Radiotherapy and Oncology 109 (2013) 241–245

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate brachytherapy

Outcomes following iodine-125 prostate brachytherapy with or without neoadjuvant androgen deprivation

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ARTICLE INFO

Article history:
Received 3 December 2012
Received in revised form 27 June 2013
Accepted 7 September 2013
Available online 31 October 2013

Keywords:
Prostate cancer
Brachytherapy
Seed
implant

ABSTRACT

Purpose: To report the biochemical failure-free survival (BFFS), cause-specific survival (CSS), and overall survival (OS) outcomes of patients treated with iodine-125 (I-125) brachytherapy for clinically localized prostate cancer.

Methods and materials: Between 2003 and 2009, I-125 permanent prostate brachytherapy without supplemental external-beam radiotherapy was performed for 663 patients with low-risk and low-tier intermediate-risk (defined as organ-confined disease, PSA <10 ng/mL, and Gleason score 3 + 4 with biopsy positive core rate <33%) prostate cancer. Early in the study period, the preplanning method was used in the first 104 patients, and later the real-time planning method was used. Biochemical failure was determined using the American Society for Therapeutic Radiology Oncology (ASTRO) and Phoenix definitions.

Results: The 7-year BFFS rates for the ASTRO and Phoenix definitions were 96.1% and 95.9%, respectively. The corresponding BFFS rates by risk group were 97.6% and 96.7% for low-risk, and 91.8% and 93.6% for low-tier intermediate-risk disease ($p = 0.007$ and 0.08, respectively). The median times to biochemical failure in those who failed were 29.5 and 43.9 months according to the ASTRO and Phoenix definitions, respectively. The 7-year CSS and OS were 99.1% and 96.4%. There was no significant difference in CSS or OS between the low-risk and low-tier intermediate-risk groups. In multivariate Cox regression analysis, risk group and prostate D90 were independent predictors of BFFS for the ASTRO definition, while only the prostate D90 was significant for the Phoenix definition.

Conclusion: I-125 prostate brachytherapy results in excellent 7-year BFFS, CSS, and OS for low-risk and low-tier intermediate-risk prostate cancer.

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Permanent prostate brachytherapy is now an established modality in the treatment of localized prostate cancer, with several long-term studies demonstrating biochemical control rates similar to those obtained by radical prostatectomy and external beam radiation therapy (EBRT) [1–4]. Technical advances are regularly reported, including the use of transrectal ultrasound guidance for preplanned or intraoperatively planned implants. The concept of delivering high radiation doses to the prostate while sparing normal tissues makes brachytherapy an attractive treatment option. In the larger series from highly experienced institutions, the biochemical failure-free survival (BFFS) rates range from 85% to 98% for low-risk patients [5–11] undergoing brachytherapy and from 80% to 97% for intermediate-risk patients [6–12].

Permanent prostate brachytherapy using iodine-125 (I-125) seeds has grown rapidly in Japan since the establishment of guidelines for this treatment modality and revision of the dosimetric regulations related to radiation hazards and safety in 2003. In this report, we summarize the 7-year outcomes of our experience with permanent prostate brachytherapy alone. To our knowledge, this is the first report presenting outcomes more than 5 years after permanent prostate brachytherapy in an Asian country.

Materials and methods

Between 2003 and 2009, 663 Japanese patients with clinically localized prostate cancer were treated with I-125 permanent prostate brachytherapy at the National Hospital Organization Tokyo Medical Center and National Hospital Organization Saitama Hospital. All patients underwent brachytherapy more than 3 years before this analysis. Patients were classified into prognostic risk groups according to the National Comprehensive Cancer Network

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http://dx.doi.org/10.1016/j.radonc.2013.09.022

(NCCN; www.nccn.org). In general, low-risk and low-tier intermediate-risk (defined as organ-confined disease, prostate specific antigen [PSA] <10 ng/mL, and Gleason score 3 + 4 with biopsy positive core rate <33%) patients received permanent prostate brachytherapy without supplemental external-beam radiotherapy. There were no discrepancies in treatment policy between the National Hospital Organization Tokyo Medical Center and National Hospital Organization Saitama Hospital. Two hundred and ninety-five patients (44.5%) received neoadjuvant androgen deprivation with the aim of prostate volume reduction or a longer waiting time. Because the Japanese national policy for patient discharge criteria mandates that total seed activity be kept below 1300 MBq, patients with prostate volumes >40 cc usually must undergo hormonal therapy to downsize the prostate prior to implantation. None of our present patients received adjuvant androgen deprivation.

The implant technique was previously described in detail [13,14]. Early in the study period, the preplanning method was used in the first 104 patients, and from December 2004 onward, the procedure was changed to the real-time planning method. All procedures were conducted utilizing I-125 free seeds, being the only approved radioisotope available for permanent prostate brachytherapy in Japan. Post-implant dosimetry was performed 1 month after implantation, and the minimal dose received by 90% of the prostate (prostate D90) was the post-implant variable analyzed.

Planned follow-up was by PSA blood tests and physical examination every 3 months for the first 2 years, every 6 months thereafter. The primary outcome measure was BFFS. Biochemical failure was determined using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition [15] and the nadir +2 ng/mL definition (the Phoenix definition) [16]. Patients meeting the criteria for biochemical failure but showing a subsequent decrease to <0.5 ng/mL without intervention were classified as having a benign bounce, and were excluded from the analysis of failure. Late toxicity was defined as any symptom developing after the first year, or symptoms that developed during the first year and persisted $\geqslant$12 months. Late toxicity was scored by the Common Terminology Criteria for Adverse Events version 4.0.

Actuarial survival curves were calculated by the Kaplan–Meier method to determine BFFS, cause-specific survival (CSS), and overall survival (OS), with differences between time-adjusted rates evaluated with the log-rank test. Multivariate Cox regression analysis was used to assess the predictors of biochemical failure. Analyses were carried out using SPSS 20.0 (SPSS Inc., Chicago, IL). All tests were two-sided, and statistical significance was set at the level of $p < 0.05$.

Results

Clinical, treatment, and dosimetric parameters for the 663 patients included in the analysis are detailed in Table 1. Median follow-up time was 60 (range, 6–101) months. In our study, in 655 patients (98.7%) with implants, prostate D90 was above 140 Gy. The median nadir PSA values among biochemically controlled patients were 0.08 (range, <0.01–2.28) ng/mL for the entire cohorts and 0.14 (range, <0.01–2.28) ng/mL for the neoadjuvant hormone-naïve group, respectively.

The 7-year BFFS rate for the group overall was 96.1% according to the ASTRO definition and 95.9% by the Phoenix definition. The median times to biochemical failure in those who failed were 29.5 and 43.9 months according to the ASTRO and Phoenix definitions, respectively. The 7-year BFFS rates for low-risk and low-tier intermediate-risk patients were 97.6%, and 91.8%, respectively ($p = 0.007$) according to the ASTRO definition. The 7-year BFFS rates for low-risk and low-tier intermediate-risk patients were 95.9%, and 93.6%, respectively, ($p = 0.08$) according to the Phoenix definition (Fig. 1).

The 7-year CSS for the cohort overall was 99.1%. CSS stratified by risk group was 98.9% for low-risk and 100% for low-tier intermediate-risk disease ($p = 0.43$). The 7-year OS for the cohort overall was 96.4%. OS stratified by risk group was 96.4% for low-risk and 96.5% for low-tier intermediate-risk disease ($p = 0.87$) (Fig. 2). There were 19 deaths (2.9%), of which 2 were due to prostate cancer.

Multivariate Cox regression analysis including age, PSA, Gleason score, biopsy positive core rates, risk group, neoadjuvant hormone administration, planning technique, and prostate D90 was conducted to test for predictors of BFFS. Risk group and prostate D90 were independent predictors of BFFS by the ASTRO definition, while only the prostate D90 was significant by the Phoenix definition (Table 2). The prostate D90 doses were divided into three groups: <150 Gy ($n = 25$, 3.8%); 150–180 Gy ($n = 271$, 40.9%); and >180 Gy ($n = 367$, 55.3%). As shown in Fig. 3, the 7-year BFFS rates for patients in the prostate D90 >180 Gy group and the 150–180 Gy group were 97.3% and 96.2%, respectively, compared with 81.5% for those treated with D90 <150 Gy ($p = 0.001$), according to the Phoe-

Table 1
Clinical, treatment, and dosimetric parameters.

	Low risk ($n = 488$)		Low-tier intermediate risk ($n = 175$)		p Value	Total (n = 663)	
	Median	Range/count (%)	Median	Range/count (%)		Median	Range/count (%)
Continuous variables							
Age (yr)	67.0	38–83	68.0	50–87	0.24	67.0	38–87
Initial PSA (ng/mL)	6.48	3.0–9.9	6.50	3.4–9.9	0.78	6.49	3.0–9.9
Positive biopsy rate (%)	20.0	5.0–100	21.0	5.0–100	0.59	20.0	5.0–100
Prostate volume (cc)	24.7	8.3–45.5	23.1	9.8–40.9	0.08	24.4	8.3–45.5
Prostate D90 (Gy)	182.7	128.9–228.3	184.2	143.8–229.1	0.31	183.1	128.9–229.1
Categorical variables							
Clinical stage							
T1c-2a		488 (100%)		149 (85.1%)	<0.01		637 (96.0%)
T2b-2c		0		26 (14.9%)			26 (4.0%)
Neoadjuvant hormone therapy							
Yes		222 (45.5%)		73 (41.7%)	0.22		295 (44.5%)
Planning technique							
Preplanning		92 (18.9%)		12 (6.9%)	<0.01		104 (15.7%)
Real-time planning		396 (81.1%)		163 (93.1%)			559 (84.3%)

Abbreviations: PSA = prostate specific antigen; D90 = the minimal dose received by 90% of the prostate.