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Results of multiparametric transrectal ultrasound–based focal high-dose-rate dose escalation combined with supplementary external beam irradiation in intermediate- and high-risk localized prostate cancer patients

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ABSTRACT

PURPOSE: Clinical results of a biologic information–based focused dose escalation combined with dose de-escalation for the whole organ in external beam radiotherapy + high-dose-rate brachytherapy (HDR-BT) boost application for localized prostate cancer in a consecutively treated patient cohort.

METHODS AND MATERIALS: One hundred thirty patients were treated with external beam radiotherapy (50 Gy) complementary to two multiparametric transrectal ultrasound–guided 15 Gy HDR-BT fractions. Real-time multiparametric transrectal ultrasound–based biologic planning for high-dose-rate boost dose planning used the summation of gray scale and Doppler sonography imaging + biopsy information. Target subvolumes received HDR-BT dose escalation up to 60 Gy/fraction. Dose-volume histogram parameters, organ at risks doses, and toxicity results were investigated.

RESULTS: The median followup was 4.3 years, the median age was 68.62 years, and the mean initial prostate-specific antigen was 18.69 ng/mL. Low-, intermediate-, and high-risk constituted 69%, 21%, and 10% of the patients, respectively. The mean peripheral dose was 3.9 Gy per fraction. Prostate-specific antigen nadir was in 93% of the patients ≤1 ng/mL. Quality parameters were as follows: D_{90}: 6.58 Gy, V_{100}: 30.36%, V_{150}: 9.96%, V_{200}: 3.16%, $uD_{0.1}$: 7.34 Gy, uD_2: 9.34 Gy, rD_{01}: 10.56 Gy, and rD_2: 8.32 Gy, respectively. We observed G1, G2, G3 urinary toxicity in 17/130, 11/130, and 2/130 patients, respectively. Rectal toxicity: G1 and G2 occurred in 19/130 and 2/130 patients with mean dose values G1: 8.2 Gy and G2: 8.76 Gy. Analysis of variance test resulted in no correlation between toxicities and any other investigated factors.

CONCLUSIONS: Focused extreme dose escalation with low prostate mean peripheral dose results in excellent long-term outcome data and very high focal boost doses and is causing no enhancement in late treatment toxicity. © 2016 Published by Elsevier Inc. on behalf of American Brachytherapy Society.

Keywords: Prostate cancer; HDR brachytherapy; Focal therapy; Biologic planning; Multiparametric TRUS

Introduction

Brachytherapy techniques have evolved with progressive improvements in imaging technology as well by software developments, offering maximal individuality in dose delivery. Due to the steep dose falloff in high-dose-rate brachytherapy (HDR-BT), the method is ideal for delivering very high dose in dedicated small volumes by

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a precise placement of source positions in these volumes. Tumor biologic information is rarely involved in treatment planning procedures; however, imaging technology and technical performance of interstitial brachytherapy offer this potential. Precision targeting of subvolumes requires higher radiation doses leading to focal dose escalation within a given target volume is an exciting field of clinical research and carries the potential to avoid unnecessary higher mean peripheral doses of the prostate.

In 2006, we introduced the new treatment philosophy of biologic information−based focused dose escalation combined with dose de-escalation for the whole organ in HDR-BT boost applications complementary to external beam radiation for localized prostate cancer patients (1). In this first report of its kind in the literature, we analyze the long-term outcome of this treatment philosophy of the consecutively treated patients.

Patients and treatment methods

Between 1 January, 2006, and 31 December, 2011, 130 prostate cancer patients were treated with conventionally fractionated external beam radiotherapy (EBRT) (50 Gy) combined with two complementary transrectal ultrasound (TRUS)−guided 15 Gy HDR-BT fractions. Treatment eligibility was defined as described in our previous methodology publication (1). HDR-BT prescription dose was defined on real-time multiparametric TRUS detected tumor area and positive biopsy matched tumor areas (1). Total treatment time was 6 weeks. The biologic planning was performed by summation of the gray scale and the Doppler sonography imaging with relevant biopsy information. Dedicated prostate subvolumes (dominant lesions) received an HDR-BT integrated local dose escalation up to 60 Gy/fraction. The TRUS probe was extracted for the time of radiation, and rectal *in vivo* dosimetry was performed with the AM6/PTW chambers. Dose-volume histogram parameters (D_{90}, V_{100}, V_{150}, V_{200}, D_{max} urethra [uD_{max}], $D_{0.1}$ mL urethra [$uD_{0.1}$], $D_{2.0}$ mL urethra [uD_2], D_{max} rectum [rD_{max}], $D_{0.1}$ mL rectum [$rD_{0.1}$], $D_{2.0}$ mL rectum [rD_2], and observed late toxicity) were investigated for correlations.

Late radiation toxicities were reported during the follow-up visits according to Common Terminology Criteria for Adverse Events version 4.0.

All data were collected in Microsoft Excel 2010 (Redmond, WA, USA). The statistical analysis was performed with SPSS, version 12.0 (SPSS IC. Chicago, IL). The χ^2 test was applied to test statistical significance. Analysis of variance F statistic was used to analyze the differences among group means and the associated toxicities. Results with a p-value < 0.05 were stated significant.

The presented study was approved by the Ethic Committee of the University of Lübeck (Nr.14-101A).

Results

The median followup time was 4.3 years (1−7 years), and the overall survival (OS) rate was 90.77%. The mean age of the cohort was 68.62 (48−81; standard deviation [SD] ± 6.24) years. Mean Gleason was 6.78 (3−9; SD ± 1.08), and the mean initial prostate-specific antigen (iPSA) was 18.69 ng/mL (0.75−140 ng/mL; SD ± 23.29). Low-, intermediate-, and high-risk patients were represented in 69%, 21%, and 10%, respectively (according to D'Amico risk categories). An overview of patient cohort characteristics is given in Table 1.

The mean prostate volume was 28.11 cm^3. We implanted mean 2.56 cm^3 prostate volume per needle and median 10 needles per implant. The mean peripheral dose was 3.91 Gy (2.07−5.83 Gy) per fraction. PSA nadir was in 93% of the patients ≤1 ng/mL.

Implant quality parameter were D_{90}: 6.58 Gy (SD ± 1.31), V_{100}: 30.31% (SD ± 9.72), V_{150}: 10.03% (SD ± 4.72), V_{200}: 3.1% (SD ± 2.8), $uD_{0.1}$: 10.06 Gy (7.02−15.8; SD ± 1.2), uD_2: 9.34 Gy (6.59−11.17; SD ± 0.73), rD_{01}: 10.56 Gy (5.43−34.34; SD ± 2.95), rD_2: 8.32 Gy (4.68−16.51; SD ± 1.53), respectively. Technical parameters of the implants are listed in Table 2, and Fig. 1 shows a typical dose distribution.

We observed no urinary toxicity in 74/130 patients. G1, G2, and G3 urinary toxicities were 17/130, 11/130, and 2/130, respectively. The mean urethral dose in this patients was in G1: 9.35 Gy (6.59−10.6; SD ± 1.17), in G2: 9.59 Gy (8.86−10.47; SD ± 0.47), in G3: 9.84 Gy

Table 1
Patient characteristics

Characteristic	Value
Total number of patients	130
Mean age	68.7 (48−81; ±6.24)
Mean initial PSA (ng/mL)	18.69 (0.75−140; ±23.29)
<20 ng/mL	67%
Median Gleason score	7 (3−9)
Risk categories (D'Amico risk groups)	
Low risk	90 (69.23%)
Intermediate risk	27 (20.77%)
High risk	13 (10%)
Median number of biopsy probes	7
Hormonal treatment	69 (53.07%)
GnRH agonists/antagonists	44
Antiandrogens (ADT)	9
Both in combination	9
Not specified	7
External beam radiation (50 Gy)	130 patients (100%)
Urinary flow before HDR-BT (mean)	
Qmax	19.37 mL/s
Residual urine	33.6 mL
Urinary flow 6 weeks following HDR-BT (mean)	
Qmax	14.2 mL/s
Residual urine	42.5 mL
Median followup period	3.97 years (1−7)

PSA = prostate-specific antigen; HDR-BT = high-dose-rate brachytherapy; Qmax = maximum flow rate.