

# Prostate-specific Antigen Levels Following Brachytherapy Impact Late Biochemical Recurrence in Japanese Patients With Localized Prostate Cancer

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**Abstract.** *Background/Aim:* Evaluation of long-term outcomes is essential for the successful treatment of localized prostate cancer; however, the risk of late recurrence following brachytherapy is still not clear. This study aimed to evaluate the long-term outcomes of low-dose-rate brachytherapy (LDR-BT) for localized prostate cancer in Japanese patients and identify factors associated with late recurrence after treatment. *Patients and Methods:* This single-center, cohort study included patients who underwent LDR-BT at the Tokushima University Hospital in Japan between July 2004 and January 2015; 418 patients, who were followed-up at least 7 years after LDR-BT, were included in the study. *Biochemical progression free survival (bPFS) was defined according to the Phoenix definition (nadir PSA+2 ng/ml) and bPFS and cancer specific survival (CSS) were calculated using Kaplan-Meier survival curves. Univariate and multivariate analyses were performed using Cox proportional hazard regression models. Results:* Approximately half of the patients with PSA >0.5 ng/ml at 5 years after LDR-BT had a

recurrence within the next 2 years. However, only 1.4% of the patients with a PSA ≤0.2 ng/ml at 5 years post-treatment showed tumor recurrence, including those at high risk of treatment failure according to the D'Amico classification. In multivariate analysis, PSA level at 5 years post-treatment was the only predictor of late recurrence after 7 years of treatment. *Conclusion:* PSA levels at 5 years post-treatment were associated with long-term recurrence of localized prostate cancer, which can help alleviate patient anxiety concerning prostate cancer recurrence if PSA levels remain low at 5 years after LDR-BT.

Prostate cancer is the most common malignancy in men, with 1.41 million newly diagnosed patients and 370,000 deaths worldwide in 2021 (1). In Japan, approximately 94,000 men were newly diagnosed with prostate cancer in 2019, and the number of deaths from prostate cancer in the same year was about 12,500, with an increasing trend (2, 3). For localized prostate cancer, guidelines list total prostatectomy, external-beam radiation, and low-dose-rate brachytherapy (LDR-BT) as treatment options with good outcomes (4-6). The disease progression of local prostate cancer has already been clarified, and while active surveillance is an option, even with conservative therapy alone, the 15-year prostate cancer-specific survival rate is 88% and 65% for those with low- and intermediate-risk of treatment failure, respectively (7). These facts suggest the need to choose treatment according to long-term outcomes in order to assess the effectiveness of treatment for localized prostate cancer.

LDR-BT was first introduced in Denmark in 1981 and has been widely used in Japan since 2003. Many reports on

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**Key Words:** Prostate cancer, brachytherapy, long-term outcomes.



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Table I. Clinicopathological characteristics of all patients and those without biochemical progression-free survival at 5 and 7 years after low-dose-rate brachytherapy.

	ALL (n=418)	No bPFS at 5 years (n=380)	No bPFS at 7 years (n=343)
Age (years)			
Median [range]	67.00 [49.00, 86.00]	68.00 [49.00, 86.00]	67.00 [49.00, 86.00]
≤70 (%)	295 (70.6)	268 (70.5)	246 (71.7)
>70 (%)	123 (29.4)	112 (29.5)	97 (28.3)
iPSA (ng/ml)			
Median [range]	7.42 [2.39, 30.60]	7.30 [2.39, 30.60]	7.33 [3.12, 30.60]
≤10 (%)	310 (74.2)	286 (75.3)	256 (74.6)
10-20 (%)	97 (23.2)	84 (22.1)	78 (22.7)
>20 (%)	11 (2.6)	10 (2.6)	9 (2.6)
Gleason grade (%)			
1	230 (55.0)	213 (56.1)	198 (57.7)
2	95 (22.7)	88 (23.2)	76 (22.2)
3	46 (11.0)	40 (10.5)	34 (9.9)
4	38 (9.1)	31 (8.2)	27 (7.9)
5	9 (2.2)	8 (2.1)	8 (2.3)
T stage (%)			
1c	349 (83.5)	318 (83.7)	288 (84.0)
2a	30 (7.2)	28 (7.4)	26 (7.6)
2b	31 (7.4)	28 (7.4)	23 (6.7)
2c	8 (1.9)	6 (1.6)	6 (1.7)
PBCP (%)			
≤33.3	290 (74.2)	269 (75.1)	250 (77.2)
>33.3	101 (25.8)	89 (24.9)	74 (22.8)
D'Amico risk (%)			
Low	171 (40.9)	159 (41.8)	151 (44.0)
Intermediate	185 (44.3)	168 (44.2)	144 (42.0)
High	62 (14.8)	53 (13.9)	48 (14.0)
NHT (%)			
No	152 (36.4)	138 (36.3)	126 (36.7)
Yes	266 (63.6)	242 (63.7)	217 (63.3)
P-vol at BT (ml)			
Median [range]	26.10 [10.00, 59.50]	26.50 [12.50, 59.50]	26.40 [12.50, 59.50]
D90 (Gy)			
Median [range]	182.10 [70.30, 260.30]	184.50 [70.30, 260.30]	184.50 [89.40, 260.30]
V100 (%)			
Median [range]	98.00 [63.00, 100.00]	98.00 [63.00, 100.00]	98.00 [68.00, 100.00]

iPSA: Initial prostate-specific antigen; PBCP: positive biopsy core percent; NHT: neoadjuvant hormonal therapy; P-vol: prostate volume; BT: brachytherapy; bPFS: biochemical progression-free survival; D90: dose to 90% of the prostate; V100: prostate volume that received at least the prescribed dose.

relatively short observation periods have been published, showing positive results (8-10).

However, only few reports present findings with more than 10 years of follow-up. The aim of this study was to demonstrate the long-term results of LDR-BT for localized prostate cancer and identify factors associated with late recurrence after treatment.

## Patients and Methods

**Patients.** This was a single-center, cohort study involving consecutive patients who underwent LDR-BT with or without hormone therapy as initial treatment at the Tokushima University Hospital in Japan between July 2004 and December 2019. This study

was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Ethics Committee of Tokushima University Hospital (ID: 4140). Patients who were followed-up for at least 7 years were enrolled in this study.

**LDR-BT procedure.** For post-planning, computed tomography (CT) and chest, kidney, ureter, and bladder radiographs were performed in all patients after implanting seeds that produced a radiation dose up to 90% of the prostate volume (D90) to evaluate seed migration.

**Follow-up protocol and progression.** Patients were asked to revisit at 1, 3, and 6 months after seed implantation, and every 6 months thereafter. Biochemical progression-free survival (bPFS) was defined according to the Phoenix definition [nadir prostate-specific antigen (PSA)+2 ng/ml].

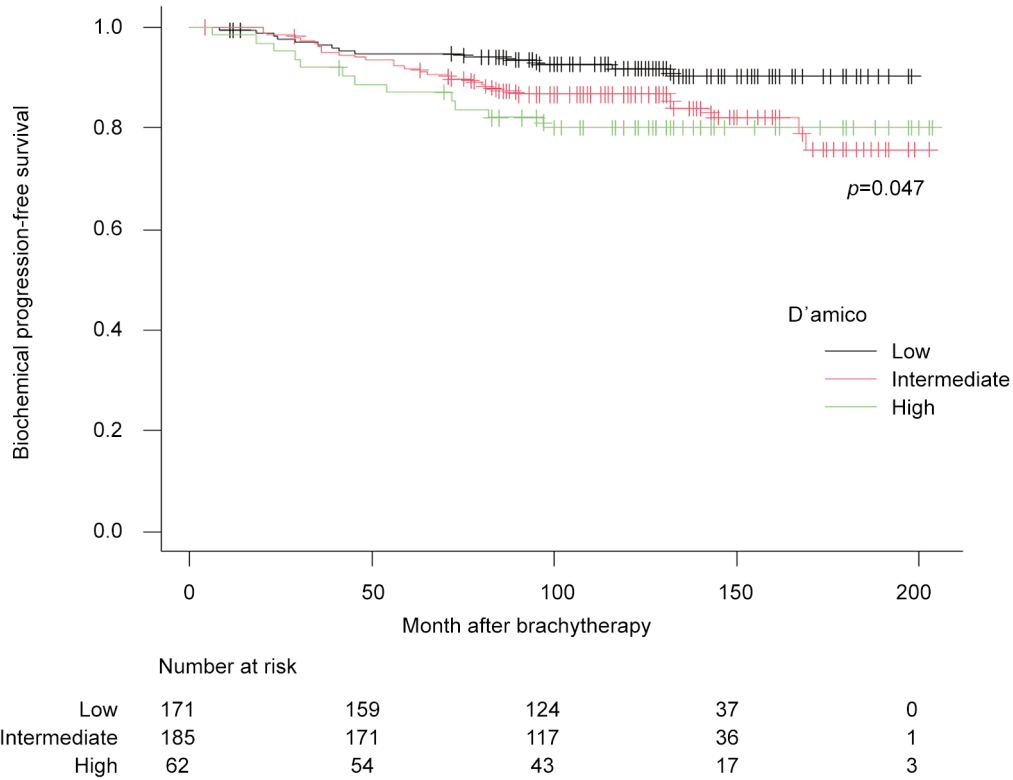


Figure 1. Biochemical progression-free survival of patients with prostate cancer and low-, intermediate-, and high-risk of treatment failure after low-dose-rate brachytherapy ( $p=0.047$ ).

**Statistical analysis.** Cancer-specific survival (CSS) and bPFS were calculated using the Kaplan-Meier survival curve method and compared using the log-rank test. To identify factors related to survival, univariate and multivariate analyses with Cox proportional hazard regression models were used. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (11), and statistical significance was set at  $p<0.05$ .

**Results**

Among patients who received LDR-BT, three died of prostate cancer progression within 7 years, 18 were confirmed to have died of other causes, and 71 patients were lost to follow-up. Excluding these cases, 418 participants were included in the study. The demographics and clinicopathological characteristics of all 418 patients including those in the subgroup with no biochemical recurrence at 5 and 7 years after LDR-BT are summarized in Table I.

Biochemical recurrence was more common in patients with higher risk of treatment failure, as determined by D’Amico classification ( $p=0.047$ , Figure 1). There were, however, no significant differences in CSS between participants ( $p=0.38$ , Figure 2). The univariate analysis revealed that D90 was the only predictor of late biochemical

recurrence, and this result persisted in the multivariate analysis [hazard ratio (HR)=0.44,  $p=0.0025$  and HR=0.46,  $p=0.0066$ , respectively; Table II]. The subsequent bPFS of patients without PSA elevation at 5 or 7 years after LDR-BT did not differ significantly as per D’Amico risk classification for treatment failure (Figure 3).

When grouped and analyzed by PSA level at 5 years, 57% of the patients with a PSA of  $\geq 0.5$  ng/ml at 5 years after LDR-BT had a recurrence within the next 2 years. In addition, 14.9% of patients with PSA levels  $\geq 0.2$  ng/ml had biochemical recurrence at 10 years, and another 7.5% of patients had biochemical recurrence later than 10 years after brachytherapy. Contrastingly, only 1.4% of patients with a PSA level  $< 0.2$  ng/ml at 5 years after treatment showed biochemical recurrence (Figure 4A). These results were not related to the D’Amico risk classification for treatment failure (Figure 4B, C, and D).

Univariate and multivariate analyses were then used to examine the risk of subsequent recurrence in patients with no biochemical recurrence at 5 years after LDR-BT. Univariate analysis showed that D90 and PSA levels at 5 years post treatment were significant predictors of recurrence, but only PSA levels at 5 years after LDR-BT remained as significant predictors of recurrence in the multivariate analysis (Table III).

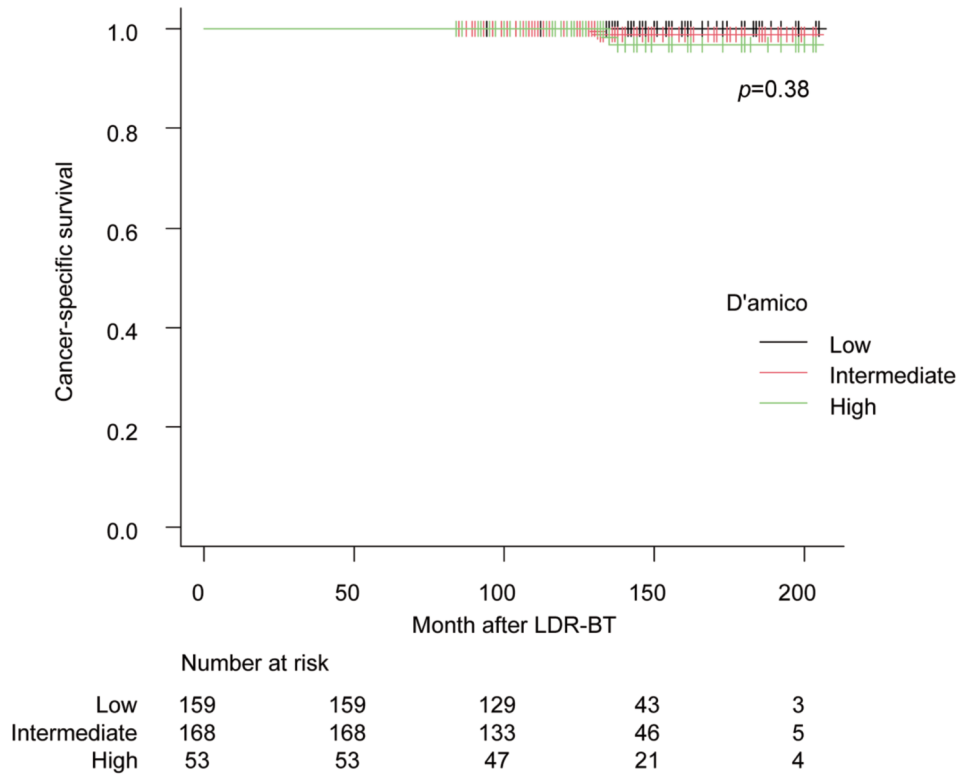


Figure 2. Long-term ( $\geq 7$  years) cancer-specific survival of patients with prostate cancer and low-, intermediate-, or high-risk of treatment failure after low-dose-rate brachytherapy ( $p=0.38$ ).

**Discussion**

Standard therapies for localized prostate cancer, including prostatectomy, external-beam irradiation, and LDR-BT, have been shown to have favorable outcomes. However, long-term evaluation is essential considering the natural history of prostate cancer. Porter *et al.* reported that PSA recurrence-free survival rates at 5, 15, and 25 years after radical prostatectomy for locally localized prostate cancer were 85%, 61%, and 55%, respectively (12). Han *et al.* reported similar results of recurrence after long-term follow-up (13). Additionally, Zumsteg *et al.* reported that external radiation for localized prostate cancer showed good results with a bPFS of 90.3% for low-risk, 77.3% for intermediate-risk, and 57.1% for high-risk patients at a median observation period of 83 months (14). However, as with the results of prostatectomy, their results also indicated several cases of recurrence after 10 years or longer.

Many studies show favorable short-term results following LDR-BT for localized prostate cancer, in part because LDR-BT is primarily administered for low- and intermediate-risk cases (8, 10). Our previous studies have also shown excellent short-term anticancer effects of LDR-BT in cases with low- and intermediate-risk of treatment failure (15). However, there

are limited reports on the long-term results of LDR-BT in patients followed-up over 10 years after treatment (16). The present study included Japanese men who had been followed for over 7 years after LDR-BT, with a median follow-up period of over 10 years. The 10-year bPFS at our Institution was 92% for low-risk and 87% for intermediate-risk patients, which is similar to previous reports in relevant risk groups. In addition, this study was unique in that it included prostate cancer cases with high-risk of treatment failure, which are usually recommended to be treated in combination with external radiation but were treated with LDR-BT alone (with or without hormone therapy). As shown in our previous study, the short-term outcome of LDR-BT was not poor, even for these patients (15). Furthermore, the results of this study demonstrated the favorable long-term outcomes of LDR-BT (with or without hormone therapy) in the high-risk group.

Differences in the pattern of recurrence after local therapy for prostate cancer have been noted between treatment modalities (14, 17). It has been reported that 45% of recurrences after total prostatectomy occur within 2 years of treatment, whereas the 2-year recurrence rate after EBRT was reported to be 26%. This may be due to differences in post-treatment PSA dynamics and in the definition of recurrence as well as the presence or absence of

Table II. Univariate and multivariate analysis of biochemical progression-free survival after low-dose-rate brachytherapy.

Covariate	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age (years)				
≤70	1		1	
>70	0.87 (0.47-1.59)	0.64		
iPSA (ng/ml)				
≤10	1		1	
>10	1.49 (0.85-2.59)	0.16		
Gleason grade				
1	1		1	
2-3	1.42 (0.80-2.54)	0.24	1.41 (0.78-2.53)	0.25
4-5	1.87 (0.87-4.01)	0.11	1.68 (0.77-3.66)	0.19
T stage	1.07 (0.54-2.13)	0.84		
T1c				
≥T2				
P-vol at BT (ml)				
≤30	1		1	
>30	0.55 (0.29-1.03)	0.063	0.71 (0.36-1.39)	0.32
PBCP (%)	1.33 (0.73-2.44)	0.36		
≤33.3				
>33.3				
NHT				
No	1			
Yes	0.87 (0.51-1.50)	0.62		
D90 (Gy)				
≤160	1		1	
>160	0.44 (0.25-0.75)	0.0025	0.46 (0.27-0.81)	0.0066

CI: Confidence interval; HR: hazard ratio; iPSA: initial prostate-specific antigen; P-vol: prostate volume; BT: brachytherapy; PBCP: positive biopsy core percent; NHT: neoadjuvant hormonal therapy; HR: hazard ratio; D90: dose to 90% of the prostate.

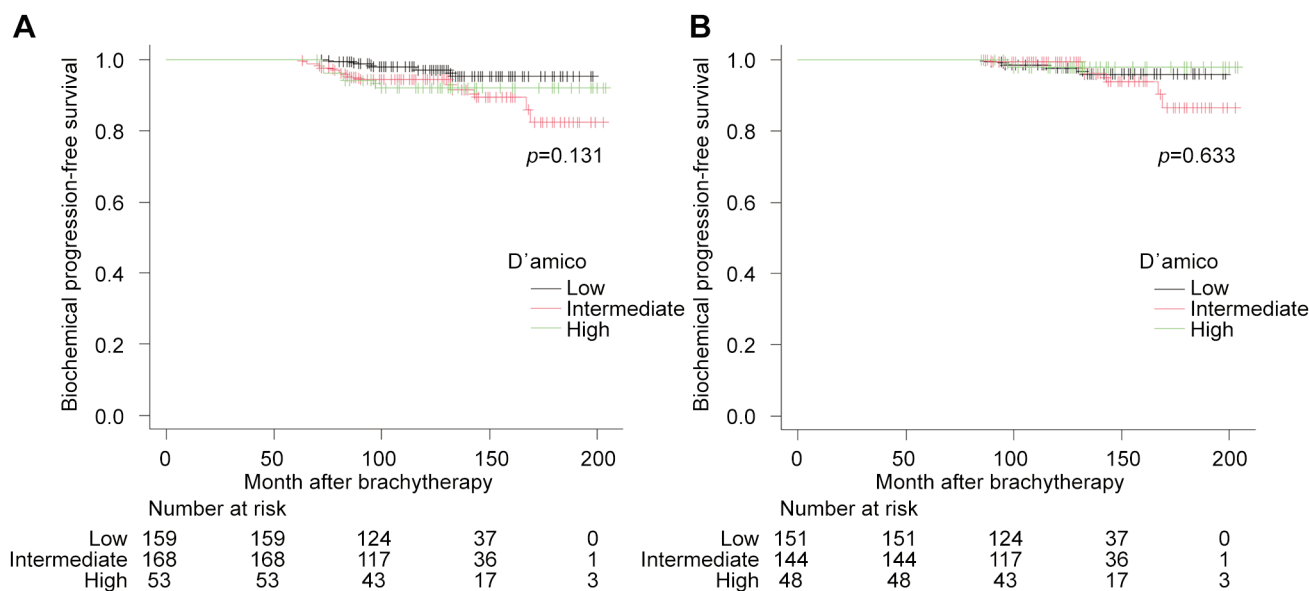


Figure 3. Long-term biochemical progression-free survival in the cohort as per D'Amico classification. (A) Biochemical progression-free survival more than 5 years after low-dose-rate brachytherapy in patients with prostate cancer and low-, intermediate-, or high-risk of treatment failure ( $p=0.131$ ). (B) Biochemical progression-free survival more than 7 years after low-dose-rate brachytherapy in patients with prostate cancer and low-, intermediate-, or high-risk of treatment failure ( $p=0.633$ ).

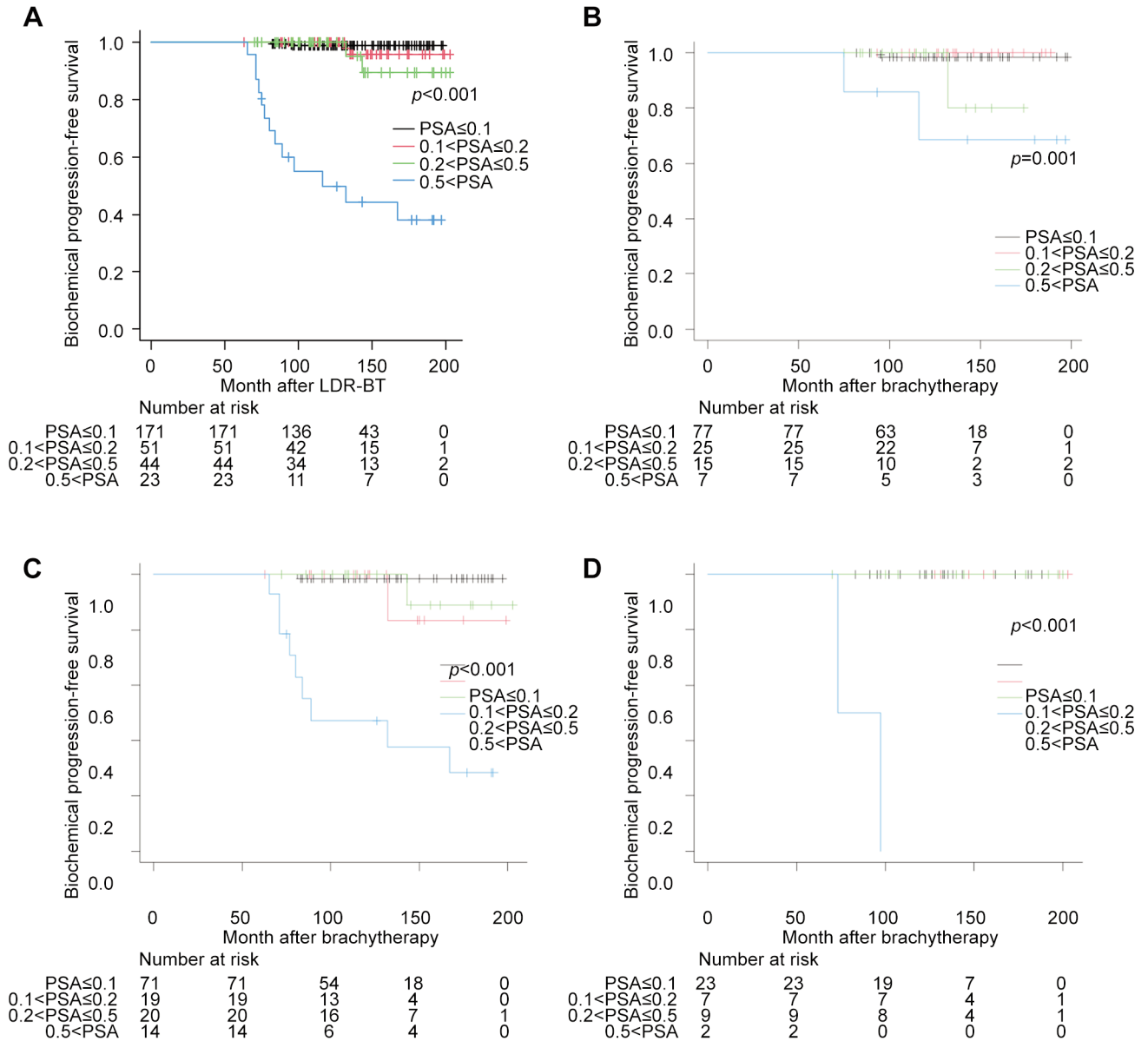


Figure 4. Biochemical progression-free survival curves in the cohort. (A) Kaplan-Meier survival curves of biochemical progression-free survival in all patients and in patients with (B) low risk ( $p < 0.001$ ), (C) intermediate risk ( $p < 0.001$ ), and (D) high risk ( $p < 0.001$ ) of treatment failure, stratified by prostate-specific antigen level at 5 years after treatment.

postoperative adjuvant hormone therapy. In LDR-BT, as in EBRT, patients at intermediate or higher risk of treatment failure are often treated with hormonal therapy, and often follow a course of treatment similar to that of EBRT.

In a study of short-term outcomes in Japanese patients, Gleason score, initial PSA level, positive biopsy rate, and radiation dose were cited as risk factors for recurrence in LDR-BT, and indeed careful observation is needed in patients with these factors (8, 9, 18-20). The results of the study also showed a significant difference in progression-

free survival according to the D'Amico risk classification. In contrast, our results showed that in patients without biochemical recurrence at 5 years after LDR-BT, there was no difference in subsequent progression-free survival according to the D'Amico risk classification. There are no clear guidelines on the consideration of patients requiring long-term follow-up or the duration of follow-up after LDR-BT. PSA levels and Gleason grade group at the time of diagnosis have been reported as predictors of late recurrence after prostatectomy (21). Moreover, PSA values

Table III. Univariate and multivariate analysis of biochemical progression-free survival more than 7 years after low-dose-rate brachytherapy.

Covariate	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
Age (years)				
≤70	1			
>70	0.33 (0.04-2.59)	0.29		
iPSA (ng/ml)				
≤10	1			
>10	0.89 (0.24-3.38)	0.87		
Gleason grade				
1	1			
2-3	0.70 (0.18-2.63)	0.59		
4-5	0.00 (0.00-Inf)	1		
T stage	0.86 (0.18-4.02)	0.85		
T1c				
≥T2				
P-vol at BT (ml)				
≤30	1			
>30	0.44 (0.09-2.03)	0.29		
PBCP (%)	0.74 (0.16-3.5)	0.71		
≤33.3				
>33.3				
NHT				
No	1			
Yes	0.51 (0.16-1.68)	0.27		
D90 (Gy)				
≤160	1		1	
>160	0.21 (0.05-0.81)	0.024	0.83 (0.17-4.17)	0.82
PSA at 5 years (ng/ml)				
≤0.1	1		1	
0.1-0.2	3.11 (0.19-49.77)	0.42	3.03 (0.19-48.96)	0.44
0.2-0.5	7.40 (0.67-81.78)	0.1	7.18 (0.64-80.58)	0.11
>0.5	42.07 (4.86-364.50)	0.00069	37.87 (3.64-394.60)	0.0024

iPSA: Initial prostate-specific antigen; P-vol: prostate volume; BT: brachytherapy; PBCP: positive biopsy core percent; NHT: neoadjuvant hormonal therapy; HR: hazard ratio; CI: confidence interval; D90: dose to 90% of the prostate.

at 4 or 5 years, when the effect of concomitant hormone therapy becomes less pronounced, are shown to be important prognostic factors in patients who underwent LDR-BT (22-24). Similarly, only 1.4% of patients with PSA <0.2 ng/ml at 5 years post-treatment had biochemical recurrence in this study. We also examined long-term results in high-risk patients, but even in this patient group, none of the patients with a PSA ≤0.2 ng/ml at 5 years after LDR-BT showed a recurrence. Moreover, the interesting thing was that this long-term follow-up study showed no significant difference in recurrence rates 7 years after treatment between high- and intermediate-risk patients. These results indicate that the risk of subsequent prostate cancer progression is very low for patients who achieve a PSA level ≤0.2 ng/ml within 5 years of treatment, regardless of their status at diagnosis. These findings could potentially reduce the frequency of follow-up visits and relieve patient anxiety about cancer recurrence.

This study has several limitations. First, it was a retrospective study. Second, although the overall outcomes of the study were good, the sample included patients with low radiation dose owing to technical factors in early years, which may have affected the results shown in the study. Third, although the number of cases was more than 400, the small number of events may lead to statistical weakness. Fourth, patients who were lost to follow-up or who died within 7 years were excluded from the study. However, only two patients were confirmed to have died due to prostate cancer during this period, and we do not expect this to have a significant impact on treatment outcomes.

In conclusion, the long-term results of LDR-BT in Japanese patients are favorable; moreover, the risk of recurrence is very low in patients who maintain a low PSA level at 5 years after treatment even if they are high-risk patients. The results of this study should help reduce patient burden and anxiety during long-term follow-up after LDR-BT.

## Conflicts of Interest

The Authors have no relevant financial or non-financial interests to disclose.

## Authors' Contributions

Material preparation, data collection, and analysis were performed by Yoshiteru Ueno, Yoshito Kusuhar, and Tomoya Fukawa. The first draft of the manuscript was written by Yoshiteru Ueno and Tomoya Fukawa supervised the manuscript. All Authors read and approved the final manuscript.

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