Polyethylene glycol hydrogel rectal spacer implantation in patients with prostate cancer undergoing combination high-dose-rate brachytherapy and external beam radiotherapy

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ABSTRACT

PURPOSE: To present rectal toxicity rates in patients administered a polyethylene glycol (PEG) hydrogel rectal spacer in conjunction with combination high-dose-rate brachytherapy and external beam radiotherapy.

METHODS AND MATERIALS: Between February 2010 and April 2015, 326 prostate carcinoma patients underwent combination high-dose-rate brachytherapy of 16 Gy (average dose 15.5 Gy; standard deviation [SD] = 1.6 Gy) and external beam radiotherapy of 59.4 Gy (average dose 60.2 Gy; SD = 2.9 Gy). In conjunction with the radiation therapy regimen, each patient was injected with 10 mL of a PEG hydrogel in the anterior perirectal fat space. The injectable spacer (rectal spacer) creates a gap between the prostate and the rectum. The rectum is displaced from the radiation field, and rectal dose is substantially reduced. The goal is a reduction in rectal radiation toxicity. Clinical efficacy was determined by measuring acute and chronic rectal toxicity using the National Cancer Center Institute Common Terminology Criteria for Adverse Events v4.0 grading scheme.

RESULTS: Median followup was 16 months. The mean anterior–posterior separation achieved was 1.6 cm (SD = 0.4 cm). Rates of acute Grade 1 and 2 rectal toxicity were 37.4% and 2.8%, respectively. There were no acute Grade 3/4 toxicities. Rates of late Grade 1, 2, and 3 rectal toxicity were 12.7%, 1.4%, and 0.7%, respectively. There were no late Grade 4 toxicities.

CONCLUSIONS: PEG rectal spacer implantation is safe and well tolerated. Acute and chronic rectal toxicities are low despite aggressive dose escalation. © 2015 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Prostate; Cancer; Rectal; Spacer; Toxicity; Brachytherapy; Radiation; IMRT; HDR

Introduction

Prostate cancer is the most common cancer diagnosis among men in the United States (1). Prostate cancer represents 15% of all cancers in males (1). Eighty percent of men reaching age 80 will have developed cancer of the prostate (2). Prostate cancer is the sixth leading cause of cancer mortality in men worldwide. In 2010, it resulted in 256,000 deaths (3).

When detected early, radiation therapy is highly effective at treating prostate cancer. Cure rates are strongly correlated with increased radiation dose. Advances in treatment delivery and target localization have enabled dose escalation to a degree not possible only a decade ago. Despite revolutionary advances in technology, the rectum remains the primary dose-limiting normal tissue.

Because the rectum is in such close proximity to the prostate, rectal toxicity and rectal injury are a primary concern in prostate radiation therapy. The rectum is separated from the prostate by only a thin fibromuscular layer called Denonvillier's fascia. To deliver an escalated dose

to the prostate while simultaneously limiting the dose to the rectum requires great skill and advanced technology. The use of a spacer material to separate prostate and rectum makes rectal dose sparing readily achievable.

In previous studies, a decrease in rectal side effects was observed when a cross-linked hyaluronic acid gel was injected posterior to the Denonvillier's fascia (4). Mariados et al. (5) recently conducted a randomized control trial which showed improvement in rectal side effects with the use of a polyethylene glycol (PEG) spacer in patients undergoing external beam radiation alone. In this study, we evaluate the usage of a PEG hydrogel in 326 patients treated with combination high-dose-rate (HDR) brachytherapy and intensity-modulated radiation therapy (IMRT).

Methods and materials

This was a single center study performed at the Cancer Center of Irvine (Irvine, CA) to evaluate rectal symptoms with the usage of a rectal spacer. Study candidates included nonmetastatic patients with T1−T3 tumors with prostate glands less than 60 cc. All Gleason and prostate specific antigen scores were included. Acute and chronic rectal toxicity was evaluated for 326 patients administered a rectal spacer in conjunction with combination HDR and external beam IMRT. The median followup was 16 months with a range between 3 and 62 months. The percentage of patients receiving followup at 6, 12, and 18 months after treatment was 249 (76%), 185 (57%), and 141(43%), respectively. All patients provided informed consent for treatment. Please refer to Table 1 for a summary of patient characteristics.

HDR brachytherapy

The HDR treatments consisted of two HDR implants spaced 1 week apart. Rigid needles were implanted transperineally via ultrasound guidance. Patients were placed in the dorsal lithotomy position under spinal or general

Table 1
Patient characteristics

	Results
Median age (y) (range)	74 (46−96)
Median followup (mo) (range)	16 (0−63)
Clinical T stage (%)	
T2a	21 (71)
T2b−T2c	73 (237)
T3	6 (18)
Gleason score (%)	
6	28 (92)
7	47 (155)
8−10	24 (79)
PSA (%)	
<10 ng/mL	81 (264)
10−20 ng/mL	12 (43)
>20 ng/mL	6 (19)

anesthesia. A Foley catheter was placed into the bladder and inflated with 5 mL of contrast material. A 6.5-MHz endorectal ultrasound probe was inserted, and an interstitial template was secured against the perineum. The needle placement was arranged to provide optimal dose conformality. On average, 13 needles were used for each implant.

Most patients received 4 Gy twice daily with each implant for a total of 16 Gy. The average HDR dose was 15.5 Gy with a standard deviation (SD) of 1.6 Gy. The rectal spacer was injected during the second implant. It was found that injecting the spacer during the first implant would cause ultrasound image distortion for the second implant due to the presence of the spacer material. For that reason, the spacer was injected during the second implant.

HDR plans were generated using the Varian Brachyvision program (Varian Medical Systems). Inverse planning was available, but the HDR dosimetry was fairly conventional and forward planning was sufficient to meet the planning goals. The prostate gland was contoured as both the clinical tumor volume (CTV) and planning target volume (PTV) for treatment planning. The brachytherapy dose was prescribed to the 100% isodose line. Treatment planning goals were as follows: prescribed dose to at least 90% of the CTV ($V_{100} \geq 90$), maximum urethral dose under 120%, and maximum rectal and bladder dose less than 100%. Meeting the maximum urethral dose goal inherently limits excessively high doses, and every attempt was made to keep V_{150} less than 40%.

Intensity-modulated radiation therapy

IMRT was started within a week after the second HDR implant. A total dose of 59.4 Gy in 33 daily fractions was delivered over a 6.5-weeks period. An initial treatment plan was treated to 45 Gy for the first 25 treatments followed by a modified plan for the final eight fractions. The average total IMRT dose was 60.2 Gy with a SD of 2.9 Gy.

If the risk of pelvic lymph node involvement was 15% or lower according to the formula [percent lymph node risk = $2/3 \times$ prostate-specific antigen + ({Gleason score − 6} × 10)] (6), the CTV was defined as the prostate gland and inferomedial 10 mm of the seminal vesicles. If the risk of pelvic lymph node involvement was greater than 15%, the CTV for the first 25 fractions also included the pelvic lymph nodes as defined by Hsu et al. (7). For the remaining eight fractions, the CTV was defined as the prostate and inferomedial 10 mm of the seminal vesicles. In each case, the CTV was expanded 5−10 mm to generate a PTV. The rectum was contoured from the ischial tuberosities to the rectosigmoid junction. MRI fusion was used to ensure proper CTV and spacer delineation.

Treatment planning goals were as follows: prescribed dose to at least 95% of the PTV ($V_{100} \geq 95\%$), maximum dose to the PTV less than 110% of prescribed dose (PTVmax < 110%). Rectal dose limits were kept within the Radiation Therapy Oncology Group protocol 0415 for IMRT involving localized prostate cancer with no more than 15%, 20%, 25%, 35%, and 50% of the rectal volume receiving 60.4 Gy, 56.3 Gy, 52.3 Gy, 48.3 Gy, and 40.3 Gy, respectively.

Image-guided radiation therapy

All patients had five gold fiducial markers placed in the prostate. The fiducial markers were used for daily image-guided radiation therapy. Using a gantry mounted kilovoltage imaging system, daily cone beam CT scans were obtained immediately pretreatment. Using an overlay of the cone beam CT images and the reference treatment planning CT, the gold fiducial markers were aligned in three dimensions.

Rescanning timeline

To observe the hydrogel kinetics in the body, the first 200 patients underwent MRI imaging every 2 weeks. Observations revealed the PEG hydrogel completely resorbs in 4−6 weeks. Based on this resorption timeline, patients were rescanned and replanned at 45 Gy (5 weeks after the initiation of IMRT).

Injection of PEG hydrogel

The spacer material was injected after the second implant. Patients were instructed to perform an enema the night before and immediately before the implantation. The perineum was also sterilized with betadine before the procedure. Patients also took Cipro 500 mg BID for 10 days, starting the day before the procedure. Patients also received gentamicin 80 mg and cefazolin 1 g intraoperatively.

The PEG hydrogel (Duraseal) is manufactured by Covidien (Irvine, CA). The spacer material was used on an off-label basis. Using real-time sagittal ultrasound images, a 17-gauge guide needle was used to form a tract behind Denonvillier's fascia. The tracking needle was advanced to the midgland/base region of the prostate. Care is taken to avoid either perforating the prostate capsule or injuring the rectum. The tracking needle was removed and replaced with a plastic catheter with a metal internal guide. The metal internal guide is then removed, and 10 cc of the PEG hydrogel is injected. Simultaneous to the injection, the plastic catheter was slowly pulled inferiorly to ensure the hydrogel was distributed into the apex of the prostate. The PEG hydrogel completely solidifies within 3 seconds of injection. The PEG hydrogel is readily visualized on T2-weighted MRI scans (Fig. 1).

The PEG hydrogel is readily visualized on T2-weighted MRI scans. MRI imaging was performed after spacer implantation both for IMRT planning and to verify the
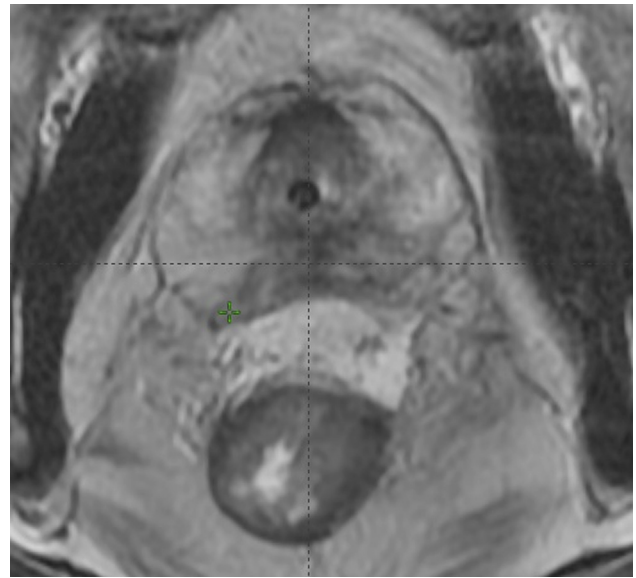

Fig. 1. T2 weighted MR image showing the presence of the PEG spacer between the prostate and rectum.

spacer material had been adequately placed. All patients with suboptimal spacer implantation had successful reimplantation before starting external beam radiotherapy. Anterior−posterior measurements determined the average separation induced by the spacer.

HDR dosimetry

Dose-volume histograms were constructed from the radiation therapy treatment plans. Because all patients received the rectal spacer on their second HDR implantation, we were able to evaluate mean and maximum rectal doses without (first HDR implant) and with (second HDR implant) the rectal spacer.

Rectal toxicity

All patients were evaluated at baseline, weekly during the external beam radiation, and every 3 months for the first year. Patients with stable PSAs were evaluated every 4−6 months after the first year. Acute toxicity is defined as toxicity occurring during radiation and within 90 days after cessation of radiation treatment. Late toxicity was defined as all adverse events 90 days after treatment cessation. All rectal adverse events from radiation treatment were recorded and graded by a board of physicians. We graded the severity of rectal symptoms during radiation treatments according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 grading scheme.

Results

The mean anterior−posterior distance of the spacer material was 1.6 cm (SD = 0.4 cm). Of the 326 patients, there

were 18 cases (5.5%) where spacer was injected into the rectal lumen. No infections resulted from these rectal penetrations. Patients with suboptimal rectal spacer implantation underwent a repeat spacer implant procedure before starting IMRT. By the fourth week of IMRT, the spacer material was completely absorbed in most patients (80%).

Mean and maximum HDR rectal doses were compared for the first and second HDR implants (i.e., without and with the spacer material). Without the spacer, the average mean dose to the rectum was 36% (SD = 6.6%) of prescribed dose. With the spacer, the average mean rectal dose was 29% (SD = 4.9%). When using a spacer, the mean rectal dose reduced by 7% of prescribed dose. Without the spacer, the average maximum dose to the rectum was 95% (SD = 9.3%) of prescribed dose. With the spacer, the average maximum dose decreased to 78% (SD = 11.9%). When using a spacer, the maximum dose was reduced by 17% of prescribed dose.

Rates of acute Grade 1 and 2 rectal toxicity were 37.4% and 2.8%, respectively. The most common acute rectal toxicity was diarrhea occurring in 40% of patients. Rectal bleeding was not tallied as a radiation toxicity. After HDR implantation, most patients exhibit some rectal bleeding, so rectal bleeding was not a meaningful factor to evaluate in relation to spacer implantation and radiation toxicity. On average, acute rectal toxicities resolved in 2.1 months (SD = 0.9 months). There were no acute Grade 3 or 4 rectal toxicities noted.

Rates of late Grade 1 and 2 rectal toxicity were 12.7% and 1.4%, respectively. Two patients (0.7%) developed Grade 3 rectal toxicities. One patient developed severe proctitis 17 months after finishing radiation. The patient presented with a mixture of severe fecal obstruction, explosive diarrhea, and fecal incontinence. He was treated with laxatives, stool softeners, and hydrocortisone suppositories. His symptoms improved and resolved after 9 months. Another patient developed a fistula 4 months after finishing radiation treatment. He was treated with steroid suppositories. The patient went on to develop necrotizing fasciitis from the rectum down to his leg. He required an elective diverting colostomy to allow his rectum to heal and to control the necrotizing fasciitis. The infection is now resolved, and the patient is doing well with a functioning colostomy. He will have the colostomy reversed after his rectum has healed.

Discussion

This is a single arm retrospective study reporting the safety and efficacy of spacer implantation for patients receiving combined HDR and IMRT. Toxicity data were collected from patient reported symptoms at the time of followup. Symptoms were then correlated with the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. At the time of this report, mean followup was limited to 16 months. Longer followup is needed to further track late toxicities. Comparison to standard radiation therapy techniques is desirable. There are other published studies of combined modality radiation (HDR/IMRT) for prostate cancer treatment (8−10); however, each study uses different radiation fractionation and imaging protocols. It should be noted that unlike the Mariados (5) study, our study did not exclude high-risk patients. We felt placement of the spacer material would not compromise cure rates among high-risk patients. Even in advanced cases, prostate cancer very rarely penetrates the Denonvillier's fascia to invade the rectum. For that reason, we felt it safe to inject the spacer as long as there was no gross visible tumor invasion of the rectum.

The fact that the PEG hydrogel resorbs in 4−6 weeks has dosimetric consequences. The physical separation between the prostate and rectum decreases during that interval, and the rectal dose sparing observed at the start of IMRT gradually diminishes over time. It is important to note, however, that IMRT dose distributions fall off rapidly outside the target and the presence of any spacer material provides a rectal dose sparing advantage. Dose sparing is significant whether the spacer separation is 1 cm or 1 mm, and it should be emphasized that even in the event of total resorption, rectal dose sparing is no worse off than a conventional IMRT plan. That being said, research into more stable compounds is warranted. In an ideal scenario, the spacer would remain constant over the entire course of therapy, and a hydrogel that resorbs more slowly would be desirable.

Maximum rectal dose sparing would occur if the spacer were in place for both HDR implants. However, the hydrogel in place for half of the HDR dose is dosimetrically significant. The rectum is protected during half the HDR brachytherapy and most of the IMRT course. For that reason, we feel comfortable delivering the first HDR implant without the spacer.

Research into the temporal dosimetric consequences of spacer resorption is desirable. New technologies are under development to provide ongoing dosimetric information on a treatment-by-treatment basis. These technologies use the daily image guidance data to reconstruct the delivered dose based on the anatomical state at the time of treatment. The organ dose is updated cumulatively throughout the course of treatment allowing one to quantify in near real time the dosimetric effect of spacer absorption. Physicians could set a threshold for both rescanning and possibly reimplanting the spacer. In this way, every patient would have an individualized treatment regimen based on his specific spacer kinetics.

It is anticipated that the rectal spacer utilization will carry over into different forms of dose escalation therapy for prostate cancer such as HDR monotherapy and stereotactic body radiotherapy (SBRT). In HDR monotherapy, the entire dose is delivered via HDR implants. In some HDR monotherapy techniques, the entire dose is delivered

in one needle implant insertion. In this scenario, issues related to the spacer material occluding the ultrasound image would not be applicable, and the spacer would provide a dose sparing advantage for the entire HDR dose. Prostate SBRT is another technique that could benefit greatly from a rectal spacer. In prostate SBRT, the standard dose regimen is compressed into five high-dose treatment fractions. Rectal dose sparing in critical and a rectal spacer would be of great value.

This study shows that despite the dose escalation with combination HDR/IMRT, rates of rectal injury were low. Implantation of the PEG spacer proved to be safe and well tolerated. There were no reports of infection or cyst formation. Currently, this is the largest reported study of patients receiving the rectal spacer who underwent combination HDR brachytherapy and external beam radiotherapy. This study contributes to the growing body of evidence for the usage of a rectal spacer to reduce rectal toxicity (11—14). At our center, we have begun further research into evaluating rectal spacer usage in patients requiring salvage or adjuvant radiation after prostatectomy (15).

Conclusions

The use of a rectal spacer is safe and effective for patients treated with combination HDR and IMRT radiation therapy for prostate cancer. Spacer implantation was successful in most patients, and no infections were noted when using our antibiotic prophylaxis regimen. Rectal spacer application resulted in an average 1.6 cm separation between the prostate and rectum. The spacer enabled significant rectal dose reduction, and patients exhibited low rates of rectal toxicity.

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