MASSACHUSETTS GENERAL HOSPITAL
IMAGING

RADIOLOGY ROUNDS
A newsletter for referring physicians

February 2018 - Volume 16, Issue 2 *Massachusetts General Hospital Department of Radiology*

Gary Boas, Author

Raul N. Uppot, M.D., Editor

Use of Spacers Limits Non-Target Radiation Exposure in Radiotherapy to Treat Prostate Cancer

- With recent advances in radiotherapy techniques to treat prostate cancer, clinicians are delivering higher doses of radiation to the prostate.
- Injection of hydrogel spacers can help to minimize the amount of radiation received by surrounding tissue, particularly in the rectum.
- Studies have shown that the use of hydrogel spacers contributes to better long-term outcomes in prostate cancer patients who undergo radiotherapy treatment.

Radiotherapy for prostate cancer has changed notably in recent years. Today, clinicians are delivering higher doses of radiation to the prostate, a practice made possible by the introduction of techniques such as intensity-modulated radiotherapy and image-guided radiotherapy, which allow for more accurate targeting and better protection of healthy, surrounding tissue.

Even with the improved protection provided by the more accurate targeting, additional efforts are needed to limit the amount of radiation delivered to surrounding tissue—most importantly, tissue in the rectum. To this end, clinicians have been using biodegradable materials called "spacers" to create a buffer between the prostate and the rectal wall attempting to limit rectal toxicity in the wake of the radiotherapy.

Spacers have taken several forms over the past few years. Radiation oncologists, urologists, and interventional radiologists have used materials including inflatable balloons, cross-linked hyaluronan gel, human collagen, and hydrogels to help spare rectal tissue. Of the injectable spacers, hydrogels have been approved for this use by the Food and Drug Administration and have emerged as the preferred option. Inflatable balloons have been shown to be less effective than hydrogels, with longer setup times and greater potential for patient discomfort. The FDA approval has spurred further investigation, with researchers exploring more closely the efficacy and long-term outcomes of the hydrogel approach.

Hydrogel Spacers Reduce Radiation Exposure in Prostate Cancer Patients

The hydrogel spacers used for radiotherapy of the prostate employ a polyethylene glycol (PEG)-based hydrogel designed for this application. After injection, the precursor materials in the hydrogel polymerize within a few seconds, resulting in a firm gel that remains in place for at least three months. Thus, only one injection is needed over the course of the treatment. After about six months the gel will be completely resorbed. In contrast, inflatable balloons require a new insertion with each radiotherapy session.

The goal when using hydrogels is to minimize rectal toxicity, the dose-limiting factor of radiotherapy for prostate cancer. Research has established that the incidence of rectal toxicity is closely associated with the volume of the rectum exposed to 70 Gy or more of radiation (V70); therefore, studies of the efficacy of the hydrogel approach have looked at minimizing this volume.

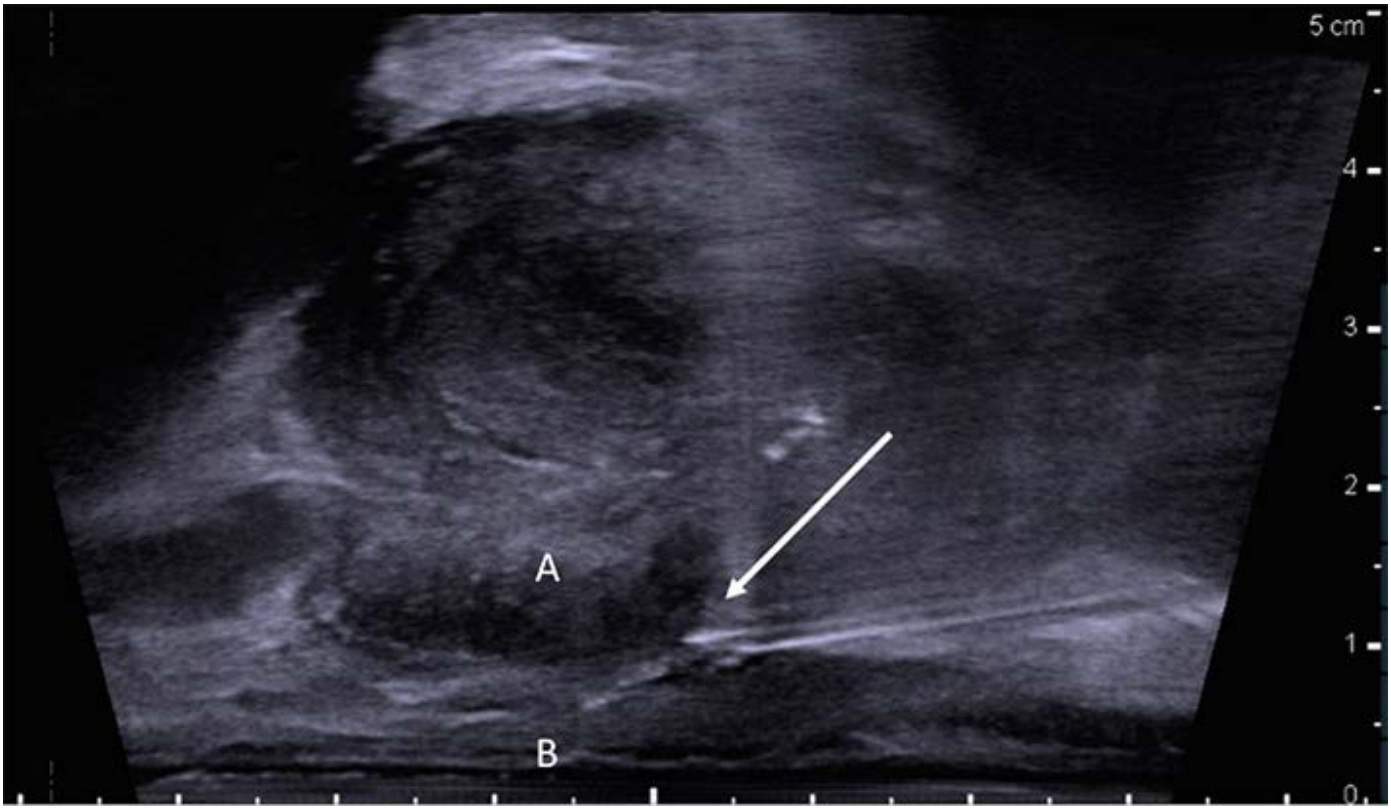

Figure 1. Injection of hydrogel spacers has been shown to limit the amount of radiation delivered to the rectum and other surrounding tissue during radiotherapy to treat prostate cancer. This image shows ultrasound-guided placement of a spacer, in which a needle is advanced via transperineal approach with the tip (arrow) between the prostate (A) and rectum (B).

In a November 2017 review paper published online in the journal Future Oncology, Padmanabhan, Pinkawa, and Song summarized the results of several previous studies. In a 2013 Phase II study by Song and colleagues, 48 patients from four institutions were treated with intensity-modulated radiotherapy, receiving 78 Gy in 2-Gy fractions. Scans performed before and after hydrogel injection showed a greater-than-25% reduction in V70 in 95.7% of patients. In a 2016 study, Whalley and colleagues compared 30 patients receiving 80 Gy in 40 fractions during intensity-modulated radiotherapy with hydrogel, and a matched cohort receiving therapy without hydrogel at about the same time. The results also demonstrated the value of using hydrogels in minimizing rectal toxicity, as the median V70 was 3.7% in the hydrogel group, in contrast with 12.3% in the no-hydrogel group. The findings were the same in other studies covered in the review paper: Employing hydrogel spacers led to smaller volumes of the rectum receiving radiation, with a low incidence of adverse effects.

In 2017 Hamstra and colleagues published the results of a randomized Phase III study of 222 men who underwent image-guided, intensity-modulated radiotherapy. The study found substantial reductions in rectal dose and improvements in both toxicity and quality of life. Also, importantly, the gains observed at a 15-month-minimum follow-up appeared to have been maintained at three years, or even to have increased.

Despite the demonstrated benefits, use of the spacers is not always advised. After a July 2013 consensus meeting of radiation oncologists and urologists, each with considerable experience using hydrogel injections, participants published a series of recommendations. For dose-escalated radiotherapy (76 Gy or more in conventional fractions), hydrogel should be used for histologically confirmed low- or intermediate-risk prostate cancer. It should not be used in cases of locally advanced prostate cancer, as clinicians cannot always create the necessary space, and tumor dissemination is a possibility. Other exclusion criteria include active bleeding disorders and significant coagulopathies.

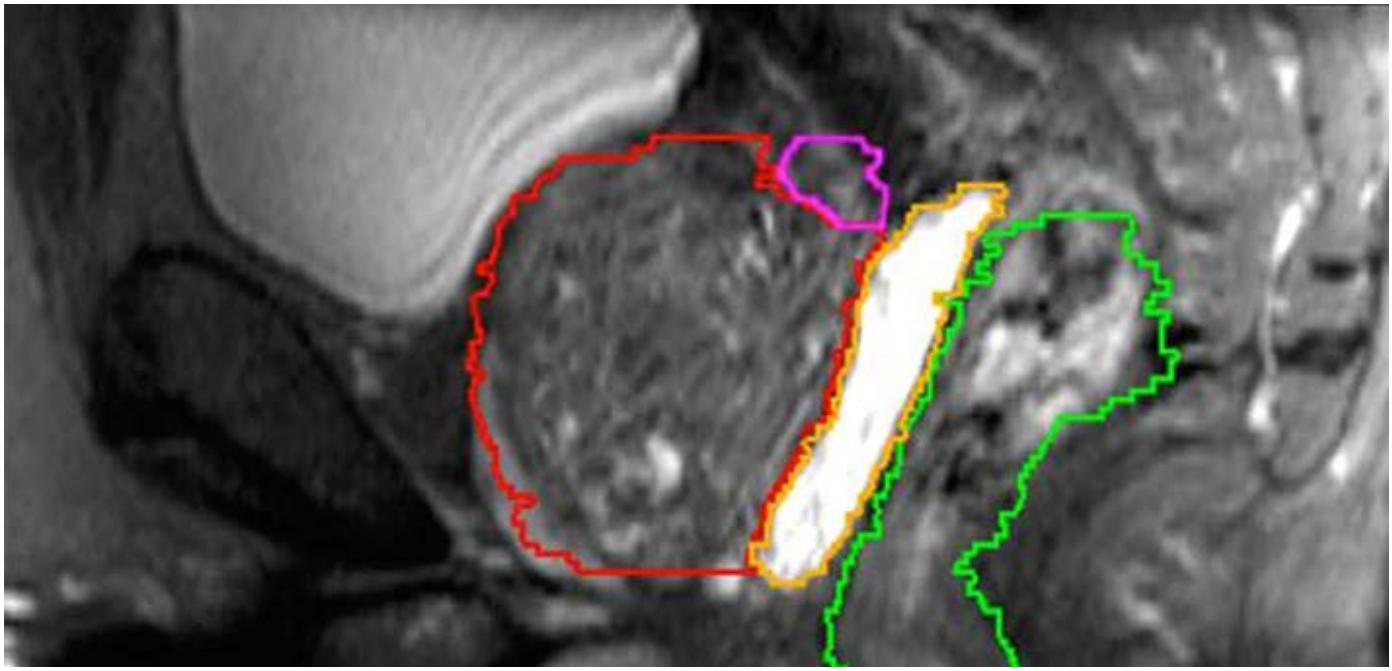

Figure 2. Sagittal MRI performed for radiation planning demonstrates that the spacer (yellow outline) provide adequate separation of the prostate (red outline) and rectum (green outline).

A Positive Impact on Prostate Cancer Patients' Quality of Life

In a study published last year, Pinkawa and colleagues investigated quality-of-life changes up to five years after treatment in prostate cancer patients who received radiotherapy with hydrogel spacers. In particular, they looked at urinary, bowel, and sexual bother, comparing these symptoms in patients treated with and without spacers. This retrospective study showed that while quality of life was largely the same for the two groups in the short term, the spacer group saw considerable advantages over the long term. After five years, these patients reported having the same bowel quality of life—including in the areas of bowel urgency and control of stools—that they had before treatment.

In a separate study published online in January 2018, Hamstra and colleagues studied sexual quality of life following prostate intensity-modulated radiotherapy with a hydrogel spacer. Previous work had shown that while use of spacers helped to protect the penile bulb from radiation, it did not result in improved sexual quality of life. It is possible, however, that the benefits of the spacers were masked by the relatively high rate of men—nearly 60% —who had moderate to severe sexual dysfunction at baseline. To get a better sense of the benefits, the researchers analyzed the data from a subgroup of men with adequate baseline sexual quality of life. They found a correlation between reduced radiation dose to the penile bulb and improved erectile function, thus demonstrating improved outcomes in sexual quality.

Scheduling

Radiation therapy to treat prostate cancer is performed on the main campus of Massachusetts General Hospital in Boston and at Newton-Wellesley Hospital, the Mass General/North Shore Cancer Center, and the Mass General Cancer Center at Emerson Hospital-Bethke. Appointments can be made through Epic (inside the Partners network) or Physician Gateway (outside the Partners network) or by calling 617-726-5866.

Further Information

For further information about radiotherapy of the prostate and use of prostate spacers, please contact Ashraf Thabet, MD, Division of Interventional Radiology, Department of Radiology, Massachusetts General Hospital, at 617-643-4723, or Jason Efstathiou, MD, DPhil, Genitourinary Division, Department of Radiation Oncology, Massachusetts General Hospital, at 617-726-5866. We would like to thank Drs. Thabet and Efstathiou for their advice and assistance in preparing this article.

References

Hamstra DA, Mariados N, Sylvester J, et al. (2017). *Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial*. Int J Radiat Oncol Biol Phys **97**(5):976-985.

Hamstra DA, Mariados N, Sylvester J, et al. (2018). *Sexual Quality of Life Following Prostate Intensity Modulated Radiation Therapy (IMRT) with a Rectal/Prostate Spacer: Secondary Analysis of a Phase 3 Trial*. Practical Radiation Oncology **8**:e7-e15.

Jones RT, Rezaeian NH, Desai NB, et al. (2017). *Dosimetric Comparison of Rectal-Sparing Capabilities of Rectal Balloon vs Injectable Spacer Gel in Stereotactic Body Radiation Therapy for Prostate Cancer: Lessons Learned from Prospective Trials*. Medical Dosimetry **42**:341-347.

Mariados N, Sylvester J, Shah D, et al. (2015). *Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy*. Int J Radiat Oncol Biol Phys **92**(5):971-977.

Müller AC, Mischinger J, Klotz T, et al. (2016). *Interdisciplinary Consensus Statement on Indication and Application of a Hydrogel Spacer for Prostate Radiotherapy Based on Experience in More than 250 Patients*. Radiol Oncol **50**(3):329-36.

Padmanabhan R, Pinkawa M, and Song DY (2017). *Hydrogel Spacers in Prostate Radiotherapy: A Promising Approach to Decrease Rectal Toxicity*. Future Oncol **13**(29):2697-2708.

Pinkawa M, Berneking V, Schlenter M, et al. (2017). *Quality of Life After Radiation Therapy for Prostate Cancer with a Hydrogel Spacer: 5-Year Results*. Int J Radiation Oncol Biol Phys **99**(2):374-377.

Gary Boas, Author
Raul N. Uppot, M.D., Editor