Title Page

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

Norihisa Katayama[*], Katsumasa Nakamura[#], Atsunori Yorozu[†], Takashi Kikuchi[††], Masanori Fukushima[††], Shiro Saito[||||], Takushi Dokiya[¶]

[*]Department of Radiology, Okayama University Medical School, Okayama, Japan

[#]Department of Radiation Oncology, Hamamatsu University School of Medicine, Hamamatsu, Japan

[†]Department of Radiation Oncology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan

[††]Translational Research Informatics Center, Kobe, Japan

[||||]Department of Urology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan

[¶]Department of Radiology, Kyoundo Hospital, Tokyo, Japan

Corresponding author:

Norihisa Katayama, M.D., Ph.D.

Department of Radiology, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

E-mail: n-katayama@bea.hi-ho.ne.jp

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 in Japan (J-POPS) 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, with factors compared using the Cox proportional hazard model.

Results: Median follow-up period was 60.0 months. The 5-year bFFF rates in all patients, 1,028 low-risk, 1,114 intermediate-risk, and 133 high-risk patients were 93.6%, 94.9%, 92.7%, and 91.1%. The 5-year bFFF rates in PI group and EBRT combination therapy group were 93.7% and 93.3%. On multivariate analysis, younger age, higher Gleason score (GS), higher percent positive biopsies (%PB), and lower prostate V100 (p=0.0012, 0.0030, 0.0026, and 0.0368) in all patients; younger age, higher pretreatment PSA, and lower prostate V100 (p=0.0002, 0.0048, and 0.0012) in low-risk; higher GS, higher %PB, and no hormonal treatment (HT) (p=0.0005, 0.0120, and 0.0022) in intermediate-risk; and higher GS and higher %PB (p=0.0329 and 0.0120) in high-risk patients were significantly associated with biochemical failure.

Conclusions: PI with or without EBRT resulted in excellent short-term biochemical outcomes in all risk groups, especially in high-risk patients. Age, pretreatment PSA, and prostate V100 in low-risk; GS, %PB, and HT in intermediate-risk; GS and %PB in high-risk patients independently affected bFFF.

KEYWORDS: Prostate cancer, Brachytherapy, External beam radiation therapy, Biochemical failure, Risk group, Predictive factors

ABBREVIATIONS

TRI Translational Research Informatics

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 below.

Patient eligibility

All participants were histologically confirmed as having adenocarcinoma of the prostate who 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. Out 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 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, Gleason score 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, Gleason score of 8–10, and clinical T stage of T3a. Locally advanced was defined as clinical T stage T3b–T4. The distribution among risk groups was as follows: 1,028 (44.4%) patients in low-risk group, 1,113 (48.1%) patients in intermediate-risk group, 133 (5.7%) patients in high-risk group, 2 patients in 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 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 1–3-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 (D90) 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 follow-up protocol

The Phoenix definition PSA failure definition ((PSA nadir + 2.0 ng/mL) was used to define bFFF (8). For patients who failed by 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 the 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 follow-up and those who died due to other causes were censored.

The scheduled follow-up 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 the bFFF. The Cox proportional hazards model was also used to identify the factors associated with the bFFF. Patient age, pretreatment PSA, percent positive biopsies, prostate volume, the percent volumes of the prostate receiving 100% of the prescribed dose (V100), prostate D90, and BED were considered continuous variables, and risk group (low, intermediate, or high), Gleason score (GS) (6 or less, or 7 [3+4], or 7 [4+3], 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 the bFFF in the univariate analysis.

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

Ethical considerations

The Ethical Review Committee of the TRI (Approval no. 05-01; May 6, 2005) and all of the institutional review boards of the participating facilities approved the study.

RESULTS

The median follow-up period was 60.0 months (interquartile range, 58.7–60.9 months).

Biochemical relapse was observed in 140 patients (6.0%) in all patients, 51 patients (5.0%) out of the 1028 low-risk patients, 75 patients (6.7%) out of the 1114 intermediate-risk patients, and 11 patients (9.7%) out 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 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 the bFFF in the univariate analysis and the results of the multivariate analysis for the effect of various factors on the bFFF in all, low-risk, intermediate-risk, and high-risk patients, respectively. On a multivariate analysis, younger age, higher Gleason score (GS), higher percent positive biopsies, and lower prostate V100 (p=0.0012, 0.0030, 0.0026, and 0.0368, respectively) in all patients; younger age, higher pretreatment PSA, and lower prostate V100 (p=0.0002, 0.0048, and 0.0012, respectively) in low-risk patients; higher GS, higher percent positive biopsies, and no HT (p=0.0005, 0.0120, and 0.0022, respectively) in intermediate-risk

patients; and higher GS and higher percent positive biopsies (p=0.0329 and 0.0120, respectively) in high-risk patients were significantly associated with biochemical failure.

DISCUSSION

The J-POPS study is the prospective cohort study on PI with the world's largest registration. In this study, we evaluated the 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, 18–23), and 78–95.2% in high-risk patients treated with EBRT combination therapy with or without HT (12, 16, 18, 19, 24–29), respectively. In our study, for the low-risk patients, 98.35% of the patients were treated with PI monotherapy and 39.40% of the patients received HT, and their 5-year bFFF rate was 94.9%. For the 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%. For the high-risk patients, 82.71% of the patients were treated with EBRT combination therapy and 80.45% of the patients received HT, and their 5-year bFFF rate was 91.1%. Our outcomes in low-risk and intermediate-risk patients were similar to those in the other studies.

Although Okamoto et al. reported their 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 the other studies. We assume that this may be attributable to the higher rate of high-risk patients who received HT. The rate of high-risk patients who received HT was 80.45% in our study. Zimmermann et al. reported that the rate of high-risk patients who received HT was 60.4%, and their 5-year bFFF rate was 79.2% in high-risk patients (12). Ohashi et al. reported that the rate of high-risk patients who received HT was 49.0%, and their 5-year bFFF rate was 84.8% in high-risk patients (27).

Conversely, Okamoto et al. reported that the rate of high-risk patients who received HT was 100%, and their 5-year bFFF rate was 95.2% in high-risk patients (28). Additionally, this might be explained by the lower rate of patients with stage T3+ in all high-risk patients than the other studies. In our study, the rate of patients with stage T3+ in all high-risk patients was 12.03%. Riaz et al. reported that the rate of patients with stage T3+ in all high-risk patients was 33.3%, and their 5-year bFFF rate was 78% in high-risk patients (26). Kauffmann et al. reported that the rate of patients with stage T3+ in all high-risk patients was 42.1%, and their 5-year bFFF rate was 82% in high-risk patients (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, 33, 34, 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 genetic features, distinct from elderly-onset PCa (37). Because of the low BED and the low rate of patients who received HT in low-risk patients (Table 1, 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 group, respectively, in the same group of PCa patients treated with PI reported that higher pretreatment PSA was significantly associated with biochemical failure only in low-risk patients (30, 32). These associations only in low-risk patients are consistent with our result. However, the reason is unclear.

Lower prostate V100 and D90 were also significantly associated with biochemical failure only in low-risk patients. Lower prostate D90 is reported to be significantly associated with biochemical failure in PI also in low-risk patients (34,

35, 40). Lower prostate V100 is reported to be significantly associated with biochemical failure in PI in low-risk plus intermediate-risk patients (41, 42). Because of the low rate of patients who received HT or EBRT in low-risk patients (Table 1, 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 with intermediate-risk disease (43). Some studies have reported that the use of HT was significantly associated with the bFFF in intermediate-risk patients (44, 45), whereas others have reported that the use of HT was not significantly associated with the 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 the bFFF in high-risk patients (32, 48), whereas others have reported that that the use of HT was not significantly associated with the 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.

Higher percent positive biopsies was significantly associated with biochemical failure in intermediate-risk and high-risk patients. Some studies have reported significantly worse biochemical outcomes of PI in patients with higher percent positive biopsies in low-risk plus intermediate-risk (42, 51, 52), intermediate-risk plus 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-risk (35) and intermediate-risk (35, 43) patients. Many studies reported that higher percent positive biopsies has been correlated with a higher likelihood of extracapsular extension (56–60). Because of the lower percent positive biopsies, the probably low rate of extracapsular extension, and the low standard deviation of percent positive biopsies in

low-risk patients (Table 1), the percent positive biopsies 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 low-risk patients for the first time. They should provide the helpful information concerning the treatment selection and the follow-up after PI for Japanese PCa patients.

The limitation of this study included the following: the discrepancies in Gleason scores 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 prostate cancer-specific survival (CSS) and overall survival (OS). In the future, we will investigate and provide the definitive predictive factors of CSS and OS.

CONCLUSIONS

PI with or without EBRT resulted in excellent short-term biochemical outcomes at all risk groups, especially at high-risk group in Japanese PCa patients. Younger age, higher pretreatment PSA, and lower prostate V100 in low-risk

patients; higher GS, higher percent positive biopsies, and no HT in intermediate-risk patients; and higher GS and higher percent positive biopsies in high-risk patients independently affected biochemical failure.

CONFLICT OF INTEREST: None

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FIGURE CAPTIONS

Fig. 1. (a) Biochemical freedom from failure (bFFF) in all patients. (b) bFFF by risk group. (c) bFFF by treatment modality.

Table 1 Descriptive statistics for patient information

Factors	n	Mean	SD	Minimum	Median	Maximum	Missing
Age (year)	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)*	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)[†]	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 V100 (%)	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 V150 (%)	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 D90 (%)	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, *VXX* the percent volumes receiving XX% of the prescribed dose, *DXX* the values of the minimal dose received by XX% of the volume, *RXX* the rectal volume in cubic centimeters receiving XX% of the prescribed dose

*Pretreatment PSA was measured before the latest biopsy

†Prostate volume was measured preimplantation

Table 2 Baseline characteristics of patients

Factors	Low-risk group		Intermediate-risk group		High-risk group		Total	
	n	%	n	%	n	%	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

Table 3 Multivariate analyses for biochemical freedom from failure

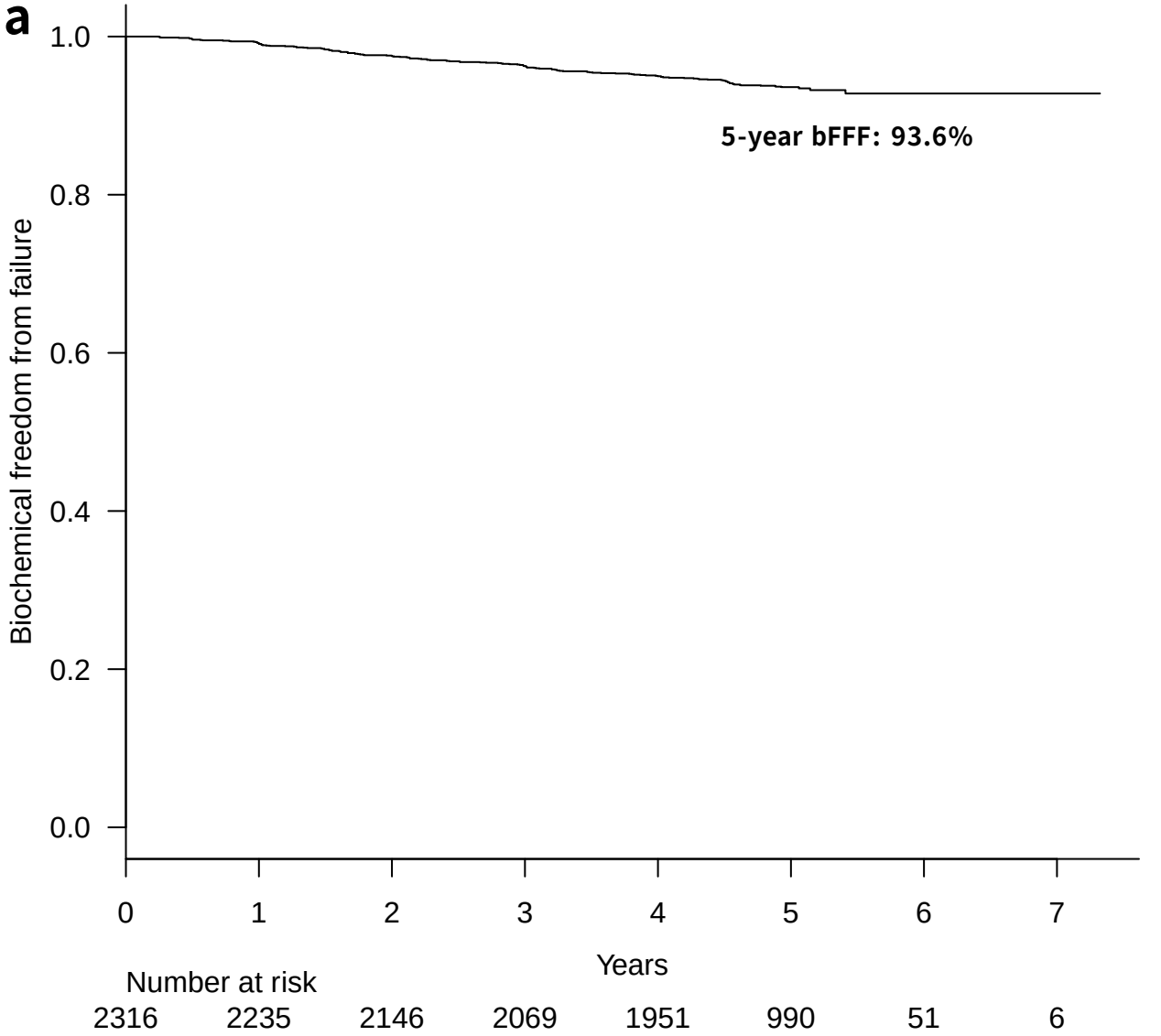
Factors		Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*	HR	95% CI	*p*
All cases							
Age		0.960	0.936–0.985	0.0016*	0.957	0.932–0.983	0.0012*
Pretreatment PSA		1.040	1.007–1.074	0.0161*	1.019	0.985–1.054	0.2830
Gleason score		—	—	<0.0001*	—	—	0.0030*
	6 or less		Reference			Reference	
	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*	2.149	1.380–3.347	0.0007*
% Positive biopsies		1.016	1.009–1.024	<0.0001*	1.012	1.004–1.020	0.0026*
Prostate V100 (%)		0.968	0.943–0.995	0.0187	0.970	0.942–0.998	0.0368*
Low-risk group							
Age		0.928	0.891–0.967	0.0004*	0.926	0.889–0.964	0.0002*
Pretreatment PSA		1.219	1.044–1.423	0.0123*	1.246	1.069–1.452	0.0048*
Prostate D90 (%)#		0.983	0.967–0.999	0.0397*	—	—	—
Prostate V100 (%)		0.944	0.907–0.982	0.0044*	0.936	0.899–0.974	0.0012*
Intermediate-risk group							
Gleason score		—	—	0.0005*	—	—	0.0005*
	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*	4.538	1.879–10.960	0.0008*
% Positive biopsies		1.014	1.003–1.024	0.0110*	1.014	1.003–1.025	0.0120*
Hormonal treatment	Yes	0.560	0.353–0.886	0.0133*	0.470	0.290–0.762	0.0022*
	No		Reference			Reference	

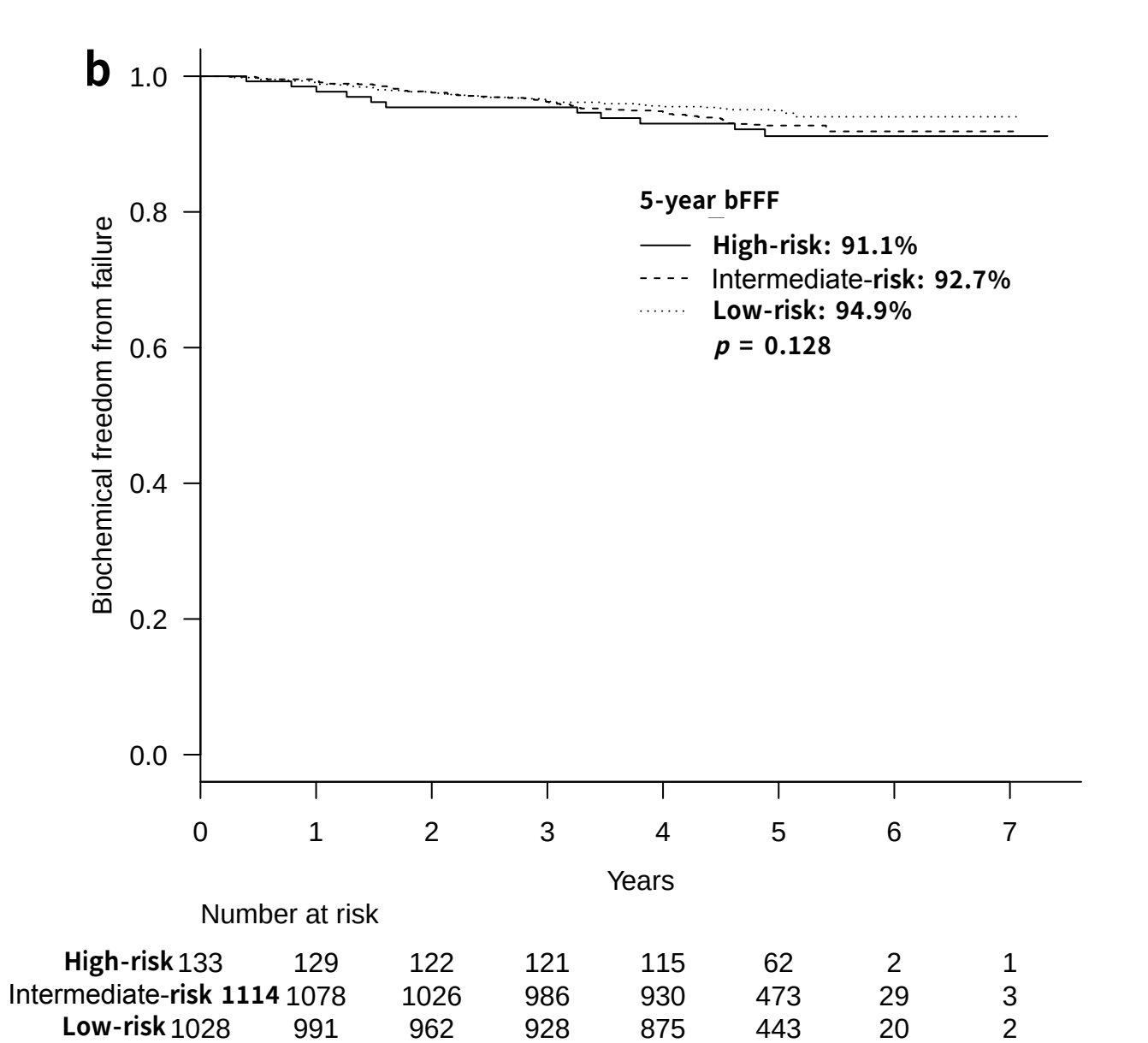
High-risk group							
Gleason score		—	—	0.0035*	—	—	0.0329*
	7 or less		Reference			Reference	
	8	0.503	0.084–3.010	0.4514	0.9587	0.1455–6.317	0.9651
	9	5.544	1.386–22.170	0.0154*	5.553	1.201–25.670	0.0282*
% Positive biopsies		1.036	1.015–1.057	0.0007*	1.028	1.006–1.051	0.0120*
Prostate D90 (%)		1.041	1.003–1.081	0.0327*	1.047	0.9991–1.097	0.0545

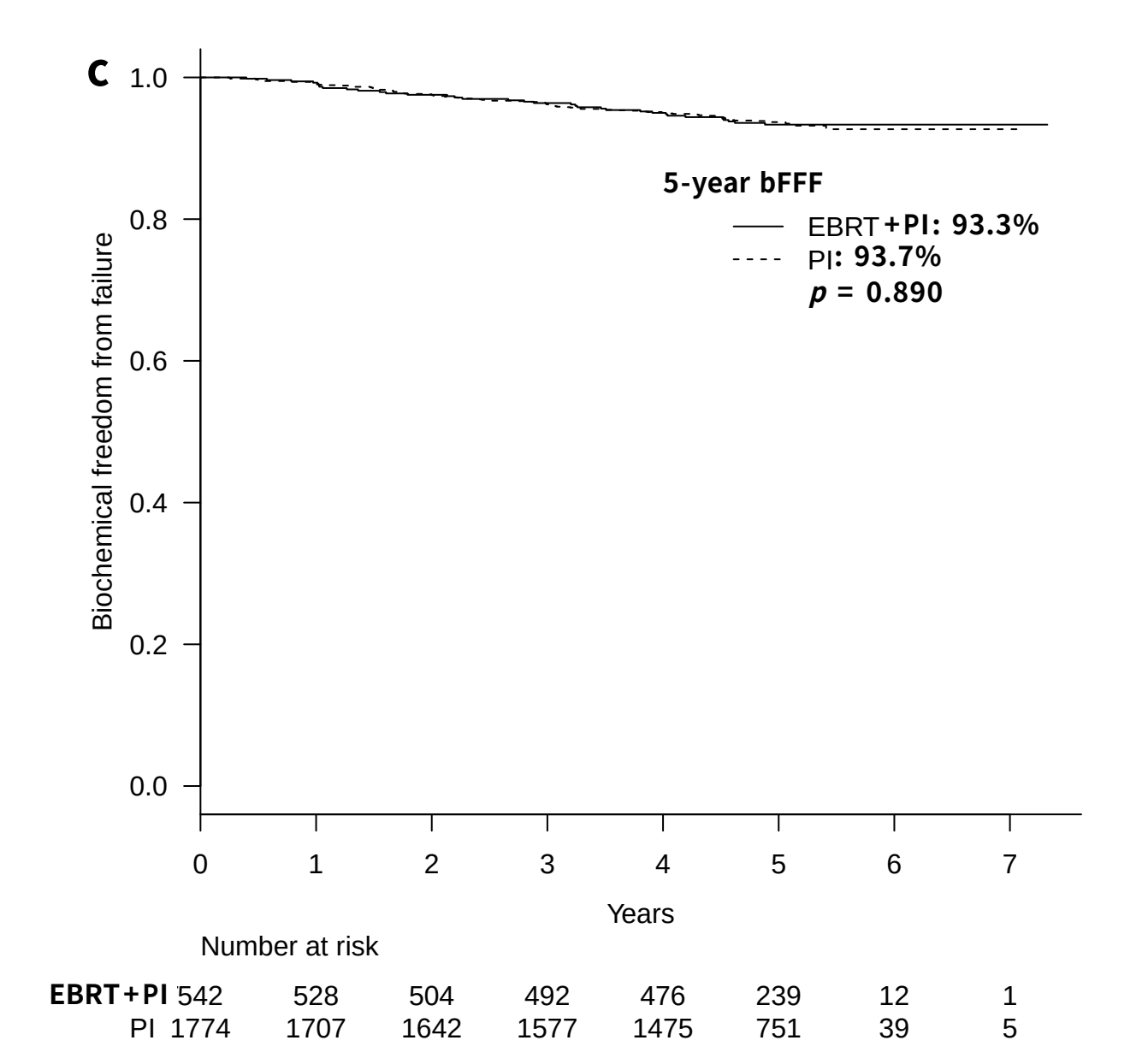
HR hazard ratio, *CI* confidence interval, other abbreviations as in Table 1.

*Significant risk factor

#Prostate D90 is the collinearity factor of prostate V100; therefore, prostate D90 is excluded in the multivariate analysis


a
1.0
0.8
0.6
0.4
0.2
0.0
Biochemical freedom from failure
5-year bFFF: 93.6%
0
1
2
3
4
5
6
7
Years
Number at risk
2316
2235
2146
2069
1951
990
51
6


b
1.0
0.8
0.6
0.4
0.2
0.0
Biochemical freedom from failure
5-year bFFF
High-risk: 91.1%
Intermediate-risk: 92.7%
Low-risk: 94.9%
p = 0.128
0
1
2
3
4
5
6
7
Years
Number at risk
High-risk 133 129 122 121 115 62 2 1
Intermediate-risk 1114 1078 1026 986 930 473 29 3
Low-risk 1028 991 962 928 875 443 20 2


C
1.0
0.8
0.6
0.4
0.2
0.0
Biochemical freedom from failure
5-year bFFF
EBRT+PI: 93.3%
PI: 93.7%
p = 0.890
0
1
2
3
4
5
6
7
Years
Number at risk
EBRT+PI 542 528 504 492 476 239 12 1
PI 1774 1707 1642 1577 1475 751 39 5