ELSEVIER

Brachytherapy ■ (2017) ■

BRACHYTHERAPY

Salvage of locally recurrent prostate cancer after external beam radiation using reduced-dose brachytherapy with neoadjuvant plus adjuvant androgen deprivation

Brian C. Baumann[1,2,*,4], John C. Baumann[3,4], John P. Christodouleas[2], Edward Soffen[3]

[1]*Department of Radiation Oncology, Washington University in Saint Louis, Saint Louis, MO*
[2]*Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA*
[3]*Princeton Radiation Oncology, Princeton, NJ*

ABSTRACT

PURPOSE: Local recurrence (LR) of prostate cancer after external beam radiotherapy (EBRT) is a serious problem. Our purpose was to determine if reduced-dose salvage brachytherapy could achieve high rates of biochemical control with acceptable toxicity if combined with androgen deprivation therapy (ADT).

METHODS AND MATERIALS: Thirty-three consecutive patients with LR after EBRT were treated with salvage brachytherapy plus ADT from 1998 to 2013. All had pathologically confirmed LR, disease-free interval ≥18 months after EBRT, no distant/nodal metastasis, and International Prostate Symptom Score ≤15. Whole-gland salvage treatment was delivered using low-dose-rate (median 100 Gy with ^{103}Pd, $n = 25$) or high-dose-rate brachytherapy (30 Gy in 6 fractions over 4 weeks, $n = 8$) plus 4−6 months of neoadjuvant plus adjuvant ADT.

RESULTS: Fifty-five percent had high-risk disease at diagnosis. Median EBRT dose was 70.2 Gy; median prostate-specific antigen nadir was 0.8 ng/mL. Median time to recurrence was 56 months; median presalvage prostate-specific antigen was 5.0 ng/mL. Median postbrachytherapy followup was 61 months (range 7−150 months). Five and 7-year relapse-free survival, distant metastasis-free survival, and overall survival were 79% and 67%; 93% and 86%; and 94% and 85%, respectively. Freedom from late Grade 3 GU toxicity at 5 years was 85%. There were no late Grade ≥2 GI toxicities.

CONCLUSIONS: This is the largest series of salvage brachytherapy combined with neoadjuvant plus adjuvant ADT and uses reduced-dose brachytherapy. Results suggest that reduced-dose salvage brachytherapy is feasible and reasonably well tolerated when combined with ADT. Compared to prior series, this approach was associated with favorable relapse-free survival. Prospective studies of reduced-dose salvage brachytherapy plus ADT are warranted.

Keywords: Salvage brachytherapy; Prostate cancer; Androgen deprivation therapy

Introduction

Local recurrence (LR) after external beam radiotherapy (EBRT) for localized prostate cancer is a serious problem with 8-year local-only recurrence rates for intermediate- and high-risk disease of 10% and 15%, respectively (1, 2). Although these patients have potentially salvageable disease, most receive noncurative androgen deprivation therapy (ADT) (1). Data for curative salvage options are limited. No prospective studies compare options such as salvage prostatectomy, cryotherapy, high-intensity focused ultrasound (HIFU), or reirradiation to each other or to ADT (3).

Evidence from small series suggests that prostate brachytherapy is a potentially curative salvage therapy, but there are concerns about toxicity (3−6). Unfortunately, data are insufficient to guide patient selection or to determine the optimal salvage brachytherapy dose because all prior reports used similar doses typically

Received 25 August 2016; received in revised form 22 December 2016; accepted 22 December 2016.

* Corresponding author. Department of Radiation Oncology, Siteman Cancer Center, Center for Advanced Medicine, Washington University in Saint Louis, 4921 Parkview Place, Lower Level, St. Louis, MO 63110. Tel.: (609) 655-5755; fax: (609) 655-5725.

E-mail address: brian.baumann@wustl.edu (B.C. Baumann).

[4] The above authors contributed equally to the manuscript.

1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2016.12.011

used to treat previously untreated cancers. Reports combining salvage brachytherapy with ADT are limited even though ADT coupled with EBRT seems beneficial for the initial treatment of higher-risk prostate cancers and for salvage radiation after prostatectomy (7, 8). There is suggestive evidence that adding ADT to radiation may have a synergistic effect given the larger improvement in outcomes from adding ADT to radiotherapy compared to adding ADT to prostatectomy (9, 10). In this study, we hypothesized that a combination of whole-gland salvage brachytherapy preceded by neoadjuvant ADT and followed by additional adjuvant ADT would be well tolerated and permit a reduction in the brachytherapy dose without compromising long-term biochemical control.

Methods and materials

This institutional review board-approved retrospective study examined 39 consecutive patients with biopsy-proven locally recurrent prostate cancer after EBRT treated with salvage brachytherapy from 1998 to 2013. All patients with locally recurrent disease were included who had no distant/nodal metastases on bone scan and CT and/or MRI of the abdomen/pelvis, no extracapsular extension/seminal vesicle invasion on rectal examination and/or MRI, a disease-free interval ≥18 months after EBRT, ECOG score of 0−2, an International Prostate Symptom Score ≤15, no severe residual late toxicity from prior EBRT, and the ability to tolerate general anesthesia. A review of the cases confirmed that all met both the ASTRO and Phoenix definitions of biochemical recurrence before their ultrasound-guided core biopsies confirming recurrent disease.

Thirty-three of 39 patients received neoadjuvant + adjuvant ADT as part of their salvage regimen consisting of 2−3 months of ADT before brachytherapy followed by 2−3 months of ADT after the implant. The remaining six were excluded from the primary analysis: five did not receive ADT with their implants because they refused or had cardiac comorbidities, and one received neoadjuvant-only ADT. ADT was administered as several weeks of bicalutamide before leuprolide injections.

Brachytherapy treatments

Salvage brachytherapy to the whole prostate was delivered to 25 patients using low-dose-rate (LDR) ^{103}Pd seed implants to a median dose of 100 Gy with 72% receiving 100 Gy and 28%, predominantly patients treated before 2000, receiving 90 Gy. Eight patients received high-dose-rate (HDR) ^{192}Ir brachytherapy to a dose of 30 Gy in 6 fractions with two separate insertions separated by ~4 weeks. Fractions were separated by at least 4 hours (Table 1). The distribution of sources within the prostate was planned as if treating a previously unirradiated prostate. Given the absence of data on optimal dose for salvage brachytherapy at the initiation of this series, we chose implant doses typically used in combination with EBRT to boost previously untreated prostates (11). These prescription doses are lower than doses reported in other salvage brachytherapy series.

LDR brachytherapy was preplanned using transrectal ultrasound and CT simulation. No patients were excluded due to pubic arch interference, which could not exceed 3−5 mm. Linked seeds were inserted under ultrasound guidance with the patient anesthetized in the lithotomy position. Plan evaluation was performed 1-month postimplant. Target volume constraints included dose received by 90% of the prostate to be >90% of the prescription dose (D_{90}) and volume of prostate receiving 100% of the prescription dose >90% (V_{100}). Volume of the urethra getting ≥125% of the prescription dose (V_{125}) should be equal to zero (11). Rectal dose was kept as low as possible. Postimplant dosimetry data were available for all patients who underwent salvage after 1999. D_{90}, V_{100}, and V_{125} for the urethra constraints were met. The median D_{90} was 113 Gy (range 90−119 Gy) for the 25 LDR patients who underwent salvage brachytherapy after 1999.

HDR brachytherapy was performed with placement of HD catheters using transrectal ultrasound guidance with the patient anesthetized in the lithotomy position. CT-based planning was used. The clinical target volume was the entire prostate, with a 5-mm margin around the entire gland. A dose of 5 Gy per fraction was prescribed to the periphery of the target volume. An inverse-treatment planning algorithm was used for treatment

Table 1
Details of brachytherapy treatments

Characteristics	LDR	HDR
Median prescription dose	100 Gy (^{103}Pd)	30 Gy in 6 fx (^{192}I) with two insertions, 4 h between fractions
ADT	Antiandrogen lead-in followed by LHRH agonist	Antiandrogen lead-in followed by LHRH agonist
ADT duration	4−6 months	4−6 months
CT-based planning	Yes	Yes
Planning	Preplan with linked seeds	Inverse planning
Target dosimetry	D_{90} > 90%: 100% of patients[a] V_{100} > 90%: 100%[a] of patients[a]	95% of the PTV getting >95% of the prescription dose: 100% of patients
Organs at risk dosimetry	Urethra V_{125} = 0: 100% of patients[a]	Urethra V_{125} = 0: 100% of patients

LDR = low dose rate; HDR = high dose rate; ADT = androgen deprivation therapy; LHRH = luteinizing hormone-releasing hormone; PTV = planning target volume.

[a] Postimplant dosimetry data available for all patients treated with ^{103}Pd to 100 Gy (n = 25).