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Biochemical outcomes and predictive factors by risk group after permanent iodine-125 seed implantation: Prospective cohort study in 2,316 patients

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ABSTRACT

PURPOSE: To evaluate the biochemical freedom from failure (bFFF) by risk group and treatment modality and the predictive factors of bFFF by risk group in patients with prostate cancer undergoing permanent seed implantation (PI) with or without external beam radiation therapy (EBRT) in a nationwide prospective cohort study (Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 [I-125] Seed Implantation) in Japan during the first 2 years.

METHODS AND MATERIALS: The analyses included 2,316 participants in 42 institutions; bFFF was evaluated using the Phoenix definition and calculated using the Kaplan–Meier method, and the Cox proportional hazards model was used to identify the factors associated with bFFF.

RESULTS: Median followup period was 60.0 months. The 5-year bFFF rates in all patients, 1,028 low-risk patients, 1,114 intermediate-risk patients, and 133 high-risk patients were 93.6%, 94.9%, 92.7%, and 91.1%, respectively. The 5-year bFFF rates in the PI group and EBRT combination therapy group were 93.7% and 93.3%, respectively. In a multivariate analysis, younger age, higher Gleason score (GS), higher percent positive biopsies (%PB), and lower prostate V_{100} (p = 0.0012, 0.0030, 0.0026, and 0.0368) in all patients; younger age, higher pretreatment prostate-specific antigen, and lower prostate V_{100} (p = 0.0002, 0.0048, and 0.0012) in low-risk patients; higher GS, higher %PB, and no hormonal treatment (p = 0.0005, 0.0120, and 0.0022) in intermediate-risk patients; and higher GS and higher %PB (p = 0.0329 and 0.0120) in high-risk patients were significantly associated with bFFF.

CONCLUSIONS: PI with or without EBRT resulted in excellent short-term biochemical outcomes in all risk groups, especially in high-risk patients. Age, pretreatment prostate-specific antigen, and prostate V_{100} in low-risk patients; GS, %PB, and hormonal treatment in intermediate-risk patients; and GS and %PB in high-risk patients were independently affected bFFF.
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Keywords: Prostate cancer; Brachytherapy; External beam radiation therapy; Biochemical failure; Risk group; Predictive factors

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Introduction

Permanent seed implantation (PI) with or without external beam radiation therapy (EBRT) has become a popular treatment option for patients with localized prostate cancer (PCa), with long-term local and biochemical control similar to outcomes observed after radical prostatectomy or EBRT (1, 2).

The number of patients with PCa treated with PI has rapidly increased in Japan, with over 37,000 patients treated through 2016 in 110 institutions (3, 4). To evaluate the safety and efficacy of PI in combination with or without EBRT and hormonal treatment (HT) for patients with localized PCa, a nationwide prospective cohort study entitled the Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 (I-125) Seed Implantation (J-POPS; NCT00534196) was initiated in July 2005 (5). The enrollment of the participants for this study has started in July 2005 and continued until December 2010. Finally, 6,927 participants in 46 institutions had been registered. This study is the world's largest registration study on PI.

Ito *et al*. reported the biochemical relapse-free survival (bRFS) using the Phoenix definition and the newly developed J-POPS definition, overall survival, and the associated factors of bRFS among all patients in the J-POPS study who were registered during the first 2 years: Cohort 1 (3). In this study, we evaluate the biochemical freedom from failure (bFFF) by risk group and treatment modality and the associated factors of bFFF by risk group in the same participants.

Methods and materials

Although the J-POPS study design has been previously described in detail (3, 5), a brief description of methods and materials is outlined in the following sections.

Patient eligibility

All participants were histologically confirmed as having adenocarcinoma of the prostate and were planning to undergo treatment with PI using loose I-125 seeds. Inclusion and exclusion criteria of the participants followed the recommendations of the American Brachytherapy Society (6).

A total of 2,354 participants were enrolled in this study during the first 2 years. Of the 2,354 participants, background characteristics and baseline data were available in 2,316 patients. Patients were divided into risk groups based on the presenting clinical characteristics. The low-risk group was defined as having the following characteristics: prostate-specific antigen (PSA) level less than 10 ng/mL, Gleason score (GS) less than or equal to 6, and clinical T stage less than or equal to T2a. The intermediate-risk group included one or more of the following features: PSA level of 10–20 ng/mL, GS of 7, and clinical T stage of T2b–T2c. The high-risk group included one or more of the following features: PSA level greater than 20 ng/mL, GS of 8–10, and clinical T stage of T3a. Locally advanced PCa was defined as clinical T stage of T3b–T4. The distribution among risk groups was as follows: 1,028 (44.4%) patients in the low-risk group, 1,113 (48.1%) patients in the intermediate-risk group, 133 (5.7%) patients in the high-risk group, 2 patients in the locally advanced PCa group, and 21 (0.9%) patients in a group whose PCa was localized but with unknown risk classification.

Treatment design

The prescription dose for patients undergoing PI alone without combined EBRT was 144 Gy. The clinical target volume was defined as the prostate volume including an added treatment margin of 3–5 mm in all directions, except for less than 2 mm in the posterior direction. For the EBRT combination therapy group, the recommended prescribed dose for PI was 100–110 Gy and that for EBRT was 40–50 Gy with 1.8–2.0 Gy/fraction. As for EBRT, the target volume consisted of the prostate gland, seminal vesicles, small pelvis, and/or whole pelvis.

Computed tomography images, taken at 1- to 3-mm slice width, were obtained approximately 1 month after PI (interquartile range, 27–33 days) for postimplant dosimetric evaluation. The biologically effective dose (BED) was calculated from the values of the minimal dose received by 90% of the prostate volume (D_{90}) and the EBRT dose using $\alpha/\beta = 2$ Gy, applying the formulas described previously (7).

Patient information is shown in Tables 1 and 2.

The definition of biochemical relapse and followup protocol

The Phoenix PSA failure definition (PSA nadir + 2.0 ng/mL) was used to define bFFF (8). For patients who failed to meet the Phoenix definition, if the PSA level subsequently decreased to less than or equal to 0.5 ng/mL without intervention, we considered it a PSA bounce. The event used to estimate bFFF was PSA failure or clinical relapse if it occurred earlier than the PSA failure. Patients who survived without apparent PSA failure or clinical relapse at the last followup and those who died because of other causes were censored.

The scheduled followup assessments included PSA blood tests and physical examinations every 3 months for the first 2 years and every 6 months thereafter for 5 years after the completion of radiation therapy.

Statistical analysis

The Kaplan–Meier method was used to estimate bFFF. The Cox proportional hazards model was used to identify the factors associated with bFFF. Patient age, pretreatment PSA, percent positive biopsies (%PB), prostate volume, the percent volumes of the prostate receiving 100% of the prescribed dose (V_{100}), prostate D_{90}, and BED were

Table 1
Descriptive statistics for patient information

Factors	*n*	Mean	SD	Minimum	Median	Maximum	Missing
Age (y)	2,316	68.1	6.4	45	69	89	0
Low-risk group	1,028	67.3	6.5	45	68	89	0
Intermediate-risk group	1,114	68.6	6.2	51	69	88	0
High-risk group	133	69.8	6.2	55	71	84	0
Pretreatment PSA (ng/mL)[a]	2,298	8.0	4.1	1.6	6.8	42.0	18
Low-risk group	1,028	6.2	1.7	1.6	6.0	9.98	0
Intermediate-risk group	1,114	8.8	3.7	1.9	8.1	20.0	0
High-risk group	132	14.6	9.0	3.7	11.4	42.0	1
Percent positive biopsies	2,196	27.5	19.1	3.9	21.4	100	120
Low-risk group	975	22.2	14.9	4.2	16.7	100	53
Intermediate-risk group	1,058	30.7	19.8	3.9	25	100	56
High-risk group	131	39.1	27.8	7.1	33.3	100	2
Prostate volume (mL)[b]	2,316	25.9	8.2	7.0	25.2	71.0	0
Low-risk group	1,028	26.9	8.1	7.3	26.2	60.9	0
Intermediate-risk group	1,114	25.4	8.3	8.6	24.8	71	0
High-risk group	133	22.9	7.8	7.0	22.2	45.8	0
Implanted seed number	2,316	68.3	16.6	25	69	120	0
Low-risk group	1,028	73.8	14.5	26	75	120	0
Intermediate-risk group	1,114	65.0	16.8	28	65	118	0
High-risk group	133	53.2	13.0	25	50	99	0
Activity/seed (MBq)	2,316	13.4	1.0	9.8	13.1	15.3	0
Low-risk group	1,028	13.4	1.0	9.8	13.1	15.3	0
Intermediate-risk group	1,114	13.4	1.0	10.3	13.1	15.3	0
High-risk group	133	13.1	1.1	10.6	12.8	15.3	0
Total activity (MBq)	2,316	929.3	293.7	244.8	903.9	1,836	0
Low-risk group	1,028	1,000.9	267.9	254.5	982.5	1,836	0
Intermediate-risk group	1,114	868.8	225.0	334.0	851.5	1,545.8	0
High-risk group	133	707.6	236.0	265.5	640	1,514.7	0
Prostate V_{100} (%)	2,304	93.9	5.2	56.3	95.2	100	12
Low-risk group	1,024	93.5	5.3	63.6	94.7	100	4
Intermediate-risk group	1,109	94.2	5.3	56.3	95.6	100	5
High-risk group	132	94.4	4.4	78.4	95.4	100.0	1
Prostate V_{150} (%)	2,304	62.4	13.5	16.3	63.4	98.1	12
Low-risk group	1,024	62.1	13.3	20.8	63.3	92.2	4
Intermediate-risk group	1,109	62.6	13.9	16.3	63.3	98.1	5
High-risk group	132	63.1	12.9	32.2	63.7	90.7	1
Prostate D_{90} (%)	2,304	112.0	15.5	40.1	112.4	191.6	12
Low-risk group	1,024	110.9	15.5	40.1	111.0	153.2	4
Intermediate-risk group	1,109	112.9	15.6	54.5	113.7	191.6	5
High-risk group	132	113.8	15.2	75.5	113.3	161.4	1
Biologically effective dose (Gy2)	2,305	178.9	28.4	59.0	179.4	289.8	11
Low-risk group	1,024	170.6	25.6	59.0	170.0	258.2	4
Intermediate-risk group	1,109	184.5	28.8	80.6	187.4	289.8	5
High-risk group	133	199.1	25.1	85.5	203.9	255.9	0

SD = standard deviation; PSA = prostate-specific antigen; V_{XX} = the percent volumes receiving XX% of the prescribed dose; D_{XX} = the values of the minimal dose received by XX% of the volume; R_{XX} = the rectal volume in cubic centimeters receiving XX% of the prescribed dose.

[a] Pretreatment PSA was measured before the latest biopsy.

[b] Prostate volume was measured before implantation.

considered continuous variables, and risk group (low, intermediate, or high), GS (6 or less, or 7 [3 + 4], or 7 [4 + 3], or 8 to 10 in all, low-risk, and intermediate-risk patients and 7 or less, or 8, or 9 in high-risk patients), clinical stage (T1c–T2a or T2bc–T3), treatment modalities (PI or PI with EBRT), and HT were considered the categorical variables.

Probability (p) values of less than 0.05 were considered to be significant. A multivariate analysis was performed to analyze the factors that were found to be significantly associated with bFFF in the univariate analysis.

Statistical analyses were performed using the SAS 9.3 statistical software (SAS Institute Inc., Cary, NC). All statistical analyses were performed at the Translational Research Informatics Center in the Foundation for Biomedical Research and Innovation, a public interest incorporated foundation.

Ethical considerations

The Ethical Review Committee of the Translational Research Informatics (Approval no. 05-01; May 6, 2005)

Table 2
Baseline characteristics of patients

Factors	Low-risk group *n* (%)	Intermediate-risk group *n* (%)	High-risk group *n* (%)	Total *n* (%)
Gleason score				
6 or less	1,028 (100)	241 (21.6)	15 (11.3)	1,309 (56.6)
7 (2 + 5, 3 + 4)	0 (0)	608 (54.6)	22 (16.5)	640 (27.7)
7 (4 + 3)	0 (0)	265 (23.8)	14 (10.5)	281 (12.2)
8	0 (0)	0 (0)	63 (47.4)	63 (2.7)
9	0 (0)	0 (0)	19 (14.3)	19 (0.8)
Clinical stage: T stage				
T1c	862 (84.0)	745 (67.2)	61 (45.9)	1,693 (73.4)
T2a	164 (16.0)	203 (18.3)	31 (23.3)	403 (17.5)
T2b	0 (0)	106 (9.6)	15 (11.3)	121 (5.3)
T2c	0 (0)	55 (5.0)	10 (7.5)	66 (2.9)
T3a	0 (0)	0 (0)	16 (12.0)	16 (0.7)
T3b	0 (0)	0 (0)	0 (0)	2 (0.1)
TX	0 (0)	0 (0)	0 (0)	5 (0.2)
Clinical stage: N stage				
N0	1028 (100)	1114 (100)	133 (100)	2,299 (99.4)
NX	0 (0)	0 (0)	0 (0)	14 (0.6)
Clinical stage: M stage				
M0	1,028 (100)	1,114 (100)	133 (100)	2,297 (99.3)
MX	0 (0)	0 (0)	0 (0)	16 (0.7)
Treatment modalities				
PI	1,011 (98.3)	701 (62.9)	23 (17.3)	1,774 (76.6)
PI + EBRT	17 (1.7)	413 (37.1)	110 (82.7)	542 (23.4)
Hormonal treatment				
Yes	405 (39.4)	607 (54.5)	107 (80.5)	1,138 (49.1)
No	623 (60.6)	507 (45.5)	26 (19.5)	1,178 (50.9)

PI = permanent seed implantation; EBRT = external beam radiation therapy.

and all the institutional review boards of the participating facilities approved the study.

Results

The median followup period was 60.0 months (interquartile range, 58.7–60.9 months).

Biochemical relapse was observed in 140 (6.0%) of all patients, 51 (5.0%) of the 1,028 low-risk patients, 75 (6.7%) of the 1,114 intermediate-risk patients, and 11 (9.7%) of the 133 high-risk patients. The 5-year bFFF rates in all, low-risk, intermediate-risk, and high-risk patients were 93.6%, 94.9%, 92.7%, and 91.1%, respectively (Fig. 1).

The 5-year bFFF rates in the PI group and EBRT combination therapy group were 93.7% and 93.3%, respectively (Fig. 1).

Table 3 shows the factors that were found to be significantly associated with bFFF in the univariate analysis and the results of the multivariate analysis for the effect of various factors on bFFF in all, low-risk, intermediate-risk, and high-risk patients, respectively. In a multivariate analysis, younger age, higher GS, higher %PB, and lower prostate V_{100} (p = 0.0012, 0.0030, 0.0026, and 0.0368, respectively) in all patients; younger age, higher pretreatment PSA, and lower prostate V_{100} (p = 0.0002, 0.0048, and 0.0012, respectively) in low-risk patients; higher GS, higher %PB, and no HT (p = 0.0005, 0.0120, and 0.0022, respectively) in intermediate-risk patients; and higher GS and higher %PB (p = 0.0329 and 0.0120, respectively) in high-risk patients were significantly associated with bFFF.

Discussion

The J-POPS study is the prospective cohort study on PI with the world's largest registration. In this study, we evaluated bFFF and treatment modality and the associated factors of bFFF by risk group among patients in the J-POPS study who were registered during the first 2 years.

The 5-year bFFF or bRFS rates using the Phoenix definition were reported to be 92.1–98.6% in low-risk patients treated with PI monotherapy with or without HT (8–19), 86.0–97.3% in intermediate-risk patients treated with PI monotherapy with or without HT (10–14,16,18,20–23), and 78–95.2% in high-risk patients treated with EBRT combination therapy with or without HT (12,16,18,19,24–29). In our study, of 1,028 low-risk patients, 98.35% were treated with PI monotherapy and 39.40% received HT and their 5-year bFFF rate was 94.9%. Of 1,114 intermediate-risk patients, 62.93% of the patients were treated with PI monotherapy and 54.49% of the patients received HT and their 5-year bFFF rate was 92.7%. Of 133 high-risk patients, 82.71% of the patients were treated with EBRT combination therapy

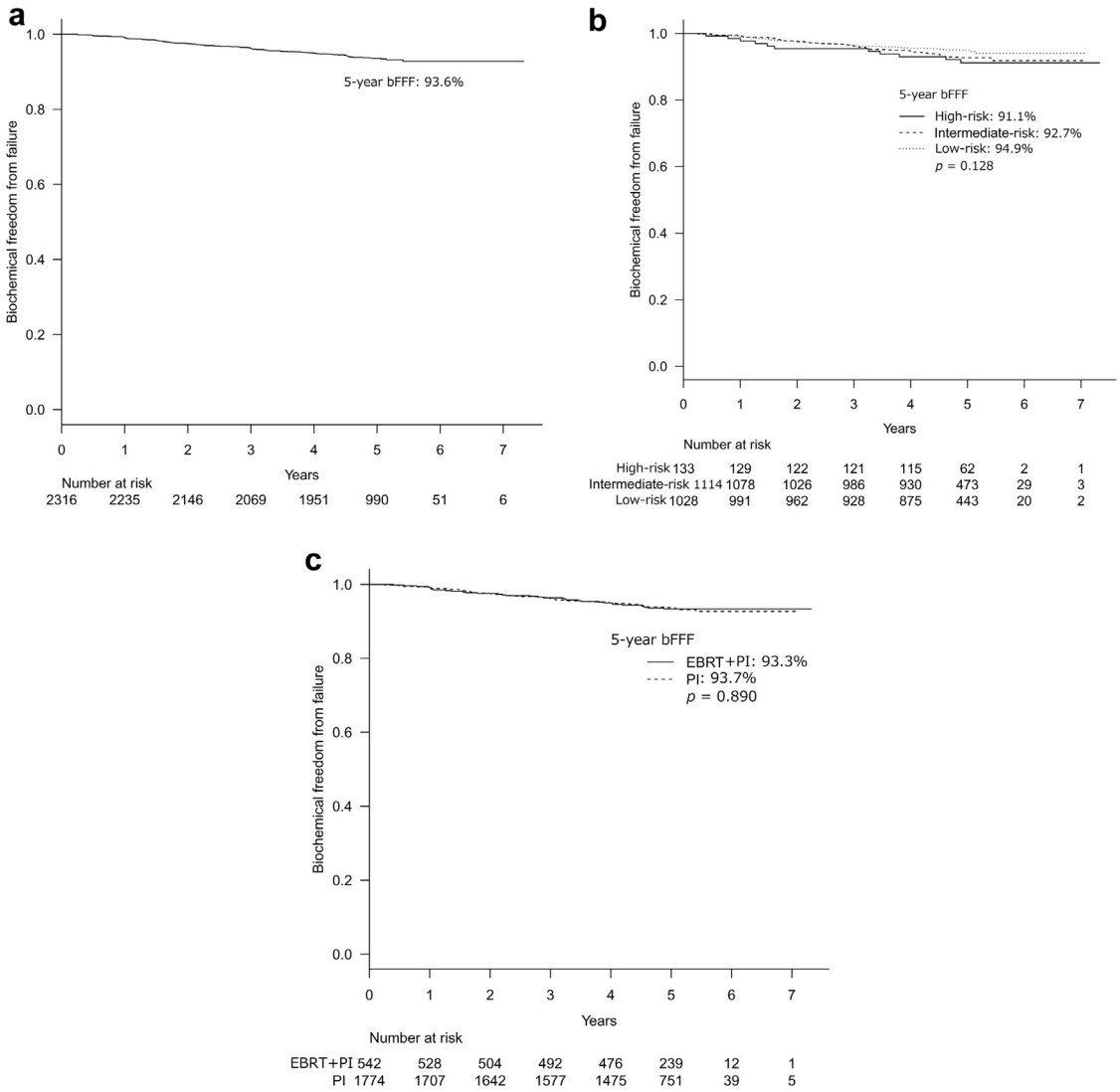

Fig. 1. (a) Biochemical freedom from failure (bFFF) in all patients; (b) bFFF by risk group; and (c) bFFF by treatment modality. EBRT = external beam radiation therapy.

and 80.45% of the patients received HT and their 5-year bFFF rate was 91.1%. Our outcomes in low- and intermediate-risk patients were similar to those in other studies.

Although Okamoto *et al*. reported the 5-year bFFF rate was 95.2% in high-risk patients, which was exceptionally high (28), our outcome in high-risk patients was relatively favorable as compared with the outcomes in other studies. We assume that this may be attributable to the higher number of high-risk patients who received HT. The percentage of high-risk patients who received HT was 80.45% in our study. Zimmermann *et al*. reported that the percentage of high-risk patients who received HT was 60.4% and their 5-year bFFF rate was 79.2% (12). Ohashi *et al*. reported that the percentage of high-risk patients who received HT was 49.0% and their 5-year bFFF rate was 84.8% (27). Conversely, Okamoto *et al*. reported that the percentage of high-risk patients who received HT was 100% and their 5-year bFFF rate was 95.2% (28). Additionally, this might be explained by the lower number of high-risk patients with stage T3+ in our study compared with other studies. In our study, the percentage of high-risk patients with stage T3+ was 12.03%. Riaz *et al*. reported that the percentage of high-risk patients with stage T3+ was 33.3% and their 5-year bFFF rate was 78% (26). Kauffmann *et al*. reported that percentage of high-risk patients with stage T3+ was 42.1% and their 5-year bFFF rate was 82% (21).

In our study, younger age was significantly associated with biochemical failure only in low-risk patients. Some studies have reported the significantly worse biochemical outcomes of PI for younger patients (9, 30, 31). Others have reported that age was not associated with biochemical failure in low-risk patients (30,32–35). The relationship between younger age and more aggressive clinical behavior of PCa has been previously documented (36), and there is evidence that young-age PCa has several biological and

Table 3
Multivariate analyses for biochemical freedom from failure

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
All cases						
Age	0.960	0.936–0.985	0.0016[a]	0.957	0.932–0.983	0.0012[a]
Pretreatment PSA	1.040	1.007–1.074	0.0161[a]	1.019	0.985–1.054	0.2830
Gleason score	–	–	<0.0001[a]	–	–	0.0030[a]
6 or less	Reference			Reference		
7 (3 + 4)	1.353	0.904–2.025	0.1412	1.261	0.826–1.925	0.2828
7 (4 + 3), 8 to 10	2.460	1.649–3.670	<0.0001[a]	2.149	1.380–3.347	0.0007[a]
% Positive biopsies	1.016	1.009–1.024	<0.0001[a]	1.012	1.004–1.020	0.0026[a]
Prostate V_{100} (%)	0.968	0.943–0.995	0.0187	0.970	0.942–0.998	0.0368[a]
Low-risk group						
Age	0.928	0.891–0.967	0.0004[a]	0.926	0.889–0.964	0.0002[a]
Pretreatment PSA	1.219	1.044–1.423	0.0123[a]	1.246	1.069–1.452	0.0048[a]
Prostate D_{90} (%)[b]	0.983	0.967–0.999	0.0397[a]	–	–	–
Prostate V_{100} (%)	0.944	0.907–0.982	0.0044[a]	0.936	0.899–0.974	0.0012[a]
Intermediate-risk group						
Gleason score	–	–	0.0005[a]	–	–	0.0005[a]
6 or less	Reference			Reference		
7 (3 + 4)	2.149	0.958–4.821	0.0634	2.187	0.919–5.205	0.0769
7 (4 + 3)	4.258	1.875–9.671	0.0005[a]	4.538	1.879–10.960	0.0008[a]
% Positive biopsies	1.014	1.003–1.024	0.0110[a]	1.014	1.003–1.025	0.0120[a]
Hormonal treatment						
Yes	0.560	0.353–0.886	0.0133[a]	0.470	0.290–0.762	0.0022[a]
No	Reference			Reference		
High-risk group						
Gleason score	–	–	0.0035[a]	–	–	0.0329[a]
7 or less		Reference			Reference	
8	0.503	0.084–3.010	0.4514	0.9587	0.1455–6.317	0.9651
9	5.544	1.386–22.170	0.0154[a]	5.553	1.201–25.670	0.0282[a]
% Positive biopsies	1.036	1.015–1.057	0.0007[a]	1.028	1.006–1.051	0.0120[a]
Prostate D_{90} (%)	1.041	1.003–1.081	0.0327[a]	1.047	0.9991–1.097	0.0545

HR = hazard ratio; CI = confidence interval; SD = standard deviation; PSA = prostate-specific antigen; V_{XX} = the percent volumes receiving XX% of the prescribed dose; D_{XX} = the values of the minimal dose received by XX% of the volume; R_{XX} = the rectal volume in cubic centimeters receiving XX% of the prescribed dose.

[a] Significant risk factor.

[b] Prostate D_{90} is the collinearity factor of prostate V_{100}; therefore, prostate D_{90} is excluded in the multivariate analysis.

genetic features, distinct from elderly-onset PCa (37). Because of the low BED and the lower number of patients who received HT in the low-risk group (Tables 1 and 2), aggressive PCa may not have been controlled. Furthermore, the number of low-risk patients was large in our study. Therefore, younger age may have been a significant factor associated with biochemical failure in low-risk patients.

Higher pretreatment PSA was also significantly associated with biochemical failure only in low-risk patients. Higher pretreatment PSA is reported to be significantly associated with biochemical failure in PI (38, 39). The two studies that analyzed the factors associated with biochemical failure by low-, intermediate-, and high-risk groups, respectively, in the same group of patients with PCa treated with PI reported that higher pretreatment PSA was significantly associated with biochemical failure only in low-risk patients (30, 32). These associations are consistent with our result only in low-risk patients. However, the reason is unclear.

Lower prostate V_{100} and D_{90} were also significantly associated with biochemical failure only in low-risk patients. Lower prostate D_{90} is reported to be significantly associated with biochemical failure in PI also in low-risk patients (34, 35, 40). Lower prostate V_{100} is reported to be significantly associated with biochemical failure in PI in low- and intermediate-risk patients (41, 42). Because of the lower number of patients who received HT or EBRT in the low-risk group (Tables 1 and 2), the prostate dose of PI may have had a strong effect on the local control.

No HT was significantly associated with biochemical failure only in intermediate-risk patients in our study. The efficacy of HT has not been established yet for patients in the intermediate-risk group (43). Some studies have reported that the use of HT was significantly associated with bFFF in intermediate-risk patients (44, 45), whereas others have reported that the use of HT was not significantly associated with bFFF in intermediate-risk patients (20, 32, 43, 46, 47). The use of HT was not associated with bFFF in high-risk patients. Some studies have reported that the use of HT was significantly associated with bFFF in high-risk patients (32, 48), whereas others have reported that

the use of HT was not significantly associated with bFFF in high-risk patients (27, 47). The American College of Radiology Appropriateness Criteria (49) and the American Society of Clinical Oncology/Cancer Care Ontario joint guideline (50) recommend that high-risk patients treated with PI should receive supplemental EBRT and HT. High-risk patients actually often receive trimodality treatment method with PI, EBRT, and HT (24, 28, 30). In the absence of a controlled predefined set of criteria that establish which patients, what duration of HT, and which agents to be administered in our study, it is difficult to draw any firm conclusions about HT use.

Higher %PB was significantly associated with biochemical failure in intermediate- and high-risk patients. Some studies have reported significantly worse biochemical outcomes of PI in patients with higher %PB in low- and intermediate-risk (42, 51, 52), intermediate- and high-risk (53, 54), and high-risk (27, 55) patients. Other studies have reported that a positive biopsy rate was not associated with biochemical failure in low- (35) and intermediate-risk (35, 43) patients. Many studies reported that higher %PB has been correlated with a higher likelihood of extracapsular extension (56–60). Because of the lower %PB, the probably low rate of extracapsular extension, and the low standard deviation of %PB in low-risk patients (Table 1), the % PB may have not been a factor associated with biochemical failure.

Our study evaluated the bFFF rate by risk group and treatment modality and the various associated factors of bFFF by risk group in J-POPS patients. Our study reported the significantly worse biochemical outcomes of PI for younger patients in the low-risk group for the first time. This should provide helpful information regarding treatment selection and followup after PI for Japanese patients with PCa.

The following are limitations of this study: the discrepancies in GSs among the institutions included in our study, absence of unified treatment modalities, presence of interobserver variability in postimplant dosimetry, and the biochemical failures that were initially judged by the physicians in each institution. To minimize interinstitutional variability in the GS in the J-POPS study, representative urologic pathologists in Japan conducted annual intensive lectures on the Gleason scoring system for general pathologists between 2004 and 2013 (3). Because the training workshops including the technical instruction of postimplant dosimetry are being held annually in Japan (4) and all the institutions in this study have participated in the workshops, interobserver variability in postimplant dosimetry should be minimized. Finally, the biochemical failures initially judged by the physicians in each institution were subsequently confirmed as appropriate by the specific committee that reviews biochemical failure in the J-POPS study (3).

The use of bFFF is a short-term endpoint, and the more meaningful endpoints are PCa-specific survival and overall survival. In the future, we will investigate and provide the definitive predictive factors of PCa-specific survival and overall survival.

Conclusions

PI with or without EBRT resulted in excellent short-term biochemical outcomes in all risk groups, especially in Japanese patients with PCa in the high-risk group. Younger age, higher pretreatment PSA, and lower prostate V_{100} in low-risk patients; higher GS, higher %PB, and no HT in intermediate-risk patients; and higher GS and higher %PB in high-risk patients independently affected biochemical failure.

References

[1] Zelefsky MJ, Daly ME, Valicenti RK. Low-risk prostate cancer. In: Halperin EC, Wazer DE, Perez CA, editors. *Perez and Brady's principles and practice of radiation oncology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins, a Wolters Kluwer business; 2013. p. 1280–1310.

[2] Chung HT, Roach M 3rd. Intermediate- and high-risk prostate cancer. In: Halperin EC, Wazer DE, editors. *Perez and Brady's principles and practice of radiation oncology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins, a Wolters Kluwer business; 2013. p. 1311–1333.

[3] Ito K, Saito S, Yorozu A, *et al*. Nationwide Japanese prostate cancer outcome study of permanent iodine-125 seed implantation (J-POPS): First analysis on survival. *Int J Clin Oncol* 2018;23: 1148–1159.

[4] Nakamura K, Ohga S, Yorozu A, *et al*. Diffusion pattern of low dose rate brachytherapy for prostate cancer in Japan. *Cancer Sci* 2013; 104:934–936.

[5] Saito S, Ito K, Yorozu A, *et al*. Nationwide Japanese prostate cancer outcome study of permanent iodine-125 seed implantation (J-POPS). *Int J Clin Oncol* 2015;20:375–385.

[6] Nag S, Beyer D, Friedland J, *et al*. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 1999;44:789–799.

[7] Stock RG, Stone NN, Cesaretti JA, *et al*. Biologically effective dose values for prostate brachytherapy: Effects on PSA failure and post-treatment biopsy results. *Int J Radiat Oncol Biol Phys* 2006;64: 527–533.

[8] Kittel JA, Reddy CA, Smith KL, *et al*. Long-term efficacy and toxicity of low-dose-rate 125I prostate brachytherapy as monotherapy in low-, intermediate-, and high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2015;92:884–893.

[9] Reis LO, Sanches BC, Zani EL, *et al*. PSA-nadir at 1 year as a sound contemporary prognostic factor for low-dose-rate iodine-125 seeds brachytherapy. *World J Urol* 2014;32:753–759.

[10] Chao M, Spencer S, Guerrieri M, *et al*. A single institution analysis of low-dose-rate brachytherapy: 5-Year reported survival and late toxicity outcomes. *J Contemp Brachytherapy* 2018;10:155–161.

[11] Atallah V, Leduc N, Creoff M, *et al*. Curative brachytherapy for prostate cancer in African-Caribbean patients: A retrospective analysis of 370 consecutive cases. *Brachytherapy* 2016;16:342–347.

[12] Zimmermann JS, Osieka R, Bruns T, *et al*. Five-year effectiveness of low-dose-rate brachytherapy: Comparisons with nomogram predictions in patients with non-metastatic prostate cancer presenting significant control of intra- and periprostatic disease. *J Contemp Brachytherapy* 2018;10:297–305.

[13] Fellin G, Mirri MA, Santoro L, *et al*. Low dose rate brachytherapy (LDR-BT) as monotherapy for early stage prostate cancer in Italy: Practice and outcome analysis in a series of 2237 patients from 11 institutions. *Br J Radiol* 2015;89:20150981.
[14] Thomas L, Chemin A, Leduc N, *et al*. Manual vs. automated implantation of seeds in prostate brachytherapy: Oncologic results from a single-center study. *Brachytherapy* 2017;17:214–220.
[15] Martin AG, Roy J, Beaulieu L, *et al*. Permanent prostate implant using high activity seeds and inverse planning with fast simulated annealing algorithm: A 12-year Canadian experience. *Int J Radiat Oncol Biol Phys* 2007;67:334–341.
[16] Zelefsky MJ, Chou JF, Pei X, *et al*. Predicting biochemical tumor control after brachytherapy for clinically localized prostate cancer: The Memorial Sloan-Kettering Cancer Center experience. *Brachytherapy* 2012;11:245–249.
[17] Pickles T, Keyes M, Morris WJ. Brachytherapy or conformal external radiotherapy for prostate cancer: A single-institution matched-pair analysis. *Int J Radiat Oncol Biol Phys* 2010;76:43–49.
[18] Taira AV, Merrick GS, Butler WM, *et al*. Long-term outcome for clinically localized prostate cancer treated with permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2011;79:1336–1342.
[19] Potters L, Morgenstern C, Calugaru E, *et al*. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2005;173:1562–1566.
[20] Tran AT, Mandall P, Swindell R, *et al*. Biochemical outcomes for patients with intermediate risk prostate cancer treated with I-125 interstitial brachytherapy monotherapy. *Radiother Oncol* 2013;109:235–240.
[21] Kauffmann G, Arif F, Patel P, *et al*. Pretreatment multiparametric MRI is independently associated with biochemical outcome in men treated with radiation therapy for prostate cancer. *Urol Oncol* 2018;36:471.e411–471.e418.
[22] Frank SJ, Pugh TJ, Blanchard P, *et al*. Prospective phase 2 trial of permanent seed implantation prostate brachytherapy for intermediate-risk localized prostate cancer: Efficacy, toxicity, and quality of life outcomes. *Int J Radiat Oncol Biol Phys* 2018;100:374–382.
[23] Herbert C, Morris WJ, Keyes M, *et al*. Outcomes following iodine-125 brachytherapy in patients with Gleason 7, intermediate risk prostate cancer: A population-based cohort study. *Radiother Oncol* 2012;103:228–232.
[24] Peters CA, Stock RG, Blacksburg SR, *et al*. Effect of family history on outcomes in patients treated with definitive brachytherapy for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;73:24–29.
[25] Koontz BF, Chino J, Lee WR, *et al*. Morbidity and prostate-specific antigen control of external beam radiation therapy plus low-dose-rate brachytherapy boost for low, intermediate, and high-risk prostate cancer. *Brachytherapy* 2009;8:191–196.
[26] Riaz N, Afaq A, Akin O, *et al*. Pretreatment endorectal coil magnetic resonance imaging findings predict biochemical tumor control in prostate cancer patients treated with combination brachytherapy and external-beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;84:707–711.
[27] Ohashi T, Yorozu A, Saito S, *et al*. Combined brachytherapy and external beam radiotherapy without adjuvant androgen deprivation therapy for high-risk prostate cancer. *Radiat Oncol* 2014;9:13.
[28] Okamoto K, Wada A, Kohno N. High biologically effective dose radiation therapy using brachytherapy in combination with external beam radiotherapy for high-risk prostate cancer. *J Contemp Brachytherapy* 2017;9:1–6.
[29] Sylvester JE, Grimm PD, Blasko JC, *et al*. 15-Year biochemical relapse free survival in clinical atage T1-T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. *Int J Radiat Oncol Biol Phys* 2007;67:57–64.
[30] Callaghan CM, Wang L, Alluri A, *et al*. Low-dose-rate prostate brachytherapy: 4-8 Week postimplant prostate-specific antigen a novel predictor of biochemical failure-free survival. *Brachytherapy* 2017;16:1119–1128.
[31] Warner A, Pickles T, Crook J, *et al*. Development of ProCaRS clinical nomograms for biochemical failure-free survival following either low-dose rate brachytherapy or conventionally fractionated external beam radiation therapy for localized prostate cancer. *Cureus* 2015;7:e276.
[32] Stone NN, Stone MM, Rosenstein BS, *et al*. Influence of pretreatment and treatment factors on intermediate to long-term outcome after prostate brachytherapy. *J Urol* 2011;185:495–500.
[33] Lubbe W, Cohen R, Sharma N, *et al*. Biochemical and clinical experience with real-time intraoperatively planned permanent prostate brachytherapy. *Brachytherapy* 2012;11:209–213.
[34] Morgia G, Castelli T, Privitera S, *et al*. Association between long-term erectile dysfunction and biochemical recurrence after permanent seed I(125) implant brachytherapy for prostate cancer. A longitudinal study of a single-institution. *Aging Male* 2015;19:15–19.
[35] Shiraishi Y, Yorozu A, Ohashi T, *et al*. A dose-response analysis of biochemical control outcomes after (125)I monotherapy for patients with favorable-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2014;90:1069–1075.
[36] Hamstra DA, Bae K, Pilepich MV, *et al*. Older age predicts decreased metastasis and prostate cancer-specific death for men treated with radiation therapy: Meta-analysis of radiation therapy oncology group trials. *Int J Radiat Oncol Biol Phys* 2011;81:1293–1301.
[37] Hussein S, Satturwar S, Van der Kwast T. Young-age prostate cancer. *J Clin Pathol* 2015;68:511–515.
[38] Sylvester JE, Grimm PD, Wong J, *et al*. Fifteen-year biochemical relapse-free survival, cause-specific survival, and overall survival following I(125) prostate brachytherapy in clinically localized prostate cancer: Seattle experience. *Int J Radiat Oncol Biol Phys* 2011;81:376–381.
[39] Hinnen KA, van Vulpen M. Predictors in the outcome of 125I brachytherapy as monotherapy for prostate cancer. *Expert Rev Anticancer Ther* 2011;11:115–123.
[40] Stock RG, Stone NN, Tabert A, *et al*. A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys* 1998;41:101–108.
[41] Genebes C, Filleron T, Graff P, *et al*. Conventional versus automated implantation of loose seeds in prostate brachytherapy: Analysis of dosimetric and clinical results. *Int J Radiat Oncol Biol Phys* 2013;87:651–658.
[42] Papagikos MA, Deguzman AF, Rossi PJ, *et al*. Dosimetric quantifiers for low-dose-rate prostate brachytherapy: Is V(100) superior to D(90)? *Brachytherapy* 2005;4:252–258.
[43] Takamoto A, Tanimoto R, Bekku K, *et al*. Oncological impact of neoadjuvant hormonal therapy on permanent iodine-125 seed brachytherapy in patients with low- and intermediate-risk prostate cancer. *Int J Urol* 2018;25:507–512.
[44] Senzaki T, Fukumori T, Mori H, *et al*. Clinical significance of neoadjuvant combined androgen blockade for more than six months in patients with localized prostate cancer treated with prostate brachytherapy. *Urol Int* 2014;95:457–464.
[45] Schlussel EM, Buckstein M, Stone NN, *et al*. Outcomes and toxicities in patients with intermediate-risk prostate cancer treated with brachytherapy alone or brachytherapy and supplemental external beam radiation therapy. *BJU Int* 2018;121:774–780.
[46] Wernicke AG, Shamis M, Yan W, *et al*. Role of isotope selection in long-term outcomes in patients with intermediate-risk prostate cancer treated with a combination of external beam radiotherapy and low-dose-rate interstitial brachytherapy. *Urology* 2012;79:1098–1104.
[47] Stone NN, Potters L, Davis BJ, *et al*. Customized dose prescription for permanent prostate brachytherapy: Insights from a multicenter analysis of dosimetry outcomes. *Int J Radiat Oncol Biol Phys* 2007;69:1472–1477.

[48] Merrick GS, Butler WM, Wallner KE, *et al*. Androgen deprivation therapy does not impact cause-specific or overall survival in high-risk prostate cancer managed with brachytherapy and supplemental external beam. *Int J Radiat Oncol Biol Phys* 2007;68:34−40.

[49] Davis BJ, Taira AV, Nguyen PL, *et al*. ACR appropriateness criteria: Permanent source brachytherapy for prostate cancer. *Brachytherapy* 2016;16:266−276.

[50] Chin J, Rumble RB, Loblaw DA. Brachytherapy for patients with prostate cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update Summary. *J Oncol Pract* 2017;13:392−394.

[51] Kindts I, Stellamans K, Billiet I, *et al*. (125)I brachytherapy in younger prostate cancer patients: Outcomes in low- and intermediate-risk disease. *Strahlenther Onkol* 2017;193:707−713.

[52] Pereira da Ponte LA, Fernandes Silva JL, Hanna SA, *et al*. Biochemical control of prostate cancer with iodine-125 brachytherapy alone: Experience from a single institution. *Clin Transl Oncol* 2012;14:369−375.

[53] Merrick GS, Wallner KE, Galbreath RW, *et al*. Is supplemental external beam radiation therapy necessary for patients with higher risk prostate cancer treated with 103Pd? Results of two prospective randomized trials. *Brachytherapy* 2015;14:677−685.

[54] Nurani R, Wallner K, Merrick G, *et al*. Optimized prostate brachytherapy minimizes the prognostic impact of percent of biopsy cores involved with adenocarcinoma. *J Urol* 2007;178:1968−1973.

[55] Bittner N, Merrick GS, Galbreath RW, *et al*. Treatment outcomes with permanent brachytherapy in high-risk prostate cancer patients stratified into prognostic categories. *Brachytherapy* 2015;14:766−772.

[56] Lotan Y, Shariat SF, Khoddami SM, *et al*. The percent of biopsy cores positive for cancer is a predictor of advanced pathological stage and poor clinical outcomes in patients treated with radical prostatectomy. *J Urol* 2004;171:2209−2214.

[57] D'Amico AV, Whittington R, Malkowicz SB, *et al*. Clinical utility of the percentage of positive prostate biopsies in defining biochemical outcome after radical prostatectomy for patients with clinically localized prostate cancer. *J Clin Oncol* 2000;18:1164−1172.

[58] Bismar TA, Lewis JS Jr, Vollmer RT, *et al*. Multiple measures of carcinoma extent versus perineural invasion in prostate needle biopsy tissue in prediction of pathologic stage in a screening population. *Am J Surg Pathol* 2003;27:432−440.

[59] Grossfeld GD, Chang JJ, Broering JM, *et al*. Under staging and under grading in a contemporary series of patients undergoing radical prostatectomy: Results from the Cancer of the Prostate Strategic Urologic Research Endeavor database. *J Urol* 2001;165:851−856.

[60] Gao X, Mohideen N, Flanigan RC, *et al*. The extent of biopsy involvement as an independent predictor of extraprostatic extension and surgical margin status in low risk prostate cancer: Implications for treatment selection. *J Urol* 2000;164:1982−1986.