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Moderate dose escalation with single-fraction high-dose-rate brachytherapy boost for clinically localized intermediate- and high-risk prostate cancer: 5-year outcome of the first 100 consecutively treated patients

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ABSTRACT

PURPOSE: To analyze the clinical outcome and toxicity data of the first 100 consecutive patients treated with a single-fraction high-dose-rate brachytherapy (HDR-BT) and external beam radiotherapy (EBRT).

METHODS AND MATERIALS: Two-hundred eighty patients have been treated with HDR-BT boost for localized intermediate- to high-risk prostate cancer. Among these, the outcome and toxicity of the first 100 patients treated with a single HDR-BT fraction were assessed. A median dose of 60 Gy EBRT was given to the prostate and vesicles. Interstitial HDR-BT of 10 Gy was performed during the course of EBRT.

RESULTS: Median followup time was 61.5 months. The 5-year actuarial rates of overall survival, cause-specific survival, disease-free survival, and biochemical no evidence of disease (bNED) for the entire cohort were 93.3%, 99.0%, 89.3%, and 85.5%, respectively. The 7-year actuarial rate of bNED was 84.2% for the intermediate-risk group and 81.6% for the high-risk group ($p = 0.8464$). The 7-year actuarial rates of bNED for Grade 1, 2, and 3 tumors were 97.5%, 80.0%, and 67.1%, respectively. The 5-year probability for developing late Grade 3 gastrointestinal and genitourinary (GU) toxicity was 2.1% and 14.4%, respectively. Grade 3 GU complications occurred significantly more frequently in patients with a history of preirradiation transurethral resection (29.1% vs. 8.8%; $p = 0.0047$).

CONCLUSIONS: Five-year outcome after 60 Gy EBRT plus a single fraction of 10 Gy HDR-BT boost is encouraging. Preradiation transurethral resection significantly increases the risk of late severe GU complications.

Keywords: Prostate cancer; High-dose-rate brachytherapy; Boost; External beam radiotherapy

Introduction

The optimal treatment for intermediate- and high-risk clinically localized or locally advanced prostate cancer remains undefined. Studies using dose escalation with external beam radiotherapy (EBRT) showed that doses more than 70 Gy in 2 Gy fractions significantly increased biochemical and clinical freedom from failure in T1–T3 localized prostate cancer (1). Other investigators using high-dose-rate brachytherapy (HDR-BT) as a boost showed that there is a strong dose–response relationship for intermediate- to high-risk prostate cancer patients, and improved locoregional control with higher radiation doses alone can significantly decrease the incidence of biochemical and clinical failures (2). Use of HDR-BT as a means of dose escalation in prostate cancer is based on the hypothesis that treatment delivery with high fractional doses will exploit the presumed fractionation sensitivity of prostate

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cancer (3). Recent data suggest a low α/β ratio for prostate cancer, implicating higher tumor sensitivity to higher dose per fraction (4).

Hypofractionated HDR-BT could consequently be of advantage with the possibility of higher local tumor control without increasing normal tissue toxicity (5). Different combined fractionation schedules, HDR-BT techniques, and planning methods have been published in the literature (6–11). An HDR-BT boost protocol for patients having intermediate- and high-risk clinically localized prostate cancer was implemented at the Hungarian National Institute of Oncology, Budapest in December 2001. Until October 2010, overall 280 patients have been treated. An EBRT dose of 60 Gy (with conventional fractionation) combined with a single-fraction HDR-BT boost of 8 Gy ($n = 6$) or 10 Gy ($n = 258$) was given to the prostate. The other 16 patients were treated with 50 Gy EBRT followed by two separated high–dose rate (HDR) implants of 10 Gy 2–3 weeks apart. In this article, we analyze the survival outcome and toxicity data for the first 100 consecutive patients treated with a single-fraction HDR-BT who had a long enough followup to assess the biochemical and clinical outcome and late treatment toxicity.

Patients and methods

Patients

Between December 2001 and October 2010, 280 patients with intermediate- and high-risk prostate cancer, without lymph node or distant metastases, were treated using the combination of three-dimensional conformal external beam radiotherapy (3D-CRT) and HDR-BT as a boost treatment. Data from the first 100 consecutive patients treated between 2001 and 2005 with a single-fraction HDR-BT boost were analyzed. Patients were divided into risk groups using D'Amico's (12) risk group stratification (Table 1). Patients' baseline characteristics are summarized in Table 2. Patients' median age was 65 years (range, 50–80 years). Sixty-one percent of the patients were stratified as high risk. Initial prostate-specific antigen (iPSA) was available in all but 1 patient (99%). The mean and median iPSA values before any treatment were 18 ng/mL (range, 4–58 ng/mL) and 15 ng/mL, respectively. Patients with iPSA >60 ng/mL were excluded from this analysis as they have a very high risk of relapse after treatment, and their results will be reported separately.

Table 1
Risk group definitions by D'Amico *et al.* (12)

Low-risk	Intermediate-risk	High-risk
PSA <10 ng/mL and GS 2–6 and Stage T1–T2a	PSA ≥10–20 ng/mL and/or GS 7 and/or Stage T2b	PSA >20 ng/mL and/or GS 8–10 and/or Stage ≥T2c

PSA = prostate-specific antigen; GS = Gleason score.

Table 2
Patients' baseline characteristics

Characteristic	*n*
T stage UICC, 2002	
T1	43
T2a–c	25
T3a–b	32
Pretreatment PSA (ng/mL)	
<10	35
10–20	36
>20–60	29
Histologic grade	
1	42
2	35
3	19
UK	4
Risk group	
Intermediate-risk	39
High-risk	61

UICC = Union for International Cancer Control; PSA = prostate-specific antigen; UK = unknown.

Histologic diagnosis was based on transrectal ultrasound (TRUS)–guided core biopsy. Pretreatment clinical investigations included physical examination, rectal digital examination (RDE), TRUS, and pelvic CT or MRI. Bone scan was done in all patients to exclude bone metastases. Patients were clinically staged according to the American Joint Committee on Cancer and the Union for International Cancer Control TNM classification system (13). In case of discrepancy in T status detected by different diagnostic methods, the worse was registered. The World Health Organization (WHO) classification system was used for histopathologic grading, because Gleason score was not available for all patients. If Gleason score or grade was given, it was corresponded to WHO grade as it is shown in Table 3.

Treatment

Endocrine therapy

Institutional protocol for endocrine therapy included neoadjuvant and concurrent (3–6 months) androgen deprivation (AD) for intermediate-risk patients. For high-risk patients, endocrine treatment was suggested to be continued for 2–3 years after the completion of radiotherapy (RT). Eighty-four patients received AD added to RT. The mean duration of hormonal treatment for these patients was 17.7

Table 3
Gleason score and grade according to WHO grade

WHO grade	Gleason grade	Gleason score
1	1–2	2–6
2	3	7
3–4	4–5	8–10

WHO = World Health Organization.