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Brachytherapy ■ (2016) ■

BRACHYTHERAPY

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.

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

Received 12 October 2015; received in revised form 7 December 2015; accepted 15 December 2015.

Financial disclosure: All authors stated that they have nothing to disclose.

A portion of the study was funded by the Medici Foundation (non-profit organization).

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1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2015.12.007

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 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.

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)

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 × 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.