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Permanent prostate brachytherapy with or without supplemental external beam radiotherapy as practiced in Japan: Outcomes of 1300 patients

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ABSTRACT

PURPOSE: To report outcomes for men treated with iodine-125 (^{125}I) prostate brachytherapy (BT) at a single institution in Japan.

METHODS AND MATERIALS: Between 2003 and 2009, 1313 patients (median age, 68 years) with clinically localized prostate cancer were treated with ^{125}I BT. Median prostate-specific antigen level was 7.6 ng/mL (range, 1.1–43.3). T-stage was T1c in 60%, T2 in 39%, and T3 in 1% of patients. The Gleason score was <7, 7, and >7 in 49%, 45%, and 6% of patients, respectively. Neoadjuvant androgen deprivation therapy was used in 40% of patients and combined external beam radiotherapy of 45 Gy in 48% of patients. Postimplant dosimetry was performed after 30 days after implantation, with total doses converted to the biologically effective dose. Survival functions were calculated by the Kaplan–Meier method and Cox hazard model.

RESULTS: Median followup was 67 months (range, 6–126). The 7-year biochemical freedom from failure for low-, intermediate-, and selected high-risk prostate cancers were 98%, 93%, and 81%, respectively ($p < 0.001$). Multivariate analysis identified the Gleason score, initial prostate-specific antigen level, positive biopsy rate, dose, and neoadjuvant androgen deprivation therapy as predictors for biochemical freedom from failure. The 7-year actuarial developing Grade 3+ genitourinary and gastrointestinal toxicity was 2% and 0.3%, respectively. Forty-four percent patients with normal baseline potency retained normal erectile function at 5 years.

CONCLUSIONS: ^{125}I prostate BT is a highly effective treatment option for low-, intermediate-, and selected high-risk prostate cancers. Side effects were tolerable. An adequate dose may be required to achieve successful biochemical control.

Keywords: Brachytherapy; Iodine-125; Prostate cancer; Radiotherapy; Dose–response; Low-dose-rate; Permanent seed implantation

Introduction

Permanent prostate brachytherapy (BT) is an established treatment for early stage prostate cancer. Since the 1990s, excellent long-term outcomes have been demonstrated for low- to intermediate-risk disease states (1–9). Selected intermediate- to high-risk patients are often considered for combination of BT with external beam radiotherapy (EBRT) as a form of dose escalation (2–4, 7, 9–11).

In Japan, iodine-125 (^{125}I) seed implants were approved in 2003, and now permanent prostate BT is widely available throughout Japan. About 27,000 cases have been treated with permanent prostate BT in 109 institutions between 2003 and 2013 (12). The ^{125}I prostate BT program at the Tokyo Medical Center commenced in 2003. We started the preplan technique at this center using a Mick applicator (Mick Radio-Nuclear Instruments, Inc.), then introduced an intraoperative planning technique (13), and eventually shifted to escalate the dose step by step with the aim to improve quality of treatment and outcomes. Demographic, dosimetric, and outcomes data were prospectively recorded in a database. Here, we report on our 10-year experience with this program with

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respect to dosimetry, biochemical control, and toxicity outcomes. To the best of our knowledge, this is the largest investigation of permanent prostate BT in Asia.

Methods and materials

Subjects

From September 2003 to December 2009, 1313 Japanese patients with localized prostate cancer were treated with BT at the Tokyo Medical Center, National Hospital Organization (Tokyo, Japan). The seed implantation cutoff date was selected to allow for 4 years of minimum potential followup. The median patient age was 68 years (range, 38–87 years).

Treatment

Patients were classified into recurrent risk groups according to the National Comprehensive Cancer Network guidelines (14). Low risk was characterized as patients with the clinical stage of T1–2a, a Gleason score of ≤6, and a pretreatment prostate-specific antigen (PSA) level of < 10 ng/mL (n = 462, 35.2%). Patients with the presence of a clinical stage of T2b or T2c, a Gleason score of 7, or a pretreatment PSA level of 10–20 ng/mL were classified as having intermediate-risk disease (n = 704, 53.6%). Patients with a clinical stage of T3, a Gleason score of ≥8, or a pretreatment PSA level of ≥20 ng/mL were classified as having high-risk disease (n = 145, 11.2%). At the Tokyo Medical Center, low-risk and low-tier intermediate-risk (defined as a clinical stage of T1–2, PSA level of <10 ng/mL, and a Gleason score of 3 + 4 with a biopsy positive core rate of <34%) patients received BT without EBRT (n = 687, 52.3%). A total of 528 men (40.2%) received neoadjuvant androgen deprivation therapy (NADT) with the aim of reducing prostate volume, or because many patients approaching us for BT experienced waiting periods for hormonal treatment provided by other hospitals throughout the country in the early study period. The length of androgen deprivation therapy (ADT) duration was decided at the discretion of the urologist, and the median duration of ADT was 8 months (range, 2–48 months). None of our patients received adjuvant hormonal therapy. ADT comprised luteinizing hormone–releasing hormone agonist alone or in combination with an antiandrogen. Patient characteristics are shown in Table 1.

Table 1
Patient characteristics

	Implant alone		Combination		Total	
Patient demographics	*n*	%	*n*	%	*n*	%
PSA						
<10 ng/mL	631	91.8	318	50.8	949	72.3
10–20	56	8.2	245	39.1	301	22.9
≥20	0	0	63	10.1	63	4.8
Gleason score						
<7	547	79.6	99	15.8	646	49.2
7	139	20.2	449	71.7	588	44.8
>7	1	0.1	78	12.5	79	6.0
Stage						
T1a–T2a	507	73.8	286	45.7	793	60.4
T2b–c	180	26.2	325	51.9	505	38.5
T3	1.0	0.1	15	2.4	15	1.1
Percent positive core						
≤33.3	562	81.9	279	44.6	841	64.1
>33.3	124	18.1	346	55.4	470	35.9

PSA = prostate-specific antigen.

Implant technique and dosimetry

A transrectal ultrasound to determine the treatment location was performed 4 weeks before implantation for volume study and preplan. A VariSeed planning system, version 7.2 (Varian Medical Systems, Inc., Palo Alto, CA) was used for preplanning and intraoperative planning. The implant procedure and dose constraints have been previously described (15, 16). Early in the study period, the preplanning method was used in the first 233 men (17.7%), and from December 2004 onward, the procedure was shifted to the real-time intraoperative planned approach (13). We investigated a potential for additional improvements with an intraoperative planning technique and dose delivery to further improve outcomes. All procedures were conducted using ^{125}I loose seeds, with a median activity of 0.34 mCi/seed (range, 0.29–0.42 mCi) and a median of 65 seeds (range, 25–127). The prescribed dose was 145 Gy for BT as monotherapy, and 100 Gy for a combined modality followed 1–2 months later by EBRT using three-dimensional conformal techniques and 6 MV photons. EBRT was directed to the prostate and seminal vesicles with 45 Gy in 25 fractions (range, 25–50.4 Gy) over 5 weeks. Intraoperative planning dosimetry aimed for 99% of the prostate to receive 100% of the prescribed dose (V_{100}) and 90% of the prostate (D_{90}) to receive 110–120% of the prescribed dose initially, and this was increased up to 130% in subsequent years.

Postimplant dosimetry was performed with CT imaging at Day 1 and Day 30 after implantation. Slice thickness was 2.5 mm with no gap. Critical organ contouring and dosimetry were performed as per American Brachytherapy Society guidelines (17) and done by one radiation oncologist. A dose applied to 5%, 10%, or 30% of the urethra (D_5, D_{10}, or D_{30}) was assessed on Day 1 because a 16-French Foley urinary catheter was inserted only on Day 1. Other parameters used as the postimplant variables were analyzed on Day 30. Postimplant doses were converted to biologically effective dose (BED) from the postplan D_{90} at Day 30 using the α/β of 2 Gy (2). Dosimetric data are shown in Table 2.

Followup

The date of BT was considered Day 0 for calculation of followup duration. Patients were monitored by symptom