Radiotherapy and Oncology 127 (2018) 81–87

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate cancer brachytherapy

Two decades of high dose rate brachytherapy with external beam radiotherapy for prostate cancer

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ARTICLE INFO

Article history:
Received 18 November 2017
Received in revised form 18 December 2017
Accepted 20 December 2017

Keywords:
Prostate cancer
Radiotherapy
Brachytherapy
High dose rate

ABSTRACT

Background: High-dose-rate brachytherapy (HDR-BT) has optimal prerequisites in radiotherapy of prostate cancer (PC) with a conformal dose distribution and high doses per fraction giving a biological dose escalation. We report the outcome after HDR-BT and external beam radiotherapy (EBRT) after 20 years of experience.

Material and methods: The study includes 623 patients, median age of 66 years, treated from 1995 to 2008 and a median follow up of 11 years (range 2–266 months). Androgen deprivation therapy was given to 429 patients (69%). The HDR-BT was given with two 10 Gy fractions and the EBRT with 2 Gy fractions to 50 Gy.

Results: The 10-year PC-specific survival was 100%, 92%, 91%, and 75% for low-, intermediate-, high- and very high-risk patients respectively, and the 10-year probability of PSA relapse was 0%, 21%, 33%, and 65% respectively. The 10-year actuarial prevalence for ≥grade 2 GU- and GI-toxicities were 28% and 12% respectively and for ≥grade 3, 4% and 1% respectively. Urethral stricture was the most frequent GU complication with a 10-year actuarial incidence of 10%. Treatment without dose constraints for the urethra conferred a higher incidence 18%, compared to 5% after 2003 ($p < 0.001$). Sixteen patients experienced grade 4 GU toxicity, of which 13 were treated before 2003. No grade 4 rectal toxicity was seen.

Conclusion: The combination of EBRT and HDR-BT with adequate dose constraints to risk organs provides satisfactory long-term tumour control even in high-risk patients. GI toxicity stabilised but GU toxicity progressed during the 10-year follow up.

High-dose-rate brachytherapy (HDR-BT) has optimal prerequisites in radiotherapy of prostate cancer (PC) giving a conformal physical dose distribution and potential radiobiological dose escalation with high doses per fraction. A dose–response relationship with higher doses corresponding to improved biochemical control has been demonstrated in PC for all risk categories [1–3]. The steep dose gradient for brachytherapy gives the possibility to escalate the dose in the prostate with relative sparing of adjacent normal tissues. Consequently, since the implementation of HDR-BT in combination with external beam radiotherapy (EBRT) [4–6], several groups have reported excellent results [7–9]. Issues of concern are the risks for late developing sequelae with dose escalated radiotherapy [10], and the biology of prostate cancer, where failures may appear first after many years. It is therefore essential with a long follow up for an accurate evaluation of treatment results. In Uppsala combined treatment with HDR-BT and EBRT in PC began in 1995. We report here the outcome for patients uniformly treated with this combination after more than 20 years of experience.

Patients and methods

Patients

Data from 623 patients treated with the combination of HDR-BT and EBRT at our institution from 1995 to 2008 were analysed. Patients referred from other hospitals, receiving only the HDR-BT in Uppsala and not followed in our department, were not included. The mean and median age was 66 years (range 47–79). T-classification was based on digital rectal examination. Pelvic

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https://doi.org/10.1016/j.radonc.2017.12.025
0167-8140/

Table 1
Patient characteristics.

	Number	Percent
T-classification (UICC 2007)		
T1	159	26
a	1	
b	7	
c	151	
T2	308	49
Unclassified	9	
a	123	
b	130	
c	46	
T3	150	24
Unclassified	4	
a	131	
b	15	
T4	4	1
TX	2	
N-classification		
pN0	371	60
pN1	4	
NX	248	40
M-classification		
M0	455	73
MX	168	27
Gleason score		
≤6	272	44
7	237	38
8–10	107	17
Not available	7	1
PSA (ng/ml)		
<10	238	38
10–20	178	29
>20	207	33
Risk group		
Low	94	15
Intermediate	201	32
High	260	42
Very High	67	11
Unclassified	1	
Endocrine therapy		
Yes	429	69
≤3 months	92	
>3 to ≤6 months	211	
>6 to ≤24 months	98	
>24 months	28	
No	194	31
Previous TURP*		
Yes	39	6
No	584	94
Total	623	100

* TURP, Transurethral resection of prostate.

lymph node dissection was performed in 60%, and bone scintigram in 70% of the patients (Table 1). Patients with stages T1-T3a ($N = 614$) and T3b/T4 ($N = 19$), negative lymph node staging and isotope bone scan, without limitation on pretreatment PSA (iPSA) were included. The medium iPSA was 12 ng/mL (range 0.1–224). Patients were classified into four prognostic groups according to the NCCN criteria [11]. High risk factors were iPSA > 20, Gleason ≥ 8 or a T3a tumour. Very high risk (VHR) was defined as having all three high risk factors, or a T3b-T4 tumour, or dominant grade 5 pattern in the biopsies, or >4 positive biopsies with Gleason ≥ 8. High risk was defined as having one or two high risk factors. Intermediate risk was defined as having iPSA between 10 and 20, or a T2b-T2c tumour, or a Gleason score of 7, and no high risk factors. Low risk was defined as having iPSA < 10, Gleason ≤ 6 and a T1c-T2a tumour. Gleason grading was missing for 7 patients and grading according to WHO was used and low differentiated adenocarcinoma (grade III) was considered a high risk factor.

The study was approved by the Regional Ethical Review Board in Uppsala.

Treatment

Androgen deprivation therapy

Neoadjuvant and concomitant short androgen deprivation therapy (ADT) was given to 429 patients (69%) in a median of five months (1–179), Table 1. Twenty percent of the patients received ADT for 6 months or more, and 4% for more than 2 years. The treatment regimes were Gonadotropine releasing hormone analogue (GnRH) alone or in combination with antiandrogen (AA) (311 patients) and monotherapy with AA (bicalutamide to 107, and flutamide to 11 patients).

Radiotherapy

The combination of EBRT and HDR-BT treatments and schedule used were described previously [4]. EBRT was given in 2 Gy fractions to a total dose of 50 Gy, prescribed at the isocentre. The EBRT-technique is presented in detail elsewhere [12]. Briefly, a 3- or 4-field CT-based conformal technique with 6–21 MV photon beams was used, with the patient in supine position. The clinical target volume (CTV) consisted of the prostate gland and the seminal vesicles for all risk groups. After 2004 the seminal vesicles were excluded for low risk patients.

The planning target volume (PTV) was defined as CTV with a 1.5 cm margin, reduced to 1 cm dorsally to the rectum. Twelve high risk patients after 2006 also received treatment to the pelvic lymph nodes with intensity-modulated radiotherapy (IMRT).

HDR-BT was given in two separate 10 Gy fractions in a pause halfway in the EBRT treatment. Based on ultrasound images a dose plan was created in Plato planning system (Nucletron, The Netherlands). From 2006 the dose plan was based on live reconstruction of the applicators with the SWIFT/Oncentra Prostate planning system (Nucletron, The Netherlands). The HDR-BT PTV was equal to the CTV defined as the prostate gland with a margin of 2 mm. The number of applicators and their positions were defined to have the PTV encompassed by the 10 Gy isodose line.

Based upon the appearing GI and GU toxicity associated with the applied dose distributions during the first 5 years of HDR-BT, dose constraints were introduced. From 2000 a dose constraint of 6.5 Gy at maximum to the anterior rectal wall was applied, and from 2002 a restriction of 120% of the total dose at maximum to the urethra was stipulated. From 2006 the rectal dose constraint was changed to a maximum D2cc of 5 Gy to the rectal mucosa, and the dose plans were based on *in situ* reconstruction of the applicators. Due to the late introduction of dose restrictions to risk organs, analyses were performed with the patients divided in an early and late cohort. The HDR-BT was performed under spinal anaesthesia with the patient in lithotomy position. Ten to 22 applicators were inserted transperineally guided by transrectal ultrasound. A remote after loading technique was used with an HDR Ir-192 source. The total treatment time for the EBRT HDR-BT combination was 7 weeks.

Follow up

Follow up was at regular visits with 3–6 month intervals during the first 5 years, thereafter each year. After ten years the follow-up was at minimum every other year. PSA failure was defined according to the ASTRO Phoenix definition (nadir + 2 ng/ml) [13]. A temporary PSA bounce was not considered as a failure. Complications were recorded retrospectively from patient records. The grading was adapted after the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v3.0).

Statistics

Outcome measures estimated with the Kaplan–Meier method include net probability of PSA-relapse and relapse of distant-metastasis,