Effect of a prostate-rectum hydrogel spacer on reducing acute radiation proctitis: A single center experience

Matthias Uhl, MD[1], Gencay Hatiboglu, MD[2], Klaus Herfarth, Dr. med.[1]
1. Dept of Rad Onc, University of Heidelberg, Heidelberg, Germany.
2. Dept of Urology, University of Heidelberg, Heidelberg, Germany.

SUMMARY: Gastrointestinal (GI) and genitourinary (GU) toxicity was assessed during and after conventional IMRT in 21 low to intermediate risk cancer patients that had received an absorbable hydrogel spacer between the prostate and the rectum. The transperineal hydrogel injection resulted in the creation of 11.5 mm space between the prostate and rectum; space that was not decreased throughout radiotherapy. The resulting rectal dose reduction following hydrogel application was 60.3%, relative to the potential rectal dose without the spacer. Hydrogel application was tolerated well, with a 38% rate of acute Grade 1 GI toxicity, and with no Grade 2 acute or chronic GI toxicity reported. The rates of acute and chronic Grade 2 or greater GU toxicity were 24% and 0% respectively. Images taken six months following application suggested hydrogel absorption, supported by a decrease in the prostate-rectum space to within 3 mm of baseline. Proctoscopy performed 15 months after hydrogel application showed no signs of telangiectasia, ulceration, stricture or necrosis.

Introduction

Prostate cancer is the second most common cancer in men worldwide. It is estimated that 910,000 men were diagnosed with prostate cancer in 2008, and is predicted to almost double (1.7 million) by 2030. In Europe, around 370,700 men were diagnosed with prostate cancer and 89,000 died from the disease in 2008 (Ferlay 2008).

An increasing number of men choose radiation therapy (RT) for the treatment of localized prostate cancer because of the perception that there is a lower risk of impotence and incontinence (Bucci et al. 2005). However, despite this potential benefit, one persistent concern associated with RT is the potential for acute and late rectal injury caused by direct mucosal damage from ionizing radiation. Since most prostate cancers arise in the peripheral zone of the gland, the rectum, due to its proximity to the prostate, is exposed to high levels of radiation if the tumor is to be effectively treated (Chen et al. 2000).

Rates of acute and chronic grade ≥ 2 rectal toxicity associated with dose-escalated (e.g., ≥78 Gy) Intensity Modulated Radiation Therapy (IMRT) have been documented to range from 3-50% and 5-24%, respectively (Zelefsky et al. 2008, Al-Mamgani, 2009). Furthermore, when evaluating toxicity from a patients' perspective, IMRT has an associated acute and late GI toxicity that has been demonstrated to have an important impact on quality of life (Fonteyne et al 2007). A patient self-assessment questionnaire analysis, performed by Koper et al., revealed that soiling and fecal loss (both surrogates for fecal incontinence) and mucus discharge were the most bothersome complaints (Koper et al 2004). In a study published by Sanda et al, radiotherapy was associated with a reduced quality of life related to bowel function early after treatment, and the change lasted for a year or more. Rectal urgency, frequency, pain, fecal incontinence, or hematochezia caused distress related to bowel function in 9% of patients one year after radiotherapy (Sanda et al. 2008). These studies certainly support the conclusion of Nguyen et al, in that rectal dose volume has a significant impact on patient reported bowel quality of life (QOL) (Nguyen et al., 2010).

Researchers have also documented a positive correlation between acute and late GI toxicity, demonstrating that late complications are more likely to occur in patients who also experienced acute complications. Indeed, in a study performed by Zelefsky et al. the incidence of late GI toxicity in those patients who experienced acute GI toxicity was significantly greater than those that had not experienced acute GI toxicity (42% vs. 9% respectively, $p<0.0001$), (Zelefsky et al. 2008).

Researchers have postulated that the application of an absorbable spacer between the prostate and rectum would allow for targeted prostate radiation with decreased radiation to the anterior rectum (Figure 1).

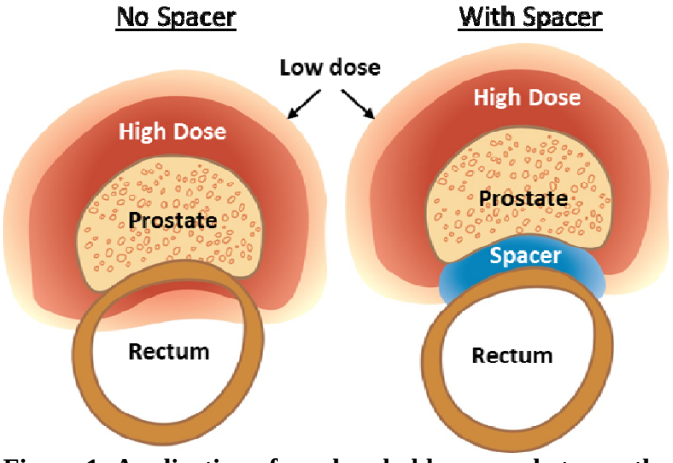

Figure 1: Application of an absorbable spacer between the prostate and rectum could reduce rectal radiation, along with the resulting rectal toxicity.

Prada et al evaluated the use of hyaluronic acid (HA) injected into the perirectal space in 36 low dose rate brachytherapy (LDR) patients, compared to 33 patients with no HA (Prada et al 2009). In his series application of the prostate-rectum

spacer decreased rectal bleeding from 12% to 0%, and decreased mucosal damage from 36% to 5%, relative to controls. Additionally, Wilder et al showed 0% acute rectal toxicity in a series of patients with HA spacers, compared to a 29.7% incidence in historical controls (Wilder et al 2010). Noyes et al evaluated the use of human collagen as a prostate-rectum spacer and observed a 50% reduction in dose to the anterior rectal wall (Noyes et al 2011). Finally, Pinkawa et al evaluated a PEG-based hydrogel (SpaceOAR System) as a perirectal spacer, resulting in an average of 8.1 mm additional prostate-rectum space, and a 59% decrease in rectal V70 (Pinkawa et al 2011).

This study was designed to evaluate the rectal toxicity in a series of patients following PEG hydrogel injection into the perirectal space.

Methods and Materials

Between October 2009 and January 2011 twenty one (21) patients with T1-T2 prostate cancer were enrolled into this prospective study to evaluate the safety and effectiveness of a hydrogel prostate-rectum spacer. Following informed consent, patients received a baseline CT image and subsequently received a transperineal hydrogel injection between their prostate and rectum (Figure 2). All patients have been followed for 6 months post implantation.

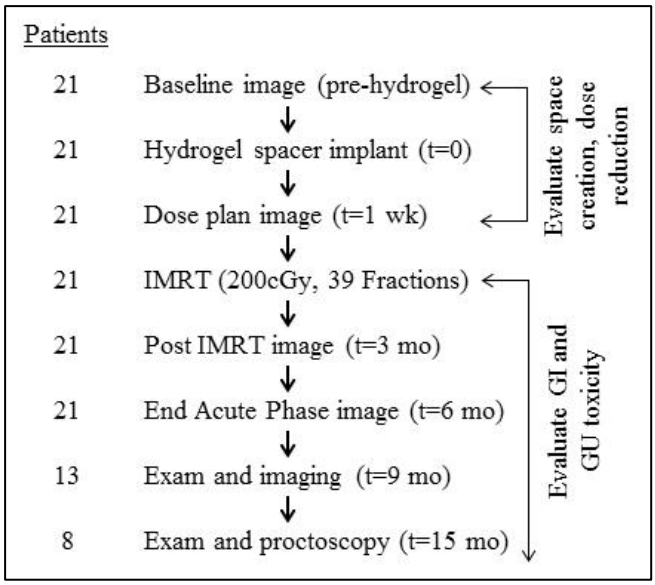

Figure 2: Study design and patient flow.

Within 3-5 days of implantation patients were again imaged, dose plans were created and patients then received 78 Gy radiation in 39 fractions. Following radiation patients were again imaged (~3 months post implant), and exams and imaging were repeated at 6 and 9 months post implantation. Exams and proctoscopy was performed at 15 months post implantation, with the proctoscopic findings scored using the Vienna Rectoscopy Scoring (VRS) method. Assessment of gastrointestinal (GI) and genitourinary (GU) toxicity was assessed weekly during radiotherapy, and then at each subsequent office visit using the RTOG scoring system.

Prostate-rectum hydrogel space created was assessed by subtracting the baseline space from the space measured in the subsequent post implant images. Also, rectal dose reduction due to hydrogel implantation was calculated by comparing dose plans created from the baseline and dose plan CTs.

PEG Hydrogel

The water and polyethylene glycol (PEG) based hydrogel (SpaceOAR System, Augmenix, Waltham, MA) is injected into the perirectal space with a 18G needle advanced through the perineum via transrectal ultrasound guidance. When injected the liquid precursor opens the potential space between the prostate and rectum and then polymerizes (solidifies) into a soft hydrogel. The hydrogel is designed to remain in place for three months and then liquefy via hydrolysis, allowing for systemic absorption, clearance from the body in the urine, and collapse of the created perirectal space.

The hydrolysis byproducts consist primarily of PEG which is widely used in the pharmaceutical industry and known for its inert nature and biocompatibility. The hydrogel is not derived from human or animal products, thus eliminating the potential for viral transfer or immunological impact.

Results

Early in the study it was recognized that many of the techniques and tools (side-fire ultrasound probe and stepper) used in brachytherapy seed placement are essential for proper application of this material. Hydrogel was applied in all 21 patients, resulting in the creation of 11.5 $\pm$ 6.6 mm (mean $\pm$ SD) space as measured at the time of dose planning (Figure 3). Created space at 3 months (post IMRT) and at 6 months was 12.3 $\pm$ 5.1 mm and 3.0 $\pm$ 2.8 mm, respectively, demonstrating maintenance of space during radiotherapy and a collapsing space as the hydrogel absorbs (Hatiboglu et al 2011).

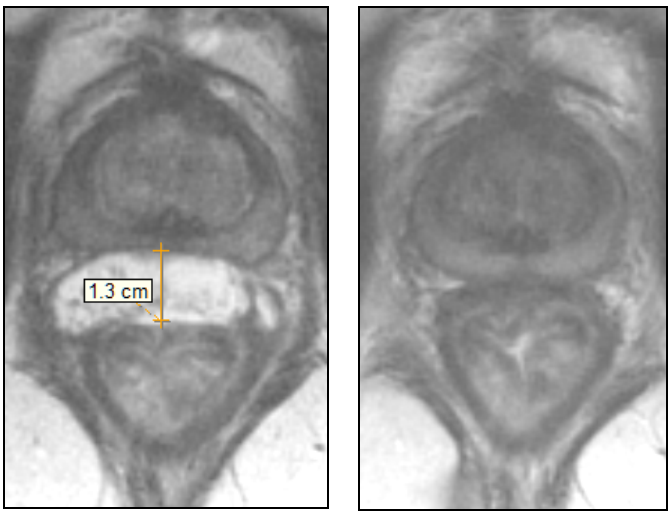

Figure 3: Axial T2 MR images of a patient showing gel present following IMRT (left, Post IMRT assessment), and then absorbed 3 months later at the End Acute Phase assessment (right).

As seen in Figure 4, hydrogel application resulted in decreased rectal radiation, when comparing the pre and post hydrogel dose plans. Calculated rectal V70 at baseline and following hydrogel application were 10.0 ± 3.3% and 3.6 ± 2.0% respectively (mean ± SD), representing a reduction of 60.3%. The bladder V70 at baseline and following hydrogel application was 15.1 ± 6.4% and 7.0 ± 3.1% respectively (mean ± SD) (Hatiboglu et al 2011).

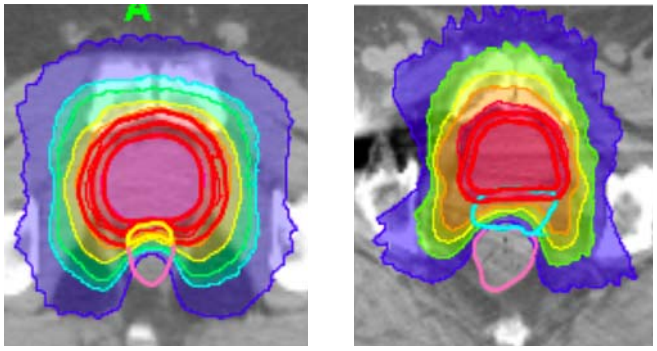

Figure 4: Dose plan before spacer application with the rectum in the high dose region (left), and after spacer application with less rectal radiation (right).

As noted in Table I, 8/21 (38%) patients experienced acute Grade 1 GI toxicity, while no other patients experienced any rectal toxicity. There were no patients with Grade 2 GI toxicity in this study. There were 5/21 (24%) patients with acute Grade 2 or greater GU toxicity, with no patients experiencing chronic Grade 2 or greater GU toxicity.

Grade	Gastrointestinal (GI)		Genitourinary (GU)	
	Acute (0-6 Mo)	Chronic (6-15 Mo)	Acute (0-6 Mo)	Chronic (6-15 Mo)
≥ 1	38% (8/21)	0% (0/13)	91% (19/21)	15% (2/13)
≥ 2	0% (0/21)	0% (0/13)	24% (5/21)	0% (0/13)

Table I: Acute (< 6 months) and Chronic (6-15 months) GI and GU toxicity. Of note is the low rate of acute GI toxicity, with no chronic toxicity.

At the 15 month proctoscopy all patients had a VRS score of 0 with no signs of telangiectasia, ulceration, stricture or necrosis.

Discussion

Rectal toxicity, typically minor, occasionally severe, has become an accepted side effect of prostate radiotherapy. While there has been great progress in prostate localization and conformal beams, the anatomical proximity of the rectum to the prostate ensures that some radiation will spill over to that sensitive structure.

Additionally, because the rectum is next to the posterior margin of the prostate, optimal cancer control is somewhat limited because aggressive prostate cancer targeting often results in unacceptable rectal toxicity. Further, advanced protocols that may result in economic benefits, improved cancer control and patient convenience (e.g. dose escalation, hypofractionation) are restrained due to potential rectal toxicity.

The ability to temporarily separate the prostate and rectum, thus reducing unintended rectal radiation, may enable improved prostate cancer targeting, higher doses, and fewer fractions without unacceptably increasing rectal toxicity.

The creation of over 1 cm space in this series of patients demonstrated the potential dose reduction, with a calculated 60.3% reduction in rectal V70. Additionally, it was observed that this space was maintained throughout radiotherapy, allowing this dose reduction to be realized throughout therapy, without the need to create new dose plans. At six months the gel appears to be substantially absorbed, as evidenced by the images at that time, along with space measurements showing the space returned to within 3 mm of baseline.

This calculated dose reduction does appear to be having the expected result in rectal toxicity reduction. In total 8/21 (38%) patients experienced any rectal toxicity, all of which was acute Grade 1. Additionally, while of limited duration, the modest amount of acute GI toxicity is predictive of low chronic toxicity rates. Heemsbergen et al demonstrated that acute mucus discharge and proctitis were strong predictors for overall toxicity (Heemsbergen et al 2006).

Finally, as this study had no concurrent controls, a comparison to the literature is required to put the observed toxicity rates into perspective. While the SpaceOAR GU toxicity is in line with the literature, the acute GI toxicity is considerably less than toxicity levels in the literature (Figure 5). Additional follow up of SpaceOAR treated patients is required in order to assess the impact on chronic toxicity.

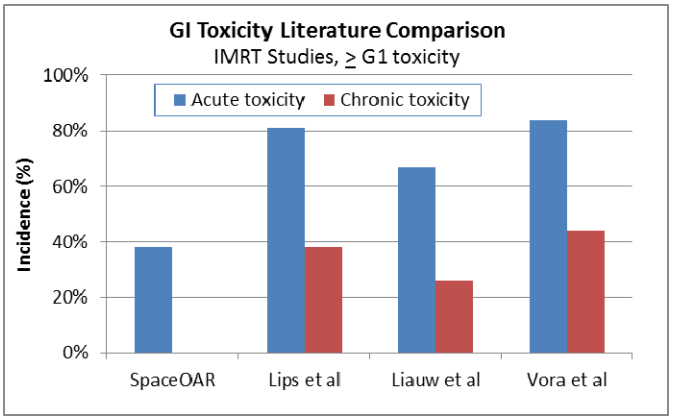

Figure 5: Acute and chronic GI toxicity from published IMRT studies.

Conclusions

Hydrogel spacer application resulted in the creation of > 1 cm additional space between the prostate and rectum, and this space was maintained throughout radiotherapy. This space resulted in a 60.3% reduction in rectal V70, without increasing radiation to the bladder. Patients experienced low rates of acute and chronic GI toxicity, as expected from reduced rectal radiation.

References

Al-Mamgani A, Heemsbergen WD, Peeters ST, et al. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. Int J Radiat Oncol Biol Phys 2009; 73:685-691.

Bucci MK, Bevan A, Roach M. Advances in radiation therapy: Conventional to 3D, to IMRT, to 4D, and beyond. CA Cancer J Clin 2005; 55:117-134.

Chen ME, Johnston DA, Tang K, Babaian RJ, Troncoso P. Detailed mapping of prostate carcinoma foci: Biopsy strategy implications. Cancer 2000; 89:1800–1809.

Ferlay J, Shin H Bray F, Forman D, et al. Estimates of worldwide burden of cancer 2008: Globan 2008. Int J Cancer 2010;127:2893-2917

Fonteyne V, De Neve W, Villeirs G, De Wagter C, De Meerleer G. L. Late radiotherapy-induced lower intestinal toxicity (RILIT) of intensity-modulated radiotherapy for prostate cancer: the need for adapting toxicity scales and the appearance of the sigmoid colon as co-responsible organ for lower intestinal toxicity. Radiotherapy Oncology 2007;84: 156-Su163.

Hatiboglu G, Pfitzenmaier J, Pahernik S, et al. Hydro - dissection technique for fast and safe transperineal spacer injection. Presented at DGU 2011.

Heemsbergen WD, Peeters ST, Koper PC, et al. Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. Int J Radiat Oncol Biol Phys. 2006 Sep 1;66(1):3-10. Epub 2006 Jul 11.

Koper PC, Heemsbergen WD, Hoogeman MS, Jansen PP, Hart GA, Wijnmaalen AJ, et al. Impact of volume and location of irradiated rectum wall on rectal blood loss after radiotherapy of prostate cancer. Int J Radiat Oncol Biol Phys 2004;58:1072–82.

Lips IM, Dehnad H, van Gils CH, et al. High-dose intensity-modulated radiotherapy for prostate cancer using daily fiducial marker-based position verification: acute and late toxicity in 331 patients. Radiat Oncol. 2008 May 21;3:15.

Liauw SL, Weichselbaum RR, Rash C, et al. Biochemical control and toxicity after intensity-modulated radiation therapy for prostate cancer. Technol Cancer Res Treat. 2009 Jun;8(3):201-6.

Noyes WR, Hosford CC, Schultz SE. Human Collagen Injections to Reduce Rectal Dose During Radiotherapy. Int J Radiat Oncol Biol Phys. 2011 Apr 22. [Epub ahead of print]

Nguyen PL, Chen RC, Hoffman KE, et al. Rectal dose-volume histogram parameters are associated with long-term patient-reported gastrointestinal quality of life after conventional and high-dose radiation for prostate cancer: a subgroup analysis of a randomized trial. Int J Radiat Oncol Biol Phys. 2010 Nov 15;78(4):1081-5. Epub 2010 Mar 6.

Pinkawa M, Djukic V, Holy R, Piroth MD, Klotz J, Frank D, et al. Application of a spacer between prostate and anterior rectal wall to optimize radiotherapy of localized prostate cancer. Strahlenther Onkol 2011; 187: Suppl. 1

Prada PJ, Gonzalez H, Menéndez C, et al. Transperineal injection of hyaluronic acid in the anterior perirectal fat to decrease rectal toxicity from radiation delivered with low-dose-rate brachytherapy for prostate cancer patients. Brachytherapy. 2009 Apr-Jun;8(2):210-7. Epub 2009 Feb 12.

Sanda MG, Dunn RL, Michalski J et al. Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors NEJM; 2008; 358;1250-1261.

Vora SA, Wong WW, Schild SE, et al. Analysis of biochemical control and prognostic factors in patients treated with either low-dose three-dimensional conformal radiation therapy or high-dose intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2007;68:1053–8.

Wilder RB, Barme GA, Gilbert RF et al. Cross-linked hyaluronan gel reduces the acute rectal toxicity of radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2010 Jul 1;77(3):824-30.

Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A, et al. Incidence of late rectal and urinary toxicities after three dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:1124–9.

SpaceOAR System is CE Mark approved and commercially available in select markets outside the United States. SpaceOAR System is not approved for use in the US.