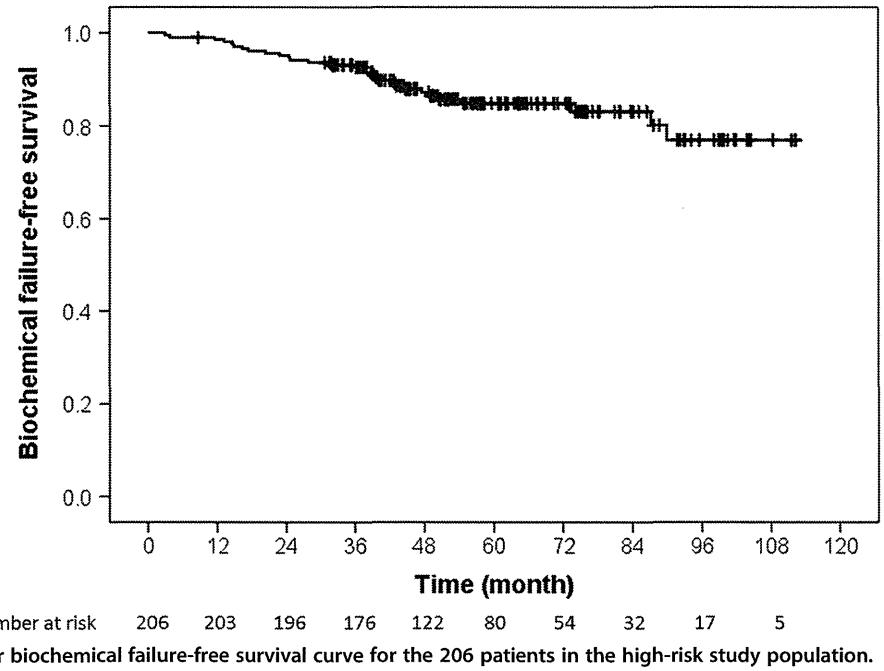


Figure 1 Kaplan-Meier biochemical failure-free survival curve for the 206 patients in the high-risk study population.

than the 81 Gy (associated BED of 154 Gy2) commonly prescribed for intensity-modulated radiotherapy.

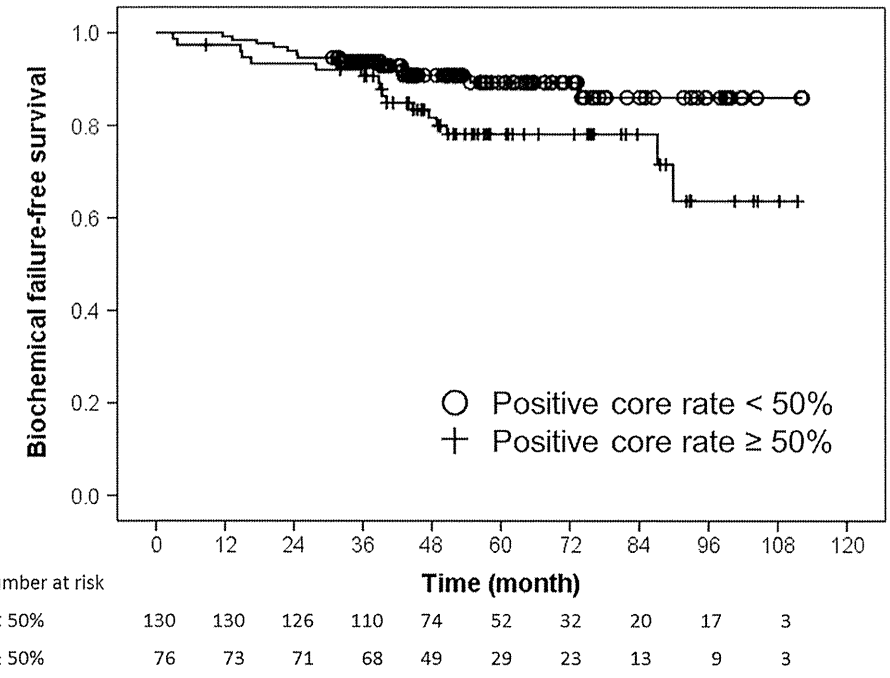
High-dose-rate (HDR) brachytherapy is also a technique that allows the delivery of very high BED. Martinez et al. performed a dose escalation investigation starting with HDR doses of 5.5 Gy × 3 and ending with 11.5 Gy × 2 for the HDR component of treatment [19]. The mean dose of EBRT was 46 Gy. They found that when the BED (α/β ratio of 1.2) was ≥ 268 Gy there was less biochemical failure, better local control, and fewer cases of distant metastasis. Kotecha et al. reported on the outcomes of 229 patients with clinically localized prostate cancer treated with a HDR brachytherapy boost (5.5 Gy × 3 to 7.5 Gy × 3) followed by EBRT (most patients were treated to 50.4 Gy) and found that a higher BED (> 190 Gy, α/β ratio of 2) resulted in improved BFFS and distant metastases free survival in high-risk patients [20].

In our present study, the prognostic significance of BFFS was investigated in high-risk prostate cancer patients and we found positive biopsy core rates and the number of high-risk factors to be independent predictors of BFFS. The positive biopsy core rates as determined by transrectal ultrasound-guided biopsy have been suggested as potential prognostic factors for enhancing the standard risk stratification for prostate cancer patients treated with EBRT [21-23]. Huang et al. analyzed 1,056 patients who were treated with modern EBRT techniques and found the positive biopsy core rate to be an independent predictor of highly relevant clinical outcomes. The association of the positive biopsy core rate

Table 2 Cox regression for biochemical freedom from failure

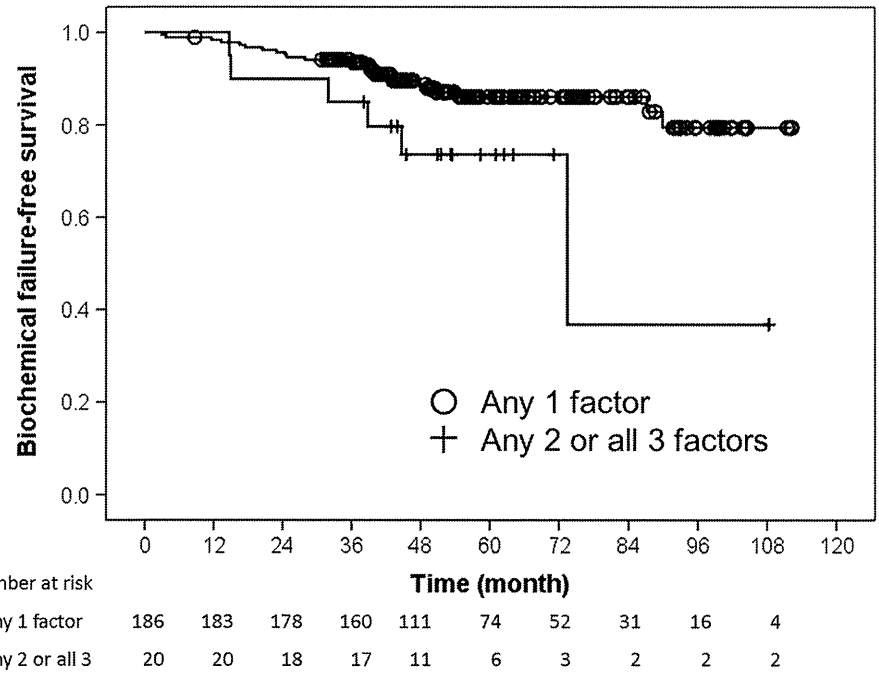
Variable	Significance (*p* value)	Hazard rate	95% CI	
			Lower	Upper
Age	0.936	0.998	0.940	1.061
PSA level	0.313	0.710	0.365	1.381
Gleason score	0.850	1.193	0.190	7.495
Positive biopsy rate	0.009*	2.940	1.314	6.577
No. of high-risk features	0.023*	4.162	1.218	14.220
Neoadjuvant ADT	0.064	0.468	0.946	1.045
Prostate D90	0.515	1.015	0.971	1.061
BED	0.833	0.995	0.946	1.046

Abbreviations: CI = confidential interval; PSA = prostate specific antigen; ADT = androgen deprivation therapy; prostate D90 = the minimal dose received by 90% of the prostate; BED = biologically effective dose.
*$p < 0.05$.



Number at risk										
< 50%	130	130	126	110	74	52	32	20	17	3
≥ 50%	76	73	71	68	49	29	23	13	9	3

Figure 2 Kaplan-Meier biochemical failure-free survival curves as a function of positive biopsy core rates. Open circles indicate the time of last follow-up for the biochemical failure-free patients with a positive core rate <50% (n = 130). Plus symbols correspond to censored patients with a positive core rate ≥50% (n = 76).



Number at risk										
Any 1 factor	186	183	178	160	111	74	52	31	16	4
Any 2 or all 3	20	20	18	17	11	6	3	2	2	2

Figure 3 Kaplan-Meier biochemical failure-free survival curves as a function of the number of high-risk factors. Open circles indicate the time of last follow-up for the biochemical failure-free patients with any single high-risk factor (n = 186). Plus symbols correspond to censored patients with any 2 or all 3 high-risk factors (n = 20).

with distant metastasis was especially robust and was unaffected by the use of either hormone therapy or high-dose EBRT [22].

The relationship between the positive biopsy core rate and BFFS has been examined in studies of patients treated with brachytherapy [24-26]. Kestin et al. reported on 190 men treated with a combination of EBRT and high-dose rate brachytherapy [24]. On multivariate analysis, the positive biopsy core rate was associated with BFFS and the development of clinical recurrence. Moreover, Merrick et al. reported on 255 men treated with seed implantation with or without EBRT. On multivariate analysis, the positive biopsy core rate and pretreatment PSA level were the only significant predictors of BFFS [25]. When low, intermediate, and high-risk patients were stratified by the positive biopsy core rate, a non-significant trend for increased biochemical recurrence was observed as positive biopsy core rates rose. The number of recurrences in their patient population was quite low, and it is possible that their study is underpowered to show a clinically significant effect of positive biopsy core rates after stratification by risk group. Rossi et al. described the 5-year estimate of the BFFS rate as being 95% for patients with a less than 50% positive biopsy core rate versus 63% in those with a rate of more than 50% [26]. These reports support the results of our present study, but the potential value of positive biopsy core rates for predicting CSS and OS requires longer follow-up and could not be quantified in our present study.

Several retrospective studies have assessed the associations of the number of high-risk factors and clinical outcomes of men given brachytherapy-based treatment [27,28]. Wattson et al. analyzed the impact of the number of high-risk factors on prostate cancer-specific mortality (PCSM) [27]. The adjusted hazard ratio for PCSM for those with at least two high-risk factors (as compared with one) was 4.8 (95% confidence interval, 2.8–8.0; $p < 0.001$). When the high-risk factors were analyzed separately, Gleason score 8–10 was most significantly associated with increased PCSM. Several studies have reported similar findings for men treated with definitive EBRT alone or EBRT plus hormone therapy, and for men undergoing radical prostatectomy [29-31].

Our study showed that clinicians may base treatment selection decisions on the number of high-risk factors and positive biopsy core rates, and found that men with more high-risk factors and a positive biopsy core rate ≥50% were likely to be selected for intensified treatments such as trimodality therapy including brachytherapy, EBRT and ADT. However, the results of this study cannot be used to conclude that brachytherapy-based trimodality therapy necessarily leads to improved rates of control and survival as compared with alternative treatments that do not include brachytherapy, such as radical prostatectomy or definitive EBRT with or without ADT.

The addition of ADT to standard dose EBRT was a significant breakthrough for men with high-risk disease and has resulted in major improvements in prostate cancer-specific survival and OS [1,2]. Although ADT has been studied in only a few trials with brachytherapy, in one study by Merrick et al. [32], ADT improved the 10-year BFFS rate when added to the combination of brachytherapy and EBRT versus combined therapy alone for high-risk prostate cancer. Meanwhile, according to the retrospective review by Lee et al. 80% of high-risk hormone-naive patients with a high-quality implant remained free of biochemical failure at 5 years [33]. In our study, there were too few patients with prostate D90 <110 Gy to obtain a dose–response curve and the results of Lee et al. are identical to our 84.8% BFFS rate at 5 years. These results in hormone-naive patients further substantiate the importance of aggressive locoregional treatment in securing long-lasting biochemical control in high-risk patients. A clinical randomized trial has been conducted to investigate the efficacy of adjuvant ADT following the combination of brachytherapy and EBRT for high-risk prostate cancer patients in Japan [34].

The limitations of this study are that the median follow-up is only 60 months and it was retrospective. Neoadjuvant ADT was administered at the discretion of the treating urologist for reasons including prostate volume reduction or to achieve a longer waiting time until seed implantation, therefore the duration of neoadjuvant ADT was not controlled, though all other treatments were uniform in most patients.

Conclusions

At a median follow-up of 60 months, high-risk prostate cancer patients who underwent combined I-125 brachytherapy and EBRT without adjuvant ADT have a high probability of achieving 5-year BFFS. Positive biopsy core rates and the number of high-risk factors significantly impact BFFS. Additional follow-up is mandatory to determine the durability of these results.

Abbreviations

EBRT: External beam radiotherapy; ADT: Androgen deprivation therapy; BFFS: Biochemical failure-free survival; CSS: Cause-specific survival; OS: Overall survival; BED: Biologic effective doses; I-125: Iodine-125; PSA: Prostate-specific antigen; Prostate D90: Minimal dose received by 90% of the prostate; GI: Gastrointestinal; GU: Genitourinary; HDR: High-dose-rate; PCSM: Prostate cancer-specific mortality.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions
TO and AY collected the data, interpreted the results, and performed the statistical analysis. SS, TM, TN and SY participated in data acquisition and helped to analyze the data. YS and NS contributed to data analysis. All authors read and approved the manuscript.

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ORIGINAL ARTICLE

Nationwide Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation (J-POPS)

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Abstract
Background To evaluate the safety and efficacy of brachytherapy with permanent iodine-125 seed implantation (PI) for prostate cancer. The nationwide Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation (J-POPS) has continued since July 2005. This manuscript presents the rationale, J-POPS study design, and the characteristics of initial participants enrolled in this study from July 2005 to June 2007.
Methods All participants were treated with PI in accordance with the American Brachytherapy Society recommendations. The primary outcome measure was biochemical progression-free survival. Progression-free survival, overall survival, cause-specific survival, longitudinal changes in health-related quality of life, disease-specific quality of life, the International Prostate Symptom Score, and the incidence of adverse events were also investigated as secondary outcome measurements.
Results Overall, 6,927 patients were enrolled by the end of 2010, that is approximately 40 % of all cases treated around the country. During the first 2 years, 2,354 participants were enrolled and 2,339 were actually treated with PI. The age range of participants was 45 to 89 years (median 69 years) and their risk classifications were 1,037 (44.3 %) at low risk, 1,126 (48.1 %) at intermediate risk, and 134 (5.7 %) at high risk, in addition to 16 participants whose classification was unknown. Of all patients, 76.6 % were treated with PI without external beam radiation therapy and 49.3 % received neoadjuvant hormone therapy.
Conclusions The J-POPS, a nationwide prospective cohort study that enrolled approximately 40 % of all PI cases in Japan, will provide highly reliable evidence, including outcomes and quality of life, after long-term follow-up.

Keywords Brachytherapy · Iodine-125 · Multi-institutional prospective cohort study · Prostate cancer

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Introduction

Surgical treatment, such as radical prostatectomy, has been performed as a major curative treatment option for localized prostate cancer [1–3]. A variety of radiation therapies have become popular for treating prostate cancer as an alternative to surgery. Because of the recent development of computer technology, radiation therapy has been performed based on highly advanced mechanisms. Three-dimensional radiation therapy followed by intensity-modulated radiation therapy (IMRT) creates a more accurate radiation field and enables higher radiation doses to the target organ without increasing the incidence of adverse events [4]. In addition, brachytherapy with permanent iodine-125 seed implantation (PI) is a procedure to deliver a high radiation dose to limited areas of the target organ, which provides higher efficacy and fewer adverse events.

Many studies have provided evidence showing the clinical effectiveness of PI. PI monotherapy is effective for localized low-risk prostate cancer when serum prostate-specific antigen (PSA) levels are <10 ng/ml, Gleason score (GS) <7, and clinical T stage is lower than T2c [5]. Furthermore, PI combined with external radiation therapy (EBRT) creates a high biologically effective dose (BED), which may provide high efficacy for intermediate-risk prostate cancer; it may also be effective for high-risk cancer, when PSA is >20 ng/ml, GS >7, or the clinical T stage is T3a, if neoadjuvant, concomitant, and adjuvant androgen deprivation therapy (ADT) are combined. The most recent National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for prostate cancer recommend trimodal treatment (PI + EBRT + long-term ADT) for high-risk cancer as well as a radical prostatectomy with pelvic lymph node dissection [6].

PI with iodine-125 (^{125}I) has grown rapidly in Japan since 2003 after the establishment of guidelines on this new treatment modality and a revision of the domestic regulations related to radiation hazards and safety. Following the first case of successfully treated prostate cancer in September 2003, 109 institutions have started to use this treatment and about 27,000 cases had been treated with PI throughout the country up to the end of 2013.

To evaluate the safety and efficacy of PI for localized prostate cancer, the nationwide Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation (J-POPS) was initiated in July 2005 and registration continued until December 2010. The data generated from this large registration study could be representative of patients treated with PI not only throughout Japan but also around the world. The purpose of this paper is to introduce the study design of J-POPS and provide background information on the participants enrolled in this study.

Patients and methods

The J-POPS study is a large multi-institutional prospective cohort study to achieve state-of-the-art clinical outcomes for localized prostate cancer treated using PI, which has become a common treatment option in Japan. Recruitment for the J-POPS study began in July 2005 and continued until December 2010. Initially, the study aimed to enroll 2000 participants within 2 years (cohort 1). However, considering the scientific importance of this study, the decision was made to extend the period of enrollment until December 2010 (cohort 2).

The J-POPS study was funded by the Foundation for Biomedical Research and Innovation (Kobe, Japan). The ethics review committee of the Translational Research Informatics Center (TRI; Kobe, Japan) of the Foundation for Biochemical Research and Innovation (approval no. 05-01, date May 6, 2005) and the individual institutional review boards of all participating facilities approved this study (TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00534196).

Participant selection

J-POPS is a prospective cohort study with the fundamental aim of collecting clinical data from patients undergoing PI treatment at participating institutions. Among 72 hospitals performing PI around the country until June 1, 2007, 46 (64 %) provided cohort 1 of the J-POPS.

Essential participant inclusion criteria were: patients with histologically confirmed adenocarcinoma of the prostate and patients planning to undergo treatment with PI. The clinical stage of participants was not restricted but most patients had clinically localized disease because the investigators of this study strongly recommended following the American Brachytherapy Society (ABS) recommendations [7–11]. No limitation on age was imposed, and all participants were informed and provided consent before enrollment into the J-POPS.

Baseline individual assessment

Participant age, height (cm), weight (kg), Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking and alcohol drinking preferences, and personal and family histories were taken as baseline characteristics. Histological findings, GS [12], the WHO tumor grading system [13] of biopsy specimens, and the number of biopsy cores taken were evaluated by local pathologists at each institution (Table 1). The clinical stage was assessed using the Union for International Cancer Control TNM Classification of Malignant Tumors (6th edition) [14]. Prostate volume was checked before ADT at the time of PI using

Table 1 Recommended schedule for checking physical condition, clinicopathological features of prostate cancer, radiation-related issues, objective treatment efficacy, and QOL for patients registered in the J-POPS

	At enrollment	Around radiation therapy	Months after completion of radiation therapy										
			3 months	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months	60 months
Background data and patient characteristics	○												
Prostate cancer-related clinicopathological information at diagnosis	○												
Physical and cancer-related information before radiation therapy	○												
PI-related information, including methodology and dosimetry at pre-planning and post-planning		○											
PS	○		○	○	○	○	○	○	○	○	○	○	○
Implanted seed discharge through urethra			○	○	○								
Implanted seed migration from the prostate to any other organ			○										
Treatment-related adverse events			○		○		○		○				
Serum PSA levels	○		○	○	○	○	○	○	○	○	○	○	○
Relapse information			○	○	○	○	○	○	○	○	○	○	○
Added adjuvant or salvage therapy after PI		○			○		○		○		○		○
Survival information			○	○	○	○	○	○	○	○	○	○	○
IPSS	○		○		○		○		○				
Disease-specific and health-related QOL[a]	○		○		○		○		○				

[a] QOL survey are conducted only for patients registered between July 2005 and June 2007

J-POPS Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation, *PI* permanent iodine-125 seed implantation, *PSA* prostate-specific antigen, *PS* performance status, *IPSS* International Prostate Symptom Score, *QOL* quality of life

transrectal ultrasonography and at the time of post-planning, usually 1 month after PI, using either computed tomography (CT) or magnetic resonance imaging.

Treatment

Although this study was not interventional, each participant was basically treated with PI in accordance with the ABS recommendation [7–11]. All participants were treated with loose ^{125}I seeds, which are only available in Japan, using a specific applicator (Mick Applicator; Mick Radio-Nuclear Instruments, Inc., Mount Vernon, NY, USA) as a seed insertion instrument. Modified peripheral loading or modified uniform loading is recommended for seed placement. Treatment with PI alone (PI monotherapy) was usually performed in low-risk cases (PSA < 10 ng/ml, GS < 7, and clinical T stage T1–T2a), and combined treatment with PI and EBRT was recommended for intermediate-risk (PSA 10–20 ng/ml or GS = 7 or clinical T stage T2b–T2c; not high-risk) and high-risk cases (PSA > 20 ng/ml or GS > 7 or clinical T stage T3a). ADT was recommended for patients with a prostate volume >40 ml of short duration and also for those who had had high-risk disease for several months.

Alpha-1 blockers were recommended for postoperative use to reduce adverse voiding events, such as voiding difficulty, urinary retention, or voiding irritability.

How, when, and why was reported for any supplemental treatment options (neoadjuvant, adjuvant and salvage hormone therapy, salvage radiation therapy, and salvage operation) that were performed.

Recommended radiation field and dosimetry

The gross target volume (GTV) was defined as the prostate volume visualized on images. The clinical target volume (CTV) was determined from the GTV with an added treatment margin of 3–5 mm in all directions, except for <2 mm in the posterior direction.

A dose of 144 Gy was prescribed for PI monotherapy. It was recommended that the percentage volume of the prostate receiving 100 % (V100) for CTV should be >90 % or that the minimal dose received by 90 % of the prostate volume (D90) should be 144–180 Gy for planning goals [8, 11]. The maximum urethral dose was <200 Gy and that for the rectum was <200 Gy in any slice [15–17]. The prescribed dose for PI should be 100–110 Gy for combination therapy with EBRT, and 40–50 Gy for EBRT with a 1.8–2.0 Gy/fraction [8, 11]. EBRT was performed either before PI or approximately 1 month after PI. It was recommended that the EBRT radiation field should be set for both the prostate and seminal vesicles for intermediate-risk and high-risk cases. Irradiation of the small pelvis was optional for those classified as intermediate or high risk [18]. The maximum urethral and rectal dose for PI should be <150 % of the prescribed dose for combination therapy with EBRT.

A CT scan was obtained approximately 1 month after implantation for the post-implant dosimetric assessment. The calculated dosimetry parameters were the prostate V100, V150, and D90. Additionally, the rectal dose, expressed as the rectal volume (ml) which received 100 and 150 % of the prescribed dose (R100 and R150, respectively), and the urethral dose, expressed as the values of the minimal dose received by 90 and 5 % of the urethral volume (urethral D90 and D5, respectively) and the volume of the urethra receiving 200 % of the prescribed dose (U200), were assessed from the dose volume histogram (DVH) obtained at post-planning. The urethral dose was defined by the urinary catheter dose or by the dose at the center of the prostate when a catheter had not been inserted. The DVH of all enrolled cases were analyzed at TRI and presented every year to all institutes attending J-POPS for the purpose of treatment quality assurance. This kind of feedback may be related to the improvement in treatment quality of PI around the country.

Follow-up

Seed discharge or migration is a brachytherapy safety issue (Table 1). Serum PSA levels were checked before the last prostate biopsy (usually at the time of cancer detection), before ADT if patients were treated, immediately before initiation of any radiation therapy, 3 and 6 months after completion of radiation therapy, and every 6 months thereafter. Adverse events related to treatment were characterized using the National Cancer Institute Common Terminology Criteria for Adverse Events Ver. 3.0 (NCI-CTCAE Ver. 3.0; translated into Japanese). The International Prostate Symptom Score (IPSS) translated into Japanese was used to evaluate adverse urination events.

Outcome measurements

The primary outcome measure was biochemical progression-free survival (bPFS). In the first version of the study protocol, bPFS was defined as the duration from enrollment to the date of biological relapse, which was defined as three consecutive PSA rises in the reflex range of 1.0 ng/ml or greater, and the date of failure was the midpoint between the first day that showed PSA levels 1.0 ng/ml or greater and the last day in which the level was below 1.0 ng/ml. The Phoenix definition for biological relapse (PSA nadir + 2.0 ng/ml) was also used for analyzing bPFS [19], as it is published and widely used around the world.

Secondary outcome measurements were: progression-free survival (PFS), which was defined as the duration from enrollment to the date of biochemical relapse or clinical

relapse, overall survival (OS), cause-specific survival (CSS), longitudinal changes in health-related quality of life (HRQOL), disease-specific quality of life (disease-specific QOL), IPSS score, and incidence of adverse events.

HRQOL and disease-specific QOL

It was recommended that questionnaires were complete before the radiation treatment and at 3, 12, 24, and 36 months after completing all radiation therapy (Table 1). SF-8 (translated into Japanese) was used for characterizing HRQOL, and the expanded Prostate Cancer Index Composite (translated into Japanese) was used to investigate disease-specific QOL of patients enrolled between July 2005 and June 2007 during the cohort 1 study.

Data collection

In the present study, 2,354 participants, who were enrolled in the J-POPS from 42 institutes during the first 2 years as cohort 1, were investigated. Of the 2,354 participants, 2 were duplicate enrollments and 1 had been previously treated with PI before enrollment. In addition, 12 participants could not undergo PI treatment. Therefore 2,339 actually underwent standard PI treatment and had completed all background and initial data checks by August 2013. Clinical data were obtained from medical charts by registered investigators at each participating facility and entered onto a standard clinical data form at a Web site prepared by the central data center at TRI.

Inclusion and exclusion policies for protocol violations

The data of all 2,339 enrolled participants were used for the analysis of safety. We excluded 23 participants from the efficacy analysis because their informed consent forms for the present study were obtained after permanent I^{125} seed implantation. There were 468 participants who signed the informed consent before undergoing the implantation but their web-registrations were carried out after implantation, which was considered a protocol violation. There were no statistical differences in V100 (%) and D90 (Gy) or treatment profiles between the 468 with a registration-related protocol violation and the 1,848 participants without a registration-related protocol violation. Therefore, members of the data-monitoring committee have decided that all 2,316 participants can be included in the analysis of efficacy including QOL.

Statistical analyses

Outcome assessment, including longitudinal serum PSA changes, clinical relapse and survival, is now ongoing. The bPFS, PFS, OS, and CSS will be analyzed using the Kaplan–Meier method, and the prognostic impact of the participants' clinicopathological baseline factors on survival will be analyzed using the Cox proportional-hazards model. Subgroup analyses will also be performed according to clinical stage, GS, risk classifications, presence or absence of ADT, PI with or without EBRT, radiation quality such as V100, D90, BED, PSA nadir, and kinetics after PI. Statistical analyses were performed using SAS statistical software (version 9.1.3., SAS Institute Inc., Cary, NC, USA). All statistical analyses were and will be performed at TRI.

Results

During the enrollment period between July 1, 2005 and December 31, 2010, 6,927 participants from 68 institutes were enrolled in the J-POPS, which means that about 40 % of all patients treated with PI in Japan were enrolled in this study. The number of enrolled participants at each institution ranged from 0 to 481 in cohort 1 and from 0 to 696 in cohort 2 (Table 2).

The age of the 2,339 cohort 1 participants ranged from 45 to 89 years (median 69 years). In total, 146 (6.2 %) had a family history of prostate cancer, 1,078 (46.1 %) and 1,604 (68.5 %) participants had past and present history of smoking and drinking alcohol, respectively. Other baseline individual characteristics (e.g., PS, history) are shown in Table 3. Prostate volume at the time of PI was 7.0–71.0 ml (median 25.2 ml). The distribution of clinical stages and histological findings evaluated by GS are shown in Table 4. The most common clinical T stage in the 2,313 participants without lymph node or distant metastases was T1c (1,693 cases; 72.4 % of the total) followed by T2a (408 cases; 17.4 % of the total). The majority of cases were N0M0, although one case was reported as metastatic disease. The details of this case was not reported. The most frequent GS was 6 (1,200 cases; 51.3 % of the total), followed by 7 (929 cases; 39.7 % of the total). There were fewer participants with GS $\geq$8 (84 cases; 3.6 % of the total). The most frequent combination of primary and secondary Gleason grades was 3 + 3 (1,196 cases; 51.1 % of the total).

The numbers (%) of participants stratified by risk classification are shown in Table 5. Of 2,313 participants, 1,037 (44.3 %), 1,126 (48.1 %), and 134 (5.7 %) were classified into the low-, intermediate-, and high-risk categories, respectively, and 16 participants had insufficient information about their risk classification. The most frequent risk classification was the intermediate-risk group, which was almost equal to the low-risk group. Table 5 shows the status of combined treatment modalities such as

Table 2 The number of registered patients in each of the institutions participating in J-POPS

Ranking[a]	Name of institution	Date of initiation into the study	Number of cases registered		
			Cohort 1 Between July 2005 and June 2007	Cohort 2 Between July 2007 and December 2010	Total
1	001 National Hospital Organization Tokyo Medical Center	05-Jul-05	481	696	1177
2	011 Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences	21-Jul-05	155	114	269
3	002 Kitasato University School of Medicine	5-Jul-05	130	370	500
4	023 The Jikei University	13-Oct-05	123	261	384
5	006 Iwate Medical University	7-Jul-05	121	283	404
6	003 Nara Medical University Hospital	5-Jul-05	106	228	334
7	021 Kyushu University Faculty of Medicine	7-Oct-05	100	65	165
8	031 Yokohama City University Hospital	9-Mar-06	99	20	119
9	017 Hamamomachi Hospital	20-Sep-05	96	121	217
10	020 National Hospital Organization Shikoku Cancer Center	4-Oct-05	88	66	154
11	007 Gifu University Graduate School of Medicine	7-Jul-05	65	110	175
11	012 Gunma University Hospital	2-Aug-05	65	21	86
13	014 National Hospital Organization Hokkaido Cancer Center	18-Aug-05	60	20	80
13	026 Showa University, School of Medicine	10-Nov-05	60	67	127
15	009 Shiga University of Medical Science	15-Jul-05	52	151	203
16	019 Hiroshima University Graduate School of Biomedical Science	4-Oct-05	49	28	77
17	013 Tama-Hokubu Medical Center	15-Aug-05	42	0	42
18	028 Nagasaki University Graduate School of Biomedical Sciences	5-Dec-06	38	10	48
19	008 Tokyo Medical and Dental University, Graduate School of Medical and Dental Sciences	8-Jul-05	37	86	123
20	010 Kyoto Prefectural University of Medicine	20-Jul-05	35	121	156
21	042 Keio University, School of Medicine	10-Jan-07	33	91	124
22	004 Nagano Municipal Hospital	5-Jul-05	32	0	32
22	005 Isesaki Municipal Hospital	5-Jul-05	32	24	56
24	024 The Cancer Institute Hospital of Japanese Foundation For Cancer Research	20-Oct-05	29	1	30
25	022 Kochi Medical School	7-Oct-05	26	25	51
25	046 National Hospital Organization Saitama National Hospital	9-Mar-07	26	349	375
27	015 National Center for Global Health and Medicine	14-Sep-05	25	0	25
27	033 St. Luke's International Hospital	17-May-06	25	35	60
29	016 Tokushima University Hospital	15-Sep-05	24	155	179
30	025 Shimane University Hospital	7-Nov-05	21	14	35
31	036 Asahi Hospital	21-Aug-06	20	49	69
32	030 Gunma Prefectural Cancer Center	1-Mar-06	11	55	66
33	027 Osaka University Hospital	24-Nov-05	9	0	9
34	034 Fujita Health University School of Medicine	21-Jul-06	7	155	162
35	039 Sapporo-Kosei General Hospital	10-Nov-06	6	12	18
36	032 The University of Tokyo Hospital	6-Apr-06	5	5	10
37	018 Tochigi Cancer Center	28-Sep-05	4	18	22
37	038 University of Fukui Hospital	11-Oct-06	4	7	11
37	041 Ehime University Hospital	13-Dec-06	4	17	21

Table 2 continued

Ranking[a]	Name of institution	Date of initiation into the study	Number of cases registered		
			Cohort 1 Between July 2005 and June 2007	Cohort 2 Between July 2007 and December 2010	Total
37	043 Kansai Medical University Takii Hospital	12-Jan-07	4	2	6
41	040 Saitama Prefectural Cancer Center	5-Dec-06	3	41	44
42	029 Sapporo Medical University	10-Feb-06	2	0	2
43	044 Kagawa University Hospital	13-Feb-07	0	46	46
43	045 Tokyo Women's Medical University	27-Feb-07	0	10	10
43	047 Saitama Medical University International Medical Center	26-Jul-07	0	3	3
43	048 Kinki University Faculty of Medicine	30-Jul-07	0	141	141
43	049 Niigata University Medical and Dental Hospital	19-Oct-07	0	17	17
43	051 Kobe City Medical Center General Hospital	6-Mar-08	0	50	50
43	052 Hamamatsu University School of Medicine	25-Mar-08	0	11	11
43	053 Japanese Red Cross Kumamoto Hospital	25-Mar-08	0	74	74
43	054 Kyoto City Hospital	27-May-08	0	1	1
43	055 Aidu Chuo Hospital	11-Jul-08	0	34	34
43	056 Harasanshin General Hospital	30-Jul-08	0	60	60
43	057 Kyorin University, School of Medicine	6-Oct-08	0	34	34
43	058 Hiroshima Prefectural Hospital	6-Oct-08	0	37	37
43	059 Kansai Electric Power Hospital	18-Nov-08	0	6	6
43	060 Kanazawa University Hospital	1-Dec-08	0	47	47
43	061 Shinshu University Hospital	13-Feb-09	0	6	6
43	062 National Hospital Organization Kanazawa Medical Center	5-Mar-09	0	45	45
43	064 Kobe University Hospital	9-Apr-09	0	3	3
43	065 Mie University Hospital	11-Jun-09	0	7	7
43	066 University of the Ryukyus, Faculty of Medicine	6-Jul-09	0	12	12
43	068 Seirei Mikatahara General Hospital	6-Oct-09	0	10	10
43	069 Matsuyama Red Cross Hospital	20-Oct-09	0	5	5
43	070 Osaka Police Hospital	17-Nov-09	0	1	1
43	071 Iizuka Hospital	18-Feb-10	0	11	11
43	072 Nihon University Itabashi Hospital	26-Mar-10	0	7	7
43	074 Saiseikai Yokohamashi Tobu Hospital	13-May-10	0	2	2
Total			2354	4573	6927

[a] Ranked according to the number of registered cases between July 2005 and June 2007

EBRT and ADT, stratified by risk classification. About three-quarters of participants (1,792 participants; 76.6 %) were treated with PI (with or without ADT), and the remainder were treated with EBRT combination therapy. Overall, 1,153 participants (49.3 %) were treated with ADT before PI, and the percentage of participants who were treated with ADT before PI increased with higher risk category. Overall, 547 participants (23.4 %) were treated with EBRT combination therapy and that percentage increased with higher risk category. The percentage of participants who were treated with trimodal therapy such as PI, EBRT, and ADT was 16.6 % (389/2,339). In participants who were classified into the low-risk category, 60.6 % (628/1,037) were treated without ADT, 98.4 % (1,020/1,037) were treated without EBRT, and 59.4 % (616/1,037) were treated with PI monotherapy without ADT. The main reason that low-risk patients had ADT before PI is for volume reduction. Other patients might have had ADT before PI to prevent disease progression if they were not treated immediately for various reasons. Alternatively, 80.6 % (108/134) of the participants who were classified into the high-risk category were treated with ADT, 83.6 % (112/134) in combination with EBRT, and 66.4 % (89/134) with trimodal therapy.

Table 3 Baseline physical status of participants in J-POPS in the first 2 years

Variables	No. of cases (%)
Performance status[a]	
0	2315 (99.0)
1	19 (0.8)
2	2 (0.1)
4	1 (0.0)
Not reported	2 (0.1)
Past history	
Diabetes mellitus	139 (5.9)
Bladder cancer	16 (0.7)
Rectal cancer	16 (0.7)
Prostatic hyperplasia	14 (0.6)
Others	539 (23.0)
Family history of cancer	
Prostate cancer	146 (6.2)
Other cancers	626 (26.8)
No	1436 (61.4)
Not reported	131 (5.6)
Present smoking status	
Yes	313 (13.4)
No, but with past smoking history	765 (32.7)
No without any smoking history	1094 (46.8)
Not reported	167 (7.1)
Present drinking status	
Every day	936 (40.0)
Sometimes	569 (24.3)
No, but with past drinking history	99 (4.2)
No without any drinking history	563 (24.1)
Not reported	172 (7.4)

[a] Proposed by Eastern Cooperative Oncology Group (ECOG)

J-POPS Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation

Table 4 Clinical stage and pathological characteristics according to the Gleason grading system of cases registered in the first 2 years of the J-POPS

Variables	No. of cases (%)
Clinical stage	
Localized/metastatic	
Clinically localized (N0M0)	2313 (98.9)
T1a	3 (0.1)
T1b	4 (0.2)
T1c	1693 (72.4)
T2a	408 (17.4)
T2b	122 (5.2)
T2c	67 (2.9)
T3a	16 (0.7)
Locally advanced (N0M0)	2 (0.1)
T3b	2 (0.1)
Metastatic (any T)	1 (0.0)
N0M1b	1 (0.0)
Insufficient information on TNM classification	23 (1.0)
Pathological findings	
Gleason score (primary Gleason grade + secondary Gleason grade)	
2–3	6 (0.3)
4	25 (1.1)
5	92 (3.9)
6	1200 (51.3)
6 (2 + 4)	4 (0.2)
6 (3 + 3)	1196 (51.1)
7	929 (39.7)
7 (2 + 5)	1 (0.0)
7 (3 + 4)	645 (27.6)
7 (4 + 3)	283 (12.1)
8	65 (2.8)
8 (3 + 5)	5 (0.2)
8 (4 + 4)	59 (2.5)
8 (5 + 3)	1 (0.0)
9	19 (0.8)
9 (4 + 5)	14 (0.6)
9 (5 + 4)	5 (0.2)
Not reported	3 (0.1)

Clinical stages are according to the Union for International Cancer Control (UICC) TNM Classification (6th edition)

J-POPS Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation

Total radiation doses ranged from 340.6 to 1,572.0 MBq (median 969.4 MBq) or from 9.2 to 42.5 mCi (median 26.2 mCi) for participants treated with PI without EBRT. In participants treated with PI in combination with EBRT, total radiation doses ranged from 332.5 to 1,310.0 MBq (median 679.3 MBq) or from 9.0 to 35.4 mCi (median 18.4 mCi). Radiation dose characterizations for the prostate, rectum, and urethra assessed from DVH at the time of post-planning are shown in Table 6.

Discussion

The Japanese guidelines have a novel limitation for radiation activity in a patient's body. At the time of discharge from the radiation-controlled room in the hospital, total radiation activity of the seed should be either <1,300 MBq (35.1 mCi) or 1.8 uSv/h at a 1-m distance from the body surface. Patients with a large prostate (>40 ml) cannot be treated without ADT volume reduction, and, if the prostate does not shrink, treating that case with PI alone is theoretically difficult. The limitation of life radiation exposure from the patient to the family is a maximum of 5 mSv for

Table 5 Risk classification of cases registered in the J-POPS and correlation of combined treatment status with androgen deprivation therapy

Variables	No. of cases (%)
Risk classification proposed by NCCN in 2011	
Clinically localized	2313 (98.9)
Low risk	1037 (44.3)
Intermediate risk	1126 (48.1)
High risk	134 (5.7)
Unclassified	16 (0.7)
Locally advanced	2 (0.1)
Metastatic	1 (0.0)
Insufficient information about clinicopathological features	23 (1.0)
Combined ADT status with PI	
Without ADT	1185 (50.7)
With ADT	1153 (49.3)
Not reported	1 (0.0)
ADT modality prescribed	
CAB	422 (18.0)
LH-RH alone	437 (18.7)
Anti-androgen alone	291 (12.4)
Others	17 (0.7)
Combined EBRT status with PI	
PI	1792 (76.6)
Without ADT	1027 (43.9)
With ADT	764 (32.7)
Not reported	1 (0.0)
Combination therapy	547 (23.4)
Without ADT	158 (6.8)
With ADT (tri-modality therapy)	389 (16.6)
Combined EBRT status with PI stratified by risk classification proposed by NCCN in 2011	
Low risk; clinically localized	
PI	1020 (43.6)
Without ADT	616 (26.3)
With ADT	404 (17.3)
Combination therapy	17 (0.7)
Without ADT	12 (0.5)
With ADT (tri-modality therapy)	5 (0.2)
Intermediate risk; clinically localized	
PI	710 (30.4)
Without ADT	387 (16.5)
With ADT	323 (13.8)
Combination therapy	416 (17.8)
Without ADT	123 (5.3)
With ADT (tri-modality therapy)	293 (12.5)
High risk; clinically localized	
PI	22 (0.9)
Without ADT	3 (0.1)
With ADT	19 (0.8)
Combination therapy	112 (4.8)
Without ADT	23 (1.0)
With ADT (tri-modality therapy)	89 (3.8)
Locally advanced	
PI	1 (0.0)
With ADT	1 (0.0)
Combination therapy	1 (0.0)
With ADT (tri-modality therapy)	1 (0.0)
Metastatic	
PI	1 (0.0)
With ADT	1 (0.0)
Insufficient information on any of PSA, Gleason score, or TNM classification	
PI	38 (1.6)
Without ADT	21 (0.9)
With ADT	16 (0.7)
Not reported	1 (0.0)
Combination therapy	1 (0.0)
With ADT (Tri-modality therapy)	1 (0.0)

J-POPS Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation, *PSA* prostate-specific antigen, *ADT* androgen deprivation therapy, *PI* permanent iodine-125 seed implantation, *LH-RH* luteinizing hormone-releasing hormone, *CAB* combined androgen Blockade, *EBRT* external beam radiation therapy, *NCCN* National Comprehensive Cancer Network

adults, 1 mSv for children, and 1 mSv per year for unrelated people. The prostate should be removed at autopsy if the patient dies within 1 year of PI because of consideration for the environment at the time of cremation. Among the 2,339 cases enrolled in J-POPS cohort 1, 8 patients (0.34 %) died within 1 year. This percentage is exactly same as that of the whole country.

Until the end of 2010, 109 hospitals achieved these regulations and were registered to perform PI around the country; about 17,000 cases were treated during 4.5 years. The J-POPS study registered 72 of 109 hospitals and enrolled approximately 40 % of all cases from around the country. No nationwide prospective database on PI is available around the world, except for the J-POPS. This kind of prospective cohort study is important because it may clarify, not only the positive impact of this treatment, but also the drawbacks of PI in terms of efficacy and safety. Recruitment bias was minimal, as all recruiting for the study was performed before patients underwent PI, and most large-volume institutions enrolled patients consecutively. An independent data-monitoring committee, specifically for the J-POPS, exists to avoid publication bias.

Table 6 Dose volume histogram (DVH) parameters prescribed to the targeted organ and adjacent risk organs

	Modality for radiation therapy					
	PI ($N = 1792$)			Combination therapy ($N = 547$)		
	Reported	Median	Range	Reported	Median	Range
Prostate	1781			546		
V100[a] (%)		94.8	56.3–100.0		96.1	56.5–100.0
V150[a] (%)		62.9	18.4–94.6		64.2	16.3–98.1
D90[a] (Gy)		160.6	57.8–231.9		120.4	60.2–191.6
Rectum	1685			546		
R100[a] (ml)		0.3	0.0–4.8		0.3	0.0–3.7
R150[a] (ml)		0.0	0.0–1.5		0.0	0.0–1.2
Urethra	1684			546		
D90[a] (Gy)		140.4	7.9–336.5		110.7	40.0–184.7
U200[a] (ml)	1479	0.0	0.0–92.9	517	0.0	0.0–0.6
D5[a] (Gy)		223.4	119.0–427.0		162.0	97.6–338.4

PI permanent iodine-125 seed implantation, *EBRT* external beam radiation therapy, [a] defined in text under *Recommended radiation field and dosimetry*

The J-POPS database will be able to survey nationwide quality of PI in terms of acceptability of indications for PI and the prescribed radiation dose to target and adjacent organs at risk. Although the J-POPS recommends that participating institutions follow the ABS recommendations, inter-institutional discrepancies may have occurred in treatment strategies on: how to combine other treatment modalities with PI, the PI technique itself, and planning the prescribed dose to the CTV. The treatment effects and safety following PI will be clarified and compared stratified by pre-PI parameters, such as subject characteristics, clinicopathological features, treatment status on additional ADT and EBRT, and various DVH parameters. Short-term posttreatment PSA kinetics, absolute PSA nadir levels, and the time to reach the PSA nadir may be very interesting to investigate in relation to long-term predictions of cancer control.

Large longitudinal surveys on HRQOL, disease-specific QOL, and IPSS were carried out between July 2005 and June 2007. Therefore, treatment modalities, such as combination with EBRT and/or ADT, and prescribed doses to the target organ and adjacent risk organs, that affect QOL-related issues will also be clarified within the J-POPS. Also, treatment effectiveness will be revealed by the long-term outcomes, PFS, OS and CSS. Comparison of these outcomes with other treatment modalities is the other major aim of this study.

Conflict of interest There is no conflict of interest to declare.

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Brachytherapy ■ (2014) ■

BRACHYTHERAPY

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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Conflict of interest: None of the authors has any potential conflicts of interest to disclose.

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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

Table 2
Dosimetric data

Parameter	Median	Range
V_{100} (%)	98.5	62.8–100
V_{150} (%)	67.8	17.0–99.3
V_{200} (%)	31.8	7.3–69.3
D_{90} (Gy) of BT alone	184.7	126.4–233.6
D_{90} (Gy) of Combination with EBRT	121.5	79.9–155.9
D_{90} (Gy) at day 1 BT alone	158.4	91.8–196.3
Urethral D_{10} (Gy) of BT alone	180.1	92.5–268.8
Rectal V_{100} (cc)	0.35	0–4.02
BED (Gy_2)	204.1	105–250.6

V_{100}, V_{150}, and V_{200} = the percent volume of the postimplant prostate receiving 100%, 150%, and 200% of the prescribed dose, respectively; D_{90} = the minimal dose received by 90% of the prostate; BT = brachytherapy; EBRT = external beam radiotherapy; Urethral D_{10} = the minimal dose received by 10% of the urethra; Rectal V_{100} = the rectal volume in cubic centimeters that received >100% of the prescribed dose; BED = biologically effective dose.

assessment, PSA test, and physical examination every 3 months for the first 2 years, every 4 months for the next 3 years, and 6 months for 5 years, and then yearly. The median followup was 6.7 years (range, 1–10.5 years). Follow-up was censored at the last PSA record or at the time of death. For PSA outcomes, 4 patients were followed up for <1 year and <2% of patients for <2 years. Systematic imaging and transrectal ultrasound–guided mapping biopsies were performed for any patient with three consecutive rises of PSA level beyond 30 months. Biochemical failure was determined using the nadir + 2 ng/mL definition (the Phoenix definition). Patients meeting the criteria for a biochemical failure, but showing a subsequent decrease to <0.5 ng/mL without intervention, were classified as having a benign bounce and were not coded as a biochemical failure. The primary outcome measure was biochemical freedom from failure (BFFF). Toxicity was defined as any symptom developing after implantation and scored by the Common Terminology Criteria for Adverse Events, version 4.0. International Prostate Symptom Score (IPSS) and erectile function were assessed by patients before treatment and at 3 months, 6 months, 1, 2, 3, 4, and 5 years after implantation. The questionnaire of the usual quality of erections during the last 4 weeks was scored as absent, not firm enough for any sexual activity (insufficient), firm enough for masturbation and foreplay only (suboptimal), and firm enough for intercourse (normal). This survey was mailed by post.

Analysis

Actuarial survival curves were calculated using the Kaplan–Meier method to determine BFFF, cause-specific survival, and overall survival, 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 performed using SPSS, version 19.0 (SPSS Inc., Chicago, IL). All tests were two-sided, and statistical significance was set at the level of $p < 0.05$.

Results

The 7-year BFFF for the entire cohort was 93.5%. The median time to biochemical failure was 47 months (range, 0–112 months). The 7-year BFFF outcomes for low-, intermediate-, and high-risk patients were 97.7%, 93.2%, and 81.2%, respectively ($p < 0.001$; Fig. 1). The 7-year overall survival for the cohort was 92.8%. There were 84 deaths (6.4%), of which eight deaths were because of prostate cancer. The 7-year cause-specific survival for the cohort was 99.2%. The median PSA nadir among biochemically controlled patients was 0.06 ng/mL (range, <0.02–0.91 ng/mL) for the hormone-naive patients and 0.05 ng/mL (range, <0.02–0.91 ng/mL) for the overall cohort.

Multivariate analyses were performed to identify predictors of PSA control (Table 3). The variables that predicted biochemical tumor control in a multivariate Cox regression analysis were the pretreatment PSA level ($p < 0.001$), Gleason score ($p < 0.001$), positive biopsy rate ($p < 0.001$), NADT ($p = 0.006$), and BED ($p = 0.001$). Among the intermediate-risk patients, the 7-year BFFF for patients treated with BED <180 Gy_2, 180–220 Gy_2, and ≥220 Gy_2 was 83.6%, 94.0%, and 96.9%, respectively ($p = 0.004$; Fig. 2). Among the intermediate-risk patients, NADT did not improve the 7-year BFFF in a univariate analysis (92.7% vs. 93.8%, $p = 0.510$).

Toxicity and sexual function

Acute urinary retention occurred in 68 patients (5.2%) within 1 year after implantation. In these 68 patients, 51 resolved in a month and eight resolved in 3 months. After 1 year postimplant, 22 patients (1.7%) developed urethral strictures requiring dilatation or minor surgery. The 7-year

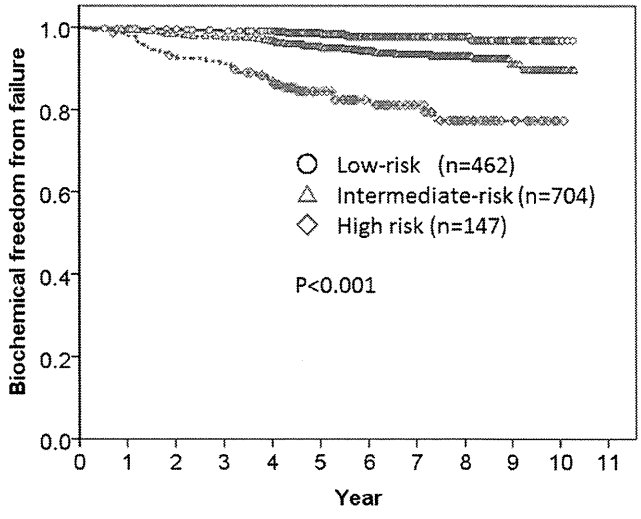

Fig. 1. Biochemical freedom from failure for low-, intermediate-, and high-risk prostate cancer patients with brachytherapy ($p < 0.001$).

Table 3
Predictors of biochemical relapse

	Univariate	Multivariate		
Characteristics	*p*-Value	*p*-Value	Hazard ratio	95% CI
Risk group	<0.001	0.219		
Low vs. high	<0.001	0.087		
Intermediate vs. high	0.006	0.275		
PSA	<0.001	<0.001	1.067	1.034–1.100
Gleason score	<0.001	<0.001		
<7 vs. >7	<0.001	<0.001	0.122	0.060–0.249
7 vs. >7	<0.001	<0.001	0.271	0.153–0.479
T stage	<0.001	0.286		
T1c–2a vs. T3	<0.001	0.115		
T2b–2c vs. T3	0.006	0.183		
Percent positive core	<0.001	<0.001	4.843	2.044–11.470
Age	0.599	0.800		
TRUS volume	0.094	0.954		
Preplan vs. intraoperative plan	0.578	0.151		
EBRT	<0.001	0.267		
NADT	0.110	0.006	1.931	1.204–3.099
BED	0.731	0.001	0.977	0.965–0.990

CI = confidence interval; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; EBRT = external beam radiotherapy; NADT = neoadjuvant androgen deprivation therapy; BED = biologically effective dose.

actuarial risk of developing Grades 2+ and 3+ genitourinary (GU) toxicity was 21% and 2%, respectively. The 7-year actuarial risk of developing Grade 2+ GU toxicity was 18.6% in monotherapy and 24.3% in combined treatment ($p = 0.016$; Fig. 3). Gastrointestinal (GI) toxicity was less common. The 7-year actuarial risk of developing Grades 2+ and 3+ GI toxicity was 7% and 0.3%, respectively. The 7-year actuarial risk of developing Grade 2+ GI toxicity was 12.6% in combined treatment, remarkably higher than 1.9% in monotherapy ($p < 0.001$; Fig. 4). The median IPSS was 7 (range, 0–35) at baseline, 14 at 3 months, eight at 1 and 2 years, and seven at 3 through 5 years. IPSS returned to within three points of the baseline value at 12 months in 71% of patients and sustained within three points of the baseline value at 60 months still in 70% of patients. Normal erectile function was reported in 215 men at baseline. Of those patients with >5 years followup and prior normal potency ($n = 147$), erectile function was normal in 65 (44.2%) of patients, suboptimal in 27 (18.4%), insufficient in 27 (18.4%), and absent in 28 (19.0%). According to age groups, erectile function at 5 years was normal in 27 of 51 (52.9%) patients who were 60 years and younger, 35 of 77 (45.5%) of those 61–70, and 3 of 19 (15.8%) of those 71 years and older. The use of phosphodiesterase type 5 (PDE-5) inhibitors was encouraged and administered in 43 of 147 (30%) of those patients.

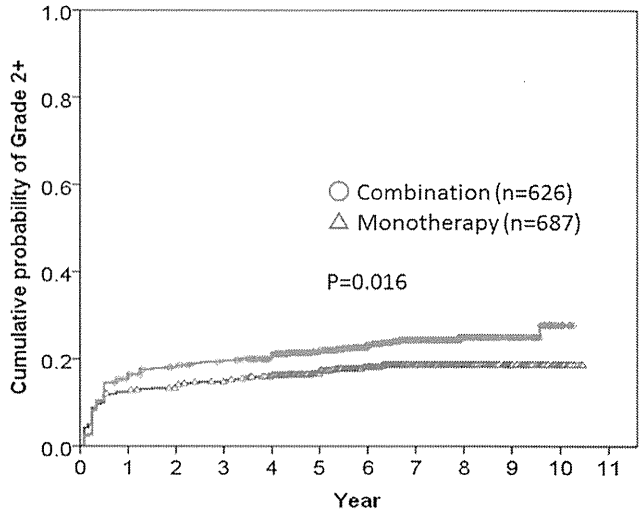

Fig. 3. Kaplan–Meier actuarial probability of Grade 2+ genitourinary toxicity.

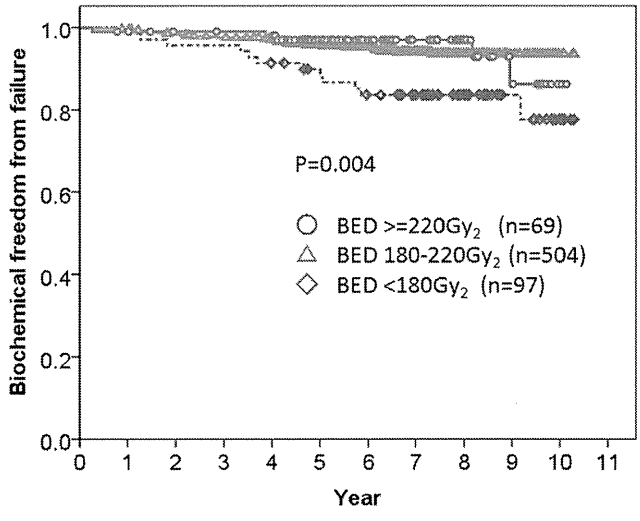

Fig. 2. Biochemical freedom from failure for patients with intermediate risk according to the BED dosimetric assessment ($p = 0.004$). BED = biologically effective dose.

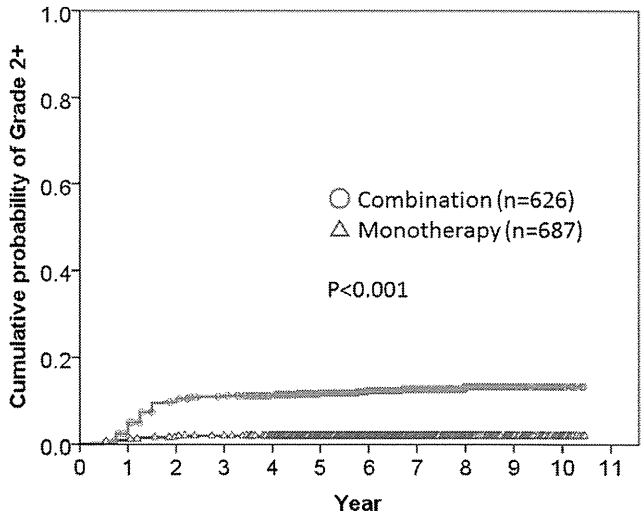

Fig. 4. Kaplan–Meier actuarial probability of Grade 2+ gastrointestinal toxicity.