Space creation, maintenance and absorption of a polyethylene glycol based prostate – rectum spacer

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Abstract
Study Objective. To evaluate the space creation, maintenance and absorption of an absorbable hydrogel injected into the perirectal space of patients prior to undergoing prostate radiotherapy.
Design. CT or MR imaging performed before hydrogel application (Baseline), one week after hydrogel application, following 8 weeks of IMRT (78Gy total) and then again 6 months following implantation.
Setting. University hospital
Patients. Twenty one prostate cancer patients with clinical stage T1 or T2 pathology
Interventions. Transperineal hydrogel injection into the perirectal space prior to IMRT
Measurements and Main Results. Measurement of space between the prostate and rectum in each patient at each time point.
Results. Hydrogel injection resulted in the creation of 11.5 $\pm$ 6.6 mm space (measured space – baseline). Space following IMRT and at six months was 12.3 $\pm$ 5.1 and 3.0 $\pm$ 2.8 mm, respectively (mean $\pm$ SD).
Conclusion. Hydrogel spacer injection into the perirectal space resulted in > 1 cm additional space between the prostate and rectum that was maintained throughout radiotherapy. The hydrogel was substantially absorbed within 6 months.

Rectal toxicity due to unintended rectal radiation in prostate cancer patients is largely a function of the close proximity of those two structures. Thus, to reduce the amount of rectal radiation, researchers have evaluated different biomaterials as temporary spacers between the prostate and rectum in patients undergoing prostate radiation therapy. Prada and colleagues were able to create an additional 1.5 cm of space between the prostate and rectum following the injection of hyaluronic acid (HA) into the perirectal space (Prada 2007). Similarly, also using HA Wilder was able to create 8-18 mm space (Wilder 2010), and more recently Noyes and colleagues evaluated the use of human collagen for the same purpose, resulting in 1.3 cm of space (Noyes 2011). While promising, issues related to HA radiation sensitivity (Daar 2010) and the potential of viral transmission from human derived products have resulted in considerable interest in synthetic polyethylene glycol (PEG) based materials used elsewhere in the body.

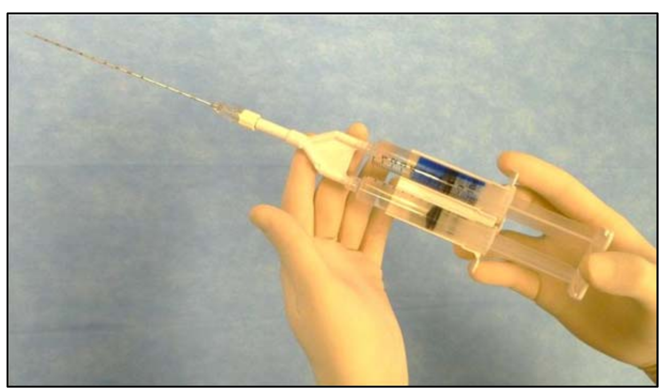
DuraSeal Dural Sealant (Covidien, Mansfield, MA) and Mynx Vascular Closure Device (AccessClosure, Mountain View, CA) are both absorbable PEG based hydrogels widely used in neurosurgery and interventional procedures, respectively. The safety profile of those products, in conjunction with the improved toxicity profile of PEGylated drugs (Jain 2010), suggests that PEG hydrogels may be ideal for use as prostate – rectum spacers.

Recently a PEG based hydrogel has been developed specifically as a prostate – rectum spacer for rectal sparing in prostate cancer patients undergoing radiation therapy. SpaceOAR™ System (Augmenix Inc, Waltham, MA) is injected into the perirectal space as a liquid via the transperineal route, where it opens the prostate rectum potential space and then polymerizes into a soft hydrogel (Figure 1). This created space can then reduce rectal radiation due to patient set up errors and to prostate / rectum movement during treatment.

However, in order to function properly this created space must be dimensionally stable and last throughout radiotherapy (typically 3 months). Dimensional stability throughout the course of radiotherapy is essential since radiation is delivered per a dose plan generated before the start of treatment, and gross changes in shape or space during treatment may lead to dosing errors.

This paper outlines the results of SpaceOAR hydrogel space creation, maintenance and absorption following application in 21 patients in our facility over an 18 month period.

Figure 1: The SpaceOAR applicator allows for simultaneous precursor injection through an 18G needle into the perirectal space. Once injected the precursors polymerizes to form an absorbable hydrogel.



Materials and Methods

A total of 21 patients were enrolled in a PEG – based hydrogel spacer evaluation initiated in October 2009, following Ethics Committee approval in our institution. Subjects with prostates < 80 cc, PSA ≤ 20 ng/mL, Gleason Score ≤ 7 (grade 3 predominant pattern) and clinical stage T1 or T2 pathology were considered eligible. Subjects with metastatic disease, prior prostate surgery or radiotherapy, or a history of inflammatory bowel disease were excluded from the study.

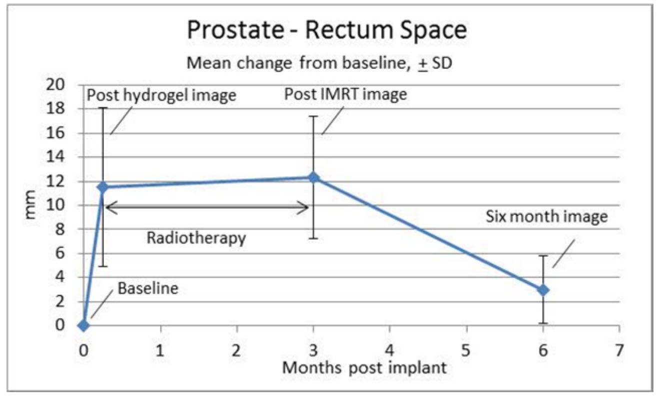
Prior to hydrogel spacer treatment all patients were imaged (CT or MRI) for the measurement of baseline prostate – rectum spacing. Using local anesthesia, an 18 G needle was used to inject the hydrogel precursors into the perirectal space, where they lifted the prostate and then solidified. Approximately one week following hydrogel spacer treatment patients were again imaged to measure the space created due to hydrogel injection. Patient dose plans for subsequent radiation delivery were then created using the post-implantation CT scan. Following delivery of radiation (200 cGy x 39 fractions) patients were again imaged for measurement of hydrogel persistence throughout radiation. Finally, six months following implantation patients were again imaged to determine the extent of hydrogel absorption.

Baseline, post hydrogel application, post IMRT and 6 month images were reviewed by an independent Radiation Oncologist who measured the mid gland space between the prostate and rectal lumen for every patient. Space resulting from hydrogel application was calculated by subtracting the baseline space from the space measured at each subsequent time point.

Results

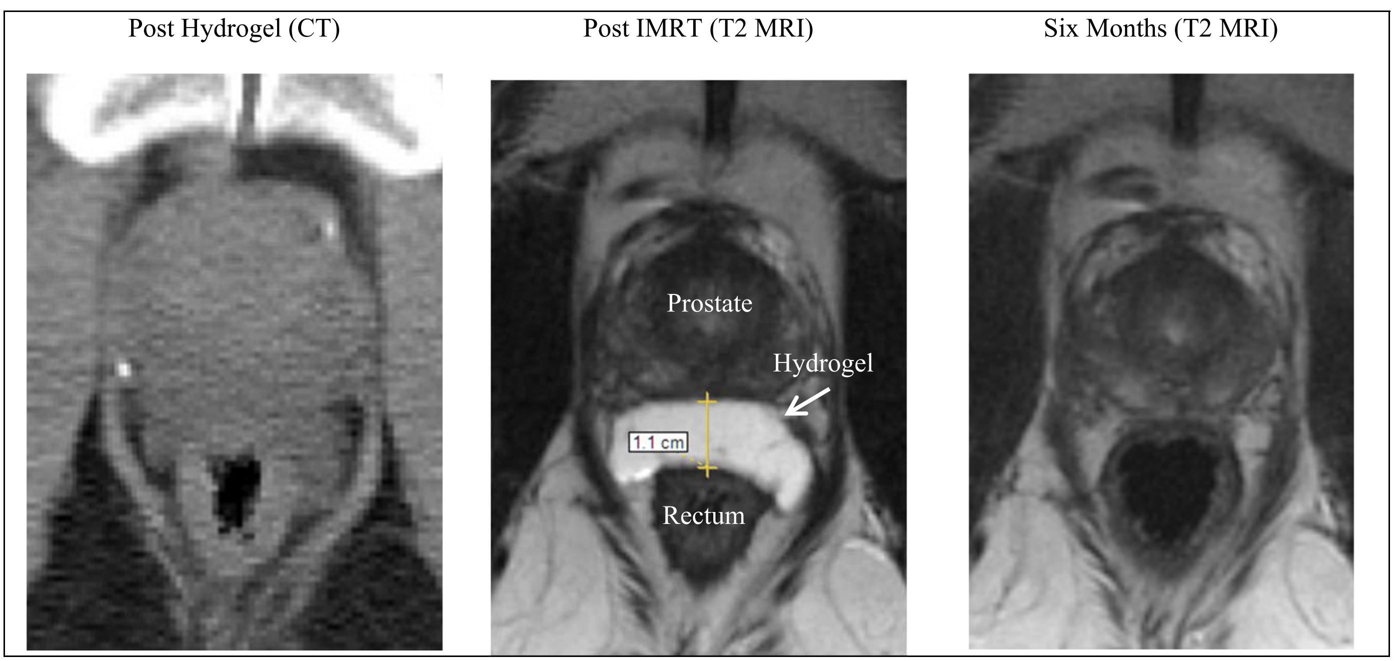
The space resulting from hydrogel implantation, along with the space remaining after radiation therapy, and at 6 months following implantation was 11.5 $\pm$ 6.6, 12.3 $\pm$ 5.1 and 3.0 $\pm$ 2.8 mm, respectively (mean $\pm$ SD, Figure 2).

Figure 2: Hydrogel space created as measured one week following implantation (Dose planning), at completion of radiotherapy (End IMRT) and at six months following implantation (End Acute Phase).



As seen in Figure 3, the hydrogel appearance is more conspicuous under T2 MR imaging than under CT. Nonetheless, the similarity in prostate – rectum space and gel morphology at both the post hydrogel and post IMRT time points is clearly evident.

Figure 3: CT and MR images from one patient within one week of implantation (Left, Post Hydrogel), at completion of radiotherapy (Middle, Post IMRT) and six months post implantation (Right, Six Months). Similarities in hydrogel and prostate morphology demonstrate gel stability during radiotherapy, with hydrogel absorption at six months.



Discussion

Application of hydrogel in this series of patients resulted in the creation of 11.5 mm additional space at the time the dose plan was created. This extra space should be sufficient to minimize rectal radiation secondary to dose expansion and intrafraction prostate / rectum movement. Typically a 4-5 mm radiation expansion on the posterior side of the prostate is created during dose planning, effectively assuring some high dose rectal radiation. Additionally, researchers tracking intrafraction prostate displacement have documented prostate movements $\geq$ 5 mm in 15% of treatment sessions (Kupelian 2006), resulting in rectum movement into and out of the high dose region.

However, in order to ensure the dose plan remains appropriate, the space created must be stable throughout the course of radiation delivery. In this study the hydrogel space increased by 0.8 mm between dose plan creation and the end of radiation therapy. This distance is easily within the error of daily set up, and will not impact dose delivery to the prostate.

Additionally it can be hypothesized that a hydrogel spacer will effectively 'stabilize' the dose distribution in the prostatic gland and therefore, makes treatment plans more robust and reliable:

- Roeske and colleagues tracked prostate movement with weekly CT's during treatment and found prostate movement up to 1 cm in the anterior-posterior direction, correlated to volume changes of the bladder and rectum (Roeske 1995). As the hydrogel takes up approximately 1 cm of anterior-posterior space, there is reason to believe that it may reduce prostate movement in that axis.

- Frank and colleagues found a decrease in prostate volume during the course of radiotherapy, with a median decrease of 11.5% over 42 fractions (Frank 2010). If treatment is guided by implanted fiducials, this prostate shrinkage effectively moves the rectum closer or into the high dose region. Hydrogel application between the rectum and prostate should reduce rectal radiation secondary to prostate shrinkage during treatment.

- Anderson and colleagues recently observed a significant decrease in rectal volume and rectal diameter during prostate IMRT (Anderson 2011). The authors conclude that "this observation is pertinent to prostate localization, planning margins, and implies that dose-volume histogram (DVH) analysis of rectal irradiation based on pre-treatment CT scanning may inaccurately estimate the risk of rectal toxicity". Hydrogel placement between the rectum and prostate could potentially shield the rectum from increased radiation as it decreases in volume and diameter during the course of radiotherapy.

- Nakamura and colleagues found significant changes in prostate shape, depending on rectal wall distension (Nakamura 2000). A stable hydrogel spacer should effectively shield the prostate from rectum volume changes, thus reducing changes in prostate morphology during radiotherapy.

Finally, the 3.0 mm space measured at 6 months post implantation demonstrate that the space is collapsing as the hydrogel is absorbed. This data is supported from the MR images at six months where the gel is no longer visible. Once hydrolyzed, the degradation byproduct is primarily PEG, which has been shown to be safely cleared from the body through renal filtration (Yamaoka, 1995).

Conclusions

Application of the PEG hydrogel spacer into the perirectal space resulted in the creation of > 1 cm space between the prostate and rectum that was maintained throughout radiotherapy. The hydrogel was substantially absorbed within 6 months of implantation, as evidenced by space measurements and imaging at that time point. This technology may prove to be an important tool in reducing the primary side effects of prostate radiotherapy.

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