ELSEVIER

Brachytherapy 13 (2014) 111–116

BRACHYTHERAPY

A Phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy

Yoshiya Yamada[1,*], Marisa A. Kollmeier[1], Xin Pei[1], Chu Cheng Kan[1], Gil'ad N. Cohen[2], Sherri M. Donat[3], Brett W. Cox[1], Michael J. Zelefsky[1]

[1]*Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY*
[2]*Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY*
[3]*Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY*

ABSTRACT

PURPOSE: We report the toxicity and biochemical tumor control outcome of a prospective Phase II study using high-dose-rate brachytherapy (HDR) alone as a salvage therapy for recurrent disease after external beam radiotherapy (EBRT).

METHODS: Forty-two patients with biopsy-proven recurrence were enrolled on a Phase II study of salvage HDR monotherapy using iridium-192. Median pretreatment EBRT dose was 8100 cGy (6840–8640 cGy) and the median time from completion of EBRT to salvage HDR was 73 months. The protocol prescription dose of 3200 cGy was delivered in four fractions over 30 hours in a single insertion. Median followup after salvage HDR was 36 months (6–67 months).

RESULTS: The actuarial prostate-specific antigen biochemical relapse-free survival and distant metastases-free survival rates at 5 years were 68.5% and 81.5%, respectively. Cause-specific survival was 90.3%. Late genitourinary Grade 1and 2 toxicities were found in 38% and 48%, respectively, and one patient developed Grade 3 urinary incontinence. Late Grade 1 and 2 gastrointestinal toxicity was noted in 17% and 8% of patients, respectively. Three patients (7%) developed Grade 2 late urinary toxicity (urethral stricture), which were corrected with urethral dilatation, and one patient developed Grade 3 urinary incontinence. No Grade 4 toxicities were observed.

CONCLUSIONS: Genitourinary toxicity was the most commonly encountered toxicity observed after salvage HDR but severe toxicities were uncommon. Salvage HDR is an effective and well-tolerated modality for locally recurrent prostate cancer and should be considered even for patients who have previously been treated with ultra-high dose levels of EBRT.

Keywords: Salvage brachytherapy; High dose rate brachytherapy

Introduction

High-dose intensity-modulated radiotherapy (IMRT) has proven to be an effective treatment for localized prostate cancer (1–6). In the case of local recurrence, salvage options are limited for these patients. These patients are often not considered optimal candidates for salvage prostatectomy because of their age or medical comorbidities even if the disease presentation at the time of recurrence demonstrates localized disease only. Prior definitive dose levels of radiation to the bladder, rectal wall, and urethra place these patients at higher risk for severe complications with additional salvage therapy. High-dose-rate brachytherapy (HDR) has dosimetric and radiobiologic advantages as a salvage treatment paradigm. One recent study (7) reported 50% biochemical tumor control outcomes with salvage HDR brachytherapy when used as monotherapy. We report on the long-term results of a prospective Phase II trial where HDR brachytherapy was used as salvage therapy for localized recurrent disease after external beam radiotherapy (EBRT).

Received 27 August 2013; received in revised form 31 October 2013; accepted 21 November 2013.

Disclosures: The authors have no disclosures.

* Corresponding author. Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. Tel.: (212) 639-212-6802; fax: (212) 639-8876.

E-mail address: yamadaj@mskcc.org (Y. Yamada).

1538-4721
http://dx.doi.org/10.1016/j.brachy.2013.11.005

Methods and materials

Forty-two patients with biopsy-proven recurrence were enrolled on an institutional review board–approved Phase II study of salvage HDR monotherapy using iridium-192. The primary end points of the trial were toxicity, assessed with the Common Toxicity Criteria for Adverse Events version 3, as well as the International Prostate Symptom Score (IPSS), and the International Index of Erectile Function. Biochemical control was evaluated using the Phoenix definition (nadir +2). Patient accrual spanned from 2007 to 2011, and patients were followed for at least 1 year after treatment on protocol and then in routine followup thereafter. Patients were seen in followup 1 month after treatment and then at 4-month intervals.

To be eligible for the trial, patients were required to have biopsy-proven recurrence after definitive EBRT. All biopsies were confirmed by pathologic review at our institution. Patients with radiographic evidence of extraprostatic disease demonstrated on an MRI with an endorectal coil, or metastatic disease seen on bone scan, were excluded from the study. Other exclusion criteria included patients with serum prostate-specific antigen (PSA) >10 ng/mL at the time of assessment and those with a baseline total IPSS >15 before planned salvage therapy. Any patient with a history of inflammatory bowel disease or rectal surgery was also excluded from enrollment. Patients were also required to be able to tolerate general anesthesia. Those with abnormal coagulation profiles (international normalized ratio >2.5, platelet count <75,000) or liver/renal function tests >1.5 × normal were also ineligible.

The method of HDR used in these patients has been previously described (8). In short, HDR catheters were placed with ultrasound guidance under general anesthesia. The entire prostate was implanted. The clinical target volume was the entire prostate, with a margin of 5 mm added around the entire gland. A dose of 800 cGy per fraction was prescribed to the periphery of the clinical target volume, except near the bladder neck, were the dose was typically 5–10% lower, at the discretion of the treating oncologist, unless tumor was thought to reside in that area. Four fractions were given a minimum of 4 hours apart, over 30 hours, in a single insertion. A genetic inverse treatment-planning algorithm was used for treatment-planning source dwell position and time optimization. The following dose–volume constraints were used for treatment planning similar to our dose thresholds used when treating non-recurrent HDR patients: minimum 95% target coverage with the prescription dose (PD), 120% of PD for maximum urethra dose, and rectal maximum dose not greater than 100% of PD. Catheter position was verified radiographically before each fraction. An iridium-192 HDR source was used for each treatment, using an afterloading technique. Table 1 summarizes key dosimetric parameters achieved for this study.

These 42 patients had a median followup of 36 months, with a range of 6–66 months. Patient characteristics are summarized in Table 2. Median pretreatment EBRT dose was 8100 cGy (6840–8640 cGy) and the median time from completion of initial EBRT to salvage HDR was 78 months. Median presalvage PSA was 3.54 ng/mL. Eighteen patients had received androgen-deprivation therapy before salvage HDR, but androgen-deprivation therapy was discontinued after treatment in all cases.

Table 1
Dosimetry

Dosimetry factors	Minimum	Lower-hinge	Median	Upper-hinge	Maximum
Prostate volume (cm^3)	17	28	33.5	43	64
V_{100} (%)	87	92	94.5	96	99
D_{90} (%)	90	103	106.5	108	119
V_{150} (%)	23	29	32.5	38	46
Urethra D_{max}	110	114	116	118	127
Urethra D_5 (%)	104	110	113	115	122
Urethra D_{20} (%)	100	108	110.5	113	119
Rectum V_{100} cm^3	0	0	0	0	0.1
Rectum D_1 cm^3 (%)	18	50	61.5	72	86
Rectum D_2 cm^3 (%)	14	45	54	63	79

Results

Tumor control outcomes

Ten patients developed a biochemical relapse at a median of 16.5 months from salvage treatment. The actuarial PSA relapse-free survival at 5 years was 68.5% (Fig. 1). Three patients have developed evidence of metastatic disease. The actuarial distant metastases-free survival at 5 years was 81.5% (Fig. 2), and the 5-year overall survival outcome was 79%.

Toxicity outcomes

Acute genitourinary (GU) Grade 1 and 2 toxicities were noted in 38% and 40% of patients, respectively. Late GU Grade 1 and 2 toxicities were observed in 38% and 48%,

Table 2
Patient characteristics

Characteristics	Patient (n = 42) I
Median months followup (range)	36 (2–66)
Median patient age (range)	72 (56–83)
Median cm^3 pretreatment gland volume (range)	33.5 (11–64)
Pretreatment PSA (%)	
<4.0	23 (55)
4.0–10	14 (33)
>10	5 (12)
Gleason score (%)	
6	3 (7)
7	25 (60)
≥8	14 (33)
Patient on ADT (%)	18 (43)

PSA = prostate-specific antigen; ADT = androgen-deprivation therapy.