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Clinical outcomes of high-dose-rate brachytherapy and external beam radiotherapy in the management of clinically localized prostate cancer

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ABSTRACT

PURPOSE: To report prostate-specific antigen (PSA) relapse-free survival and treatment-related toxicity outcomes after combining high-dose-rate (HDR) brachytherapy with external beam radiotherapy (EBRT) for patients with clinically localized prostate cancer.

METHODS AND MATERIALS: Between 1998 and 2009, 229 patients were treated with HDR brachytherapy followed 3 weeks later by supplemental EBRT. The HDR brachytherapy boost consisted of three fractions of ^{192}Ir (5.5–7.5 Gy per fraction), and EBRT consisted of intensity-modulated radiotherapy delivering an additional 45.0–50.4 Gy directed to the prostate gland and seminal vesicles. Median follow-up was 61 months.

RESULTS: Seven-year PSA relapse-free survival for low-, intermediate-, and high-risk patients were 95%, 90%, and 57%, respectively ($p < 0.001$). Among high-risk patients treated with biological equivalent doses in excess of 190 Gy, 7-year PSA relapse-free survival was 81%. In multivariate analysis, Gleason scores of ≥8 predicted for increased risk of biochemical failure, whereas the use of short-term neoadjuvant androgen deprivation therapy did not influence tumor-control outcomes even among intermediate- or high-risk patients. Seven-year incidence of distant metastases for low-, intermediate-, and high-risk patients were 5%, 3%, and 17%, respectively. Seven-year incidence of late Grade 2 and 3 genitourinary toxicities were 22.1% and 4.9%, respectively and the 7-year incidence of Grade 2 and 3 gastrointestinal toxicities were 1% and 0.4%, respectively.

CONCLUSION: HDR prostate brachytherapy in conjunction with supplemental EBRT results in excellent biochemical relapse-free survival rates with a low incidence of severe late genitourinary or gastrointestinal toxicities. The use of short-term neoadjuvant androgen deprivation did not influence long-term biochemical tumor control in this cohort.

Keywords: High-dose rate; Brachytherapy; Prostate cancer; Radiation therapy; IMRT; Toxicity

Introduction

In the radiotherapeutic management of clinically localized prostate cancer, dose escalation studies have been consistently associated with improved biochemical control outcomes and a reduction in distant metastases [DMs (1–5)]. Furthermore, this favorable treatment response to higher radiation doses is most evident in patients with intermediate- and high-risk disease. Therefore, in an effort to escalate the intraprostatic dose without compromising periprostatic dose coverage, external beam radiation therapy (EBRT) has been used in combination with a high-dose-rate (HDR) brachytherapy boost. Recent evidence from our institution has demonstrated that the use of this combination treatment approach improves tumor control in those patients with intermediate-risk disease and selected patients with high-risk disease (6).

In the present study, we report our long-term efficacy and toxicity outcomes using EBRT in combination with HDR brachytherapy for patients with clinically localized prostate cancer. Consistent with other reports (6–15), our

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data show that this combination treatment regimen is associated with excellent tumor control rates for favorable- and intermediate-risk patients and acceptably low rates of late genitourinary (GU) and gastrointestinal (GI) treatment-related toxicities.

Methods and materials

Between 1998 and 2010, 229 patients with clinically localized, biopsy-proven adenocarcinoma of the prostate were treated with HDR brachytherapy followed 3 weeks later by EBRT at Memorial Sloan-Kettering Cancer Center. The clinical characteristics of patients in this study are summarized in Table 1. The patients were stratified into prognostic risk category groups based on the National Comprehensive Cancer Network classification system (www.nccn.com). This retrospective study was approved by the internal Institutional Review Board.

The HDR brachytherapy technique in use at our institution has been described previously (15). In brief, the catheter placement is carried out under general anesthesia using a transperineal approach with a template-based technique using real-time transrectal ultrasound guidance. The clinical target volume (CTV) is defined as the prostate gland and the base of seminal vesicles, and the planning target volume is defined as a 3-mm margin around the CTV. Treatment planning for earlier cases in the series was performed using a software package developed at Memorial Sloan-Kettering Cancer Center with the following constraints relative to the prescription dose: 100% target coverage, 100–120% maximum urethra dose, and rectal maximum dose ≤100% of prescribed dose. Treatment planning for the latter part of the series was done using Brachyvision (Varian Medical Systems, Inc., Palo Alto, CA) with similar dose constraints. All patients in this series were treated with ^{192}Ir using GammaMed 12i or aGammaMed Plus remote afterloader (Varian). The first 45 patients were prescribed a peripheral dose of 550 cGy per fraction, the subsequent 40 patients received 600 cGy, the next 32 patients received 650 cGy, the next 108 patients received 700 cGy per fraction (the current dose in use at our institution), and 4 patients received 750 cGy per fraction. Each patient was treated with HDR brachytherapy delivered in three fractions at least 4 h apart. Patients were typically treated on the day of the implant and subsequent fractions were delivered on the following day with a minimum interfraction interval of 4 h to deliver the total dose within a 24-h time period.

Table 1
Patient characteristics

Characteristics	*N* (%)
Age (y)	
<65	104 (45.4)
≥65	125 (54.6)
Gleason score	
6	45 (19.7)
7	137 (59.8)
8	25 (10.9)
9	20 (8.7)
10	2 (0.9)
Pretreatment PSA (ng/mL)	
<10	177 (77.3)
10–20	43 (18.8)
>20	9 (3.9)
T-stage	
T1–T2a	151 (65.9)
T2b–T2c	60 (26.2)
T3a–T4	18 (7.9)
Neoadjuvant ADT	
No	131 (57.2)
Yes	98 (42.8)
Baseline IPSS	
<8	126 (72.8)
≥8	47 (27.2)
NCCN risk group	
Low	27 (11.8)
Intermediate	141 (61.6)
High	61 (26.6)

PSA = prostate-specific antigen; ADT = androgen deprivation therapy; IPSS = International Prostate Symptom Score; NCCN = National Comprehensive Cancer Network.

Approximately 3 weeks after the HDR procedure, EBRT was initiated using conformal techniques described previously (15). The CTV was defined for this phase of therapy as the prostate gland and seminal vesicles. The planning target volume was defined as a 1-cm margin around the CTV and a 3-mm margin at the prostate rectal interface. The first 11 patients received 4500 cGy in 25 fractions and 1 patient received 4860 cGy; all remaining patients ($n = 216$) were prescribed 5040 cGy in 28 fractions. One patient was only able to undergo two fractions of brachytherapy (1400 cGy) as prescribed and underwent a course of EBRT to a total dose of 59.4 Gy. As of 2002, all patients were treated with intensity-modulated radiotherapy (IMRT) technique where a five- to seven-field treatment plan was used. EBRT was delivered to the prostate gland and seminal vesicles. The lymph nodes were not incorporated into the treatment fields.

For patients who received neoadjuvant androgen deprivation therapy (ADT; $n = 98$; 42%), treatment was usually initiated 3 months before the three-dimensional conformal radiotherapy/IMRT and discontinued at the completion of radiotherapy. The ADT was given to patients with large prostates to achieve pretreatment volume reduction or to high-risk patients, and adjuvant ADT even for high-risk patients was not routinely given. The median duration of ADT used in these patients was 9 months (range, 1–33 months).

The median follow-up for the entire cohort of patients was 61.2 months (range, 3–150 months). Follow-up examinations consisted of an assessment of serum prostate-specific antigen (PSA), patient symptom assessment, and digital rectal examination. New or worsening acute and late