comparisons were done using CT scans taken before commencing treatment and in the last week of radiation. The average volume of spacer showed a slight (17%) and significant increase in a small group of patients (4/15), particularly at the base level. This was possibly due to acute radiation edema during early phase of treatment, possibly changing the spacer dimensions. The average distance between the anterior rectal wall and prostate before and at the end of treatment remained stable throughout treatment (1.6/1.5 at base, 1.2/1.3 at the middle, 1.0/1.1 at apex). The average displacements of the hydrogel center of mass in the x, y, z directions were 0.6 mm, -0.6 mm and 1.4 mm and were not statistically significant. The prostate position variations were similar in both the groups except for significant posterior displacements in the nonspacer group. The hydrogel insertion had a possible stabilizing effect for larger posterior displacements of the prostate.

In a case report by Sumila *et al.* [26] the effects of hydrogel on intrafractional movement was studied. A 66-year-old male with low-risk prostate cancer underwent hypofractionated stereotactic radiation of 36.25 Gy in five fractions along with hydrogel insertion. The treatment time for all the fields per fraction lasted for 59 to 68 min. The prostate movement observed during all the five fractions was low (± 4 mm) in all the directions (antero-posterior, infero-superior, left-right). This suggested that hydrogel probably acted as a prostate stabilizer to reduce intrafractional prostate movement.

Picardi *et al.* [27] studied 20 patients who received 56–60 Gy in 14–15 fractions of 4 Gy delivered twice weekly. Three fiducial markers were placed in all patients prior to treatment, along with hydrogel insertion in ten patients; the remaining ten patients were treated without hydrogel. The displacements of the prostate based on the fiducial markers and bony anatomy were measured in three axes (left-right, intero-posterior, supero-inferior) for both groups. Every week, cone beam CT taken after patient set up was compared with the planning CT. In contrast to the report from Sumila, no differences were observed in the interfraction prostate displacement (all three axes) between patients in the hydrogel and nonhydrogel groups. The mean, systematic and random set-up errors in the three axes were similar for both groups as well, suggesting that insertion of hydrogel had no effect on interfraction prostate motion and presence of hydrogel had no stabilizing effect on prostate.

In a prospective study involving 26 patients by Juneja *et al.* [28], intrafractional prostate motion was measured for patients with hydrogel ($n = 12$) and without ($n = 14$). Prostate motion was calculated using probability of vector displacement which provided a detailed representation of prostate motion. For smaller vector displacements (<4 mm) the mean probability of prostate motion seemed to be slightly higher for the hydrogel patients. No conclusions could be drawn for larger vector displacements (>10 mm). The average of mean motion in patients with and without hydrogel were 1.5 mm and 1.1 mm ($p < 0.05$), respectively. The results suggest that hydrogels did not have significant impact on intrafractional prostate motion.

Toxicities

The spacer insertion procedure has been reported to be generally well tolerated by most of the patients reported in studies to date. There is no reported evidence of irritation or allergic reaction caused by hydrogel. Some transient peri-procedural effects like perineal discomfort have been reported [8]. No reports of procedure related serious events such as perforation, rectal infection or serious rectal bleeding have been reported so far. However, Teh *et al.* have reported a case of symptomatic rectal ulceration within a month following I-125 brachytherapy with hydrogel insertion [29]. Management consisted of close monitoring, and the patient's symptoms and rectal ulcer were documented to have resolved on sigmoidoscopy by 3 months' postimplantation. The authors reported this to be their sole case of rectal ulceration among 55 insertions performed.

In the report of Strom *et al.* [16], three patients out of the first 50 developed mild to moderate infection of the prostate; these patients had received ciprofloxacin prophylaxis. No infections were noted in the subsequent 50 patient group who received ceftriaxone and gentamycin prophylaxis. Their observation of procedure-related infections may be related to the utilization of multiple kits/injections and/or their addition of contrast, as similar rates of infection have not been observed in other experiences.

Cost-effectiveness of hydrogels

In a study by Hutchinson *et al.* [30] the cost-effectiveness of hydrogel in prostate radiation was evaluated by a decision-tree model (Tree Age Pro). The model was designed to compare costs of hydrogel placement plus radiation to radiation alone using an estimated rectal toxicity reduction rate of 70% associated with hydrogel (based on the Mariados data). An assumption was made, that reduction in short-term complications would translate into reduced long-term toxicity. The cost of managing rectal toxicity (including time lost from work) was compared over a period of 10 years across three radiation delivery methods, namely conformal (3D) radiation, 'high-dose' stereotactic body radiotherapy (SBRT, ≥ 45 Gy in five fractions), and 'low-dose' SBRT (35–36.25 Gy in five fractions) with toxicity estimates based on published reports of each modality.

The model results suggested significant cost savings associated with hydrogel use in high dose SBRT (US\$2640), whereas hydrogel use was associated with incremental cost increases of US\$518 for patients receiving conformal radiotherapy and US\$2693 for low-dose SBRT. Notably there was no analysis of conventionally fractionated IMRT in this study.

To understand the cost-effectiveness of the spacer material in patients receiving IMRT with spacer (IMRT +S) and without (IMRT+O), a study by Vanneste *et al.* used the decision analytic Markov model [31]. It was constructed to understand the effect of late rectal toxicities and compare the costs and quality adjusted life years (QALYs) between the two groups. Based on the model, the two groups were assumed to be 'equal' in terms of disease progression, survival, treatment schedule, dose delivery and planning technique. Yet another assumption made in the model was that 75% of the total rectal toxicities were grade 2 requiring treatment with low cost items like diet or medication. An incremental cost-effective ratio was calculated by dividing the incremental costs by incremental QALYs.

For a treatment strategy to be considered cost effective, it depends on how much a society is willing to pay per gained in quality of life years. A ceiling limit of €80,000 was adopted based on the informal ceiling ratio for high disease burden in the Netherlands. The results suggested that the combined follow-up and toxicity costs were €1444 and €1604 for IMRT+S and IMRT+O groups respectively with a saving of €160 for IMRT+S group. The QALYs were 3.542 for IMRT+O and 3.570 for IMRT+S groups, respectively. The group IMRT+S produced 0.028 QALYs more than the other. Therefore, IMRT+S was more expensive than IMRT+O but produced a favorable QALYs. The resultant incremental cost-effective ratio was €55,880 per QALY gained which suggested a high probability (77%) of being cost effective for the ceiling ratio adopted. The study demonstrated that the use of spacer can be cost effective for prostate cancer patients due to less severe rectal toxicities and resulted in cost reductions in the management of rectal side effects.

Discussion

Several trials and retrospective reports of patients treated with hydrogel spacers have demonstrated its efficacy in reducing the volume of rectum exposed to radiation (across high through low dose values) during IMRT as well as brachytherapy. The favorable dosimetric improvements to the rectum have been consistent across studies [7–9]. These reductions have been associated with reduced rates of observed GI toxicity. More randomized prospective

studies are required and are underway to identify if further benefits of hydrogel could be extended to different methods of radiation delivery [32,33].

Based on the studies conducted so far, hydrogel appears to be well tolerated by most patients with minimal evidence of adverse reactions caused by the polymer. Hydrogels are stable compounds which do not disintegrate during radiation, in contrast with materials like hyaluronan which is potentially subject to reduced stability with radiation [34]. The procedure of insertion of hydrogel has been demonstrated to have a relatively fast learning curve, especially for those radiation oncologists who are familiar with brachytherapy.

An interdisciplinary meeting was conducted in July 2013 in Germany and was attended by radiation oncologists and urologists, each of whom had an experience of treating 23–138 hydrogel injections [35]. A total of 258 patients from different studies which included the prospective data from multi-institutional clinical trial by Uhl *et al.* [12], prospective mono institutional data from German clinical trials register DRKS00003273 [36], and retrospective data from patient charts were included in the meeting to understand the status of hydrogel application in current practice. User experiences for successful spacer implantation were discussed and answers to key questions were formulated. Following the meeting the details of hydrogel associated side effects also collected from the participants. A consensus was reached by the participants, favoring the application of hydrogel spacer. The consensus on the indication for treatment with hydrogel along with dose escalated radiotherapy (≥ 76 Gy in conventional fractions) was for histologically confirmed low- or intermediate-risk prostate cancer. It was not recommended for locally advanced prostate cancer as a space could not be effectively created and tumor dissemination could not be excluded in advanced cases. Patients with active bleeding disorders or significant coagulopathies could not be included in the procedure. Relative exclusion criteria were presence of active inflammatory disease or infection in the perineum and patients with history of previous treatment with procedures causing high risk of adhesions around prostate (high intensity focused ultrasound, cryotherapy or prior radiotherapy). The insertion of hydrogel had to be performed under transrectal ultrasound guidance via transperineal approach following a hydrodissection.

Injection-related grade 2 toxicities were noted in five out of the 258 patients studied. The most common side effect in these five patients was rectal-wall penetration. These patients were managed conservatively and all of them recovered completely within a few weeks without any long-term sequelae. The overall opinion of the interdisciplinary team members favored the use of spacer to significantly reduce radiation-induced gastrointestinal toxicity. This however had to be used with a measure of caution due to a very small but possible risk of procedure-related adverse events.

The influence of hydrogel in the reduction of acute toxicities like bowel frequency has been quite variable across the studies [7,8,12], raising questions if these symptoms are truly radiation-related or due to some irritation caused by the hydrogel. One possible origin of these acute effects could be that most patients in the studies were prescribed stool softeners prior to the procedure which could have increased the bowel frequency mimicking a grade 1 reaction. Hydrogels had a significant and consistent impact on late rectal toxicities across most of the studies [7,8] where decreased incidence of grade 1 and 2 reactions were reported and very rarely progressed beyond grade 2. This had a direct bearing on the QOL [8].

Based on the work demonstrating improvements in biochemical control rates associated with dose-escalated radiotherapy there remains interest in maximizing prescribed radiation doses to prostate [37], however late effects on rectum have been a significant limiting factor for introducing dose-escalated treatment [38]. Hydrogels have shown benefits in ameliorating these late effects, and indeed the cost-benefit analysis by Hutchinson *et al.* showed the greatest cost savings in patients receiving high-dose SBRT.

The toxicity results of the studies conducted so far are consistent with time, but currently available data are limited by relatively short follow-up. Late effects of higher grade have been shown to occur at a median of 1.5 and 4.5 years [1,39]. Longer follow-up is required to determine further possible effects of hydrogel on late toxicity.

Current data for hydrogel application support use of hydrogel in patients with localized prostate cancer with no clinical or radiological rectal involvement. Patients involved in recent studies had T1 and T2 prostate cancer with a smaller prostate volume ≤ 80 cm³ [7,8]. For disease extending to extra prostatic tissue there could be a potential hazard of displacing malignant cells toward rectum. The limitation to patients with more early-stage disease is based upon older data suggesting a 19% rate of Denonvilliers' fascia invasion in patients undergoing radical prostatectomy [40]. There is the possibility that patients in the modern prostate-specific antigen era have lower rates of such posterior fascial involvement, but data in this area are limited. Separate studies with hydrogel spacers in patients with locally-advanced prostate cancers are needed to establish the effectiveness and safety of hydrogel within this patient subgroup.

Conclusion

Hydrogels have been well tolerated by patients with low incidence of procedure-related adverse events. Early studies have demonstrated a significant rectal sparing effect and decrease in the rectal volume irradiated. These have resulted in a reduction in the incidence of acute and late rectal toxicities. Based on the results of studies so far, hydrogels show a great promise to be incorporated in the standard of care in the management of prostate cancer.

Future perspective

Hydrogels have been well tolerated, stable compounds which have been demonstrated to be easily adopted. They have shown significant favorable effect in rectal dosimetry and late toxicities. The number of published studies reporting clinical data with hydrogel for prostate cancer radiation is increasing. In the next 5 years hydrogels are more likely to be applied with newer radiation treatment techniques like SBRT and proton therapy to maximize the rectal-sparing benefits. Reports of nomograms using clinical risk factors to predict which patient is most likely to benefit from use of hydrogel are emerging [41] and a reliable prediction model can be an important tool for policy making and cost reimbursement. Newer precise models using clinical and genetic characteristics are likely to gain ground soon. The current data show promise, but further studies with longer follow-up would be useful to pave the way for hydrogels as a cost-effective standard of care in radiation therapy for prostate cancer.

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Executive summary

- The rectal wall has been subjected to high doses of radiation during dose escalation for treatment of prostate cancer causing acute and long-term adverse effects.
- Introduction of an inert material like hydrogel has shown to improve the rectal sparing by reducing the volume of rectum receiving high dose radiation.
- Hydrogel insertion procedure has been well tolerated by patients so far with a very low incidence of procedure-related side effects.
- Several studies have demonstrated a consistent dosimetric rectal sparing, with most patients having the V70 (volume of rectum receiving 70 Gy) reductions of at least 25% on intensity-modulated radiotherapy treatment plans.
- The rectal-sparing effects have resulted in significant reduction in acute and late rectal toxicities. Longer follow-ups are required to identify further possible occurrence of late effects.
- The beneficial effects of hydrogel have also been demonstrated in early studies using radiation techniques like brachytherapy and stereotactic body radiotherapy.
- Relatively lower incidence of toxicities has resulted in cost reduction in the management of adverse effects. Early analyses have suggested hydrogels to be cost effective in prostate cancer management.
- Current data are limited to use of hydrogels in localized prostate cancer, it needs to be determined if these benefits can be extended to locally advanced prostate cancer as well.
- Soon, hydrogels could be introduced along with newer radiation techniques like proton beam therapy.
- Predictive nomograms using clinical and genetic characteristics are likely to be developed in future, to identify which subset of patients are most likely to benefit from hydrogel application.
- The decrease in rectal toxicities has had a positive impact in patients; based on the studies to date, hydrogels have shown a lot of promise in lowering toxicities and improving quality of life of patients. They show a great potential to be incorporated in standard of care in management of prostate cancer.

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