Hydrogel spacers and prostate brachytherapy

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Overview

The use of brachytherapy for the definitive treatment of localized prostate cancer has been established for over four decades (1). Therapy may be delivered using either permanent seed low dose rate (LDR) or high dose rate (HDR) technique. Both techniques are recommended in the ASCO/CCO joint guidelines (2), and data suggests comparable oncologic outcomes. Brachytherapy may be used as monotherapy for low risk and selected intermediate risk patients or in conjunction with external beam radiation therapy (EBRT) for unfavorable intermediate and high risk patients.

Brachytherapy is highly conformal and provides greater sparing of surrounding normal tissues compared to EBRT. However, the anterior rectal wall may be exposed to high doses of radiation given its proximity to the prostate. The rates of ≥ grade 2 rectal complications are low, with a range of 2.2 to 26% (weighted average of 7.9%) and a fistula rate of 0.4 to 3.3% (3). The risk is increased for men on anticoagulation therapy or with inflammatory bowel disease (IBD) (4). Of the many factors that may predict for rectal injury, the rectal volume exposed to 100 percent of the prescription dose (RV100) and the maximum dose to the 2cc volume (D2cc) most often correlate (5,6).

In an effort to avoid rectal complications, bio-absorbable hydrogels have been developed. Using a transperineal approach and under ultrasound guidance, a needle is advanced into the retroprostatic fossa, the space between the rectum and Denonviller’s fascia is hydrodissected, and the hydrogel is injected. When formed, the gel increases the physical distance between the prostate and the rectum by a mean of 11 mm and lasts for 3 months (7). Phase III data in the EBRT setting demonstrated significant reduction in rectal dose, which resulted in a decreased rate of grade 1/2 rectal toxicities and improved long-term patient reported quality of life (8). Additionally, 2 systemic reviews and cohort studies comparing men who received hydrogel spacer vs. control prior to prostate radiotherapy consistently show report of lower rectal V70, fewer rectal toxic effects and higher bowel related quality of life (9) (10).

Radioactive exposure is governed by the inverse square law, meaning that even small increases in physical distance between the prostate and anterior rectal wall can have significant impacts on high-dose deposition from brachytherapy. Hydrogel has been used in both the monotherapy and boost settings, using LDR and HDR technique with demonstrated decrease in rectal dose, decreased rectal toxicity and improved quality of life (11–17). It has also been applied to the salvage setting (18) and to patients with IBD or those on anticoagulation (19).

LDR prostate brachytherapy

To date, there have been no prospective trials that have reported on the use of hydrogel rectal spacers in the setting of LDR prostate brachytherapy. However, several groups have published retrospective reports evaluating the impact of these spacers on rectal dosimetry, physician-graded toxicity and target volume coverage.

In a study from Memorial Sloan Kettering Cancer Center of patients undergoing definitive Pd-103 prostate brachytherapy, use of a rectal spacer was associated with significantly improved rectal dosimetry compared to a separate cohort of patients treated without a spacer. Notably, acute rectal toxicity occurred in 9.5% of patients, with none higher than grade 2 (20).

In a series from Japan, Morita et al. reported on 100 patients treated with iodine-125 prostate brachytherapy with placement of a hydrogel rectal spacer. Spacer placement yielded a mean distance of 11.64 mm between the prostate and rectum. Compared to a separate series of 200 patients treated without a spacer, patients treated with a spacer had statistically significantly lower mean rectal V150 and V100 values with no adverse effect on prostate target volume coverage (21).

Kahn et al. reported improvements in rectal dosimetry associated with the use of a hydrogel rectal spacer in 80 consecutive patients undergoing LDR prostate brachytherapy. In patients receiving a spacer, the adjusted mean dose
to 1 cc, 2 cc and 5 cc of the rectum was decreased by 32%, 26% and 17% respectively compared to patients treated without a spacer. There were no significant differences in physician-reported rectal toxicities between groups. Analysis of prostate gland target volume coverage also demonstrated no differences between groups (13).

Finally, Nehlsen et al. reviewed dosimetry and quality of life outcomes in 168 patients who underwent LDR prostate brachytherapy boost following prostate IMRT between 2014 and 2019. In patients with a hydrogel spacer, mean prostate-rectum separation was 7.5 mm, and the mean rectal V100 among this group was 47% lower compared to patients without a spacer. Between groups, there were no differences in the proportion of patients with prostate D90 ≥100 Gy and no differences in quality of life (22). Of note, the median follow up length was 9 months in the spacer cohort and 2 years without.

The above retrospective studies consistently demonstrate a pattern of improved rectal dosimetry with the use of a hydrogel rectal spacer in the setting of LDR prostate brachytherapy. It is unclear if these dosimetric advantages translate into meaningful improvement in rectal toxicity. In general, it is important to follow patients beyond 2 years to detect meaningful rectal toxicity (23). Accordingly, these small retrospective studies with short follow up have significant limitations. Importantly, none of these studies demonstrate any detriment in target volume coverage associated with use of a spacer.

**HDR prostate brachytherapy**

Hydrogel spacers have also been studied in the setting of HDR prostate brachytherapy, with favorable results. To date, there have been no prospective trials reported on the use of hydrogel rectal spacers in the setting of HDR prostate brachytherapy. Below is a summary of published retrospective studies evaluating the clinical benefit of hydrogel rectal spacer when utilized with HDR prostate brachytherapy.

Strom and Biagioli et al (15). retrospectively analyzed 200 patients who received 2 fraction HDR brachytherapy with or without external radiotherapy. During the first HDR procedure they injected 10 mL hydrogel and 5 mL with the second implant. The authors demonstrated feasibility, with 100% success rate of implantation. Mean rectal separation at the end of an HDR case was 12 mm with the first HDR implant, and 4 mm with the second. The insertion of gel decreased the rectal D2cc from 60% to 47% (p <0.001).

In a study from UCLA, treatment plans of 18 patients with hydrogel following HDR were compared with 36 patients without. In the 54 plans analyzed, the 2 populations were similar in all regards at baseline; however, in the patients that received hydrogel rectal spacing, there was consistently lower dose to the rectum for multiple dosimetric endpoints (24). The authors concluded that the use of hydrogel spacing in the setting of HDR brachytherapy is clinically feasible and also reduces radiation dose to the rectum.

In a series from Australia, 32 patients who received hydrogel spacer at the time of HDR prostate brachytherapy prior to external radiation were compared to 65 patients who were treated without a spacer. They showed feasibility and consistent separation between the rectum and the prostate with use of a spacer along with decreased radiation dose to the rectum. Moreover, this reduction in rectal dose corresponded to less acute and late grade 1 GI toxicity in the group treated with a spacer (11). Hydrogel spacers have also been used successfully in situations of HDR brachytherapy as salvage for radio recurrent disease and in patients with ulcerative colitis (19,25).

The above studies consistently demonstrate spacing and feasibility, decreased rectal dose, and in the Australian series, improvement in treatment related toxicity with use of a hydrogel rectal spacer in the setting of HDR prostate brachytherapy. Furthermore, based on this limited data, use of a spacer does not appear to compromise target coverage, and the spacers themselves do not seem to confer meaningful toxicity. Nonetheless, further studies are needed, including prospective trials, to more definitively quantify the effect of hydrogel spacers on rectal toxicity in this setting.

**Sequencing of hydrogel spacer with brachytherapy**

There is no consensus on the ideal sequencing of hydrogel spacer placement and brachytherapy, in part because there are many different clinical practice scenarios. The hydrogel rectal spacer may be placed either by the urologist, radiation oncologist, or, in some cases, the interventional radiologist prior to treatment planning. Hydrogel spacers have generally been utilized in the setting of MRI-based treatment planning, as the spacer can be easily visualized on T2-weighted MRI sequences. More recently, a radiopaque hydrogel rectal spacer is now also available for CT-based planning. In the setting of EBRT, a common practice is to place the hydrogel rectal spacer at the time of gold marker placement, followed a few days later by CT and MR based simulation.

Sequencing with brachytherapy presents a number of reasonable options. If brachytherapy is combined with external radiation, the hydrogel rectal spacer can be placed at the time of gold marker placement prior to MR based treatment planning for EBRT, or, if brachytherapy is done as monotherapy, at the time of LDR or first HDR implant.

**Pitfalls, cautions, and potential for toxicities associated with hydrogel spacer use**

Although the above retrospective data appears to support the relative safety of hydrogel spacer use in the setting of LDR and HDR brachytherapy, spacer-related toxicities have been reported in the literature. In a series by Yeh et al., two grade 3 toxicities were reported (17).
of these is described in the results as a necrotizing fasciitis that occurred at 4 months following spacer placement, which ultimately required a colostomy. Similarly, in a recent case report, an event of rectal infiltration of hydrogel was not appreciated prior to SBRT, and the patient sustained injury to the rectum with fistula and osteomyelitis that required pelvic exenteration (26). Additionally, in a database of toxicity events maintained by the FDA titled the Manufacturer and User Facility Device Experience (MAUDE, https://www.accessdata.fda.gov/cdrh_docs/pdf14/DEN140030.pdf), several similar events related to hydrogel spacer placement have been reported. Specific to brachytherapy, Vaggars et al preformed a systematic review on 9 studies involving 1208 prostate brachytherapy patients of which 671 had hydrogel spacers. In this review, the most serious late events were 2 cases (0.30%) of prostatorectal fistulas requiring diverting colostomies (16).

Given the goal of hydrogel spacers to purely mitigate toxicity, even a few of these severe events could dramatically impact the risk/benefit considerations associated with hydrogel spacer use. If this should be routinely done for brachytherapy patients requires careful consideration and ideally additional prospective investigation. An interventional procedure to cure a malignancy, as compared to an interventional procedure to purely mitigate a grade 2 toxicity event, are very different primary goals and require very different considerations before they are performed.

As a final note, a 2019 publication from Levy et al explored the cost effectiveness of hydrogel spacers, concluding that more information is needed for definitive conclusions (27). Early reports of hydrogel spacer placement when utilizing brachytherapy and radiotherapy for cervical cancer are also encouraging (28,29).

Conclusions

The authors’ intent is to summarize the data at this juncture with hydrogel spacing focusing on the use with prostate brachytherapy. It is clear that spacing utilized in the setting of brachytherapy, may reduce early or late gastrointestinal side effects, and does not degrade the quality of the treatment. Although toxicities associated with spacers appear to be rare, clinicians should be aware of potential complications and should be trained on appropriate spacer placement. Further study with prospective evaluation is essential. We advise adopting best practices, training, and evaluating the risk versus benefits at all times, with all patients.

References


