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Radiotherapy plus androgen deprivation therapy for prostate-specific antigen persistence in lymph node–positive prostate cancer

Masaki Shiota[1] | Dai Takamatsu[1] | Takahiro Kimura[2] | Kojiro Tashiro[2] | Yoshiyuki Matsui[3] | Ryotaro Tomida[4] | Ryoichi Saito[5] | Masakazu Tsutsumi[6] | Akira Yokomizo[7] | Yoshiyuki Yamamoto[8] | Kohei Edamura[9] | Makito Miyake[10] | Shuichi Morizane[11] | Takayuki Yoshino[12] | Akihiro Matsukawa[13] | Shintaro Narita[14] | Ryuji Matsumoto[15] | Takashi Kasahara[16] | Kohei Hashimoto[17] | Hiroaki Matsumoto[18] | Masashi Kato[19] | Shusuke Akamatsu[20] | Akira Joraku[21] | Manabu Kato[22] | Takahiro Yamaguchi[23] | Toshihiro Saito[24] | Tomoyuki Kaneko[25] | Atsushi Takahashi[26] | Takuma Kato[27] | Shinichi Sakamoto[28] | Hideki Enokida[29] | Hidenori Kanno[30] | Naoki Terada[31] | Shigetaka Suekane[32] | Naotaka Nishiyama[33] | Masatoshi Eto[1] | Hiroshi Kitamura[33] | on behalf of the Japanese Urological Oncology Group

[1]Department of Urology, Kyushu University, Fukuoka, Japan

[2]Department of Urology, The Jikei University School of Medicine, Tokyo, Japan

[3]Department of Urology, National Cancer Center Hospital, Tokyo, Japan

[4]Department of Urology, Shikoku Cancer Center, Matsuyama, Japan

[5]Department of Urology and Andrology, Kansai Medical University, Osaka, Japan

[6]Department of Urology, Hitachi General Hospital, Hitachi, Japan

[7]Department of Urology, Harasanshin Hospital, Fukuoka, Japan

[8]Department of Urology, Osaka International Cancer Institute, Osaka, Japan

[9]Department of Urology, Okayama University, Okayama, Japan

[10]Department of Urology, Nara Medical University, Kashihara, Japan

[11]Division of Urology, Department of Surgery, Faculty of Medicine, Tottori University, Yonago, Japan

[12]Department of Urology, University of Tsukuba, Tsukuba, Japan

[13]Department of Urology, Kashiwa Hospital, The Jikei University, Chiba, Japan

[14]Department of Urology, Akita University, Akita, Japan

[15]Department of Renal and Genitourinary Surgery, Hokkaido University, Sapporo, Japan

[16]Division of Urology, Department of Regenerative and Transplant Medicine, Niigata University, Niigata, Japan

[17]Department of Urology, Sapporo Medical University, Sapporo, Japan

[18]Department of Urology, Yamaguchi University, Ube, Japan

[19]Department of Urology, Nagoya University, Nagoya, Japan

[20]Department of Urology, Kyoto University, Kyoto, Japan

[21]Department of Urology, Ibaraki Prefectural Central Hospital, Ibaraki Cancer Center, Kasama, Japan

[22]Department of Nephro-Urologic Surgery and Andrology, Mie University, Tsu, Japan

Abbreviations: ADT, androgen deprivation therapy; BCR, biochemical recurrence; CRFS, castration resistance–free survival; CSS, cancer-specific survival; DFS, disease-free survival; HR, hazard ratio; LNI, lymph node involvement; MFS, metastasis-free survival; OS, overall survival; PLND, pelvic lymph node dissection; RP, radical prostatectomy; RT, radiotherapy.

[23]Department of Urology, Kumamoto University, Kumamoto, Japan
[24]Department of Urology, Niigata Cancer Center Hospital, Niigata, Japan
[25]Department of Urology, Teikyo University School of Medicine, Tokyo, Japan
[26]Department of Urology, Hakodate Goryoukaku Hospital, Hakodate, Japan
[27]Department of Urology, Kagawa University, Kagawa, Japan
[28]Department of Urology, Chiba University, Chiba, Japan
[29]Department of Urology, Kagoshima University, Kagoshima, Japan
[30]Department of Urology, Yamagata University, Yamagata, Japan
[31]Department of Urology, Miyazaki University, Miyazaki, Japan
[32]Department of Urology, Kurume University School of Medicine, Kurume, Japan
[33]Department of Urology, University of Toyama, Toyama, Japan

Correspondence
Masaki Shiota, Department of Urology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
Email: shiota.masaki.101@m.kyushu-u.ac.jp

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Abstract

The treatment for lymph node involvement (LNI) after radical prostatectomy (RP) has not been established. This study aimed to reveal the outcomes of various management strategies among patients with LNI after RP. Retrospectively, 561 patients with LNI after pelvic lymph node dissection (PLND) with RP treated between 2006 and 2019 at 33 institutions participating in the Japanese Urological Oncology Group were investigated. Metastasis-free survival (MFS) was the primary outcome. Patients were stratified by prostate-specific antigen (PSA) persistence after RP. Cox regression models were used to analyze the relationships between clinicopathological characteristics and survival. Survival analyses were conducted using the Kaplan-Meier method and log-rank test with or without propensity score matching. Prognoses, including MFS and overall survival, were prominently inferior among patients with persistent PSA compared with those without persistent PSA. In multivariate analysis, androgen deprivation therapy (ADT) plus radiotherapy (RT) was associated with better MFS than ADT alone among patients with persistent PSA (hazard ratio = 0.37; 95% confidence interval = 0.15-0.93; $p = 0.034$). Similarly, MFS and overall survival were significantly better for ADT plus RT than for ADT alone among patients with persistent PSA after propensity score matching. This study indicated that PSA persistence in LNI prostate cancer increased the risk of poor prognoses, and intensive treatment featuring the addition of RT to ADT might improve survival.

KEYWORDS
androgen deprivation therapy, lymph node involvement, PSA persistence, radical prostatectomy, radiotherapy

1 | INTRODUCTION

Although the therapeutic benefit of pelvic lymph node dissection (PLND) during radical prostatectomy (RP) has not been demonstrated, PLND remains a gold standard procedure for nodal staging to identify patients who would benefit from additional treatment.[1,2] Currently, extended PLND is recommended by most guidelines for high-risk patients with lymph node involvement (LNI).[3,4]

For LNI after RP, adjuvant androgen deprivation therapy (ADT) is a standard treatment supported by prospective randomized control trial data detailing significant improvements of cancer-specific survival (CSS) and overall survival (OS).[5] However, this trial was conducted from 1988 to 1993, and medical managements including PLND have changed. Most critically, salvage treatment performed as a control was triggered by distant metastases or symptomatic recurrences but not by biochemical recurrence (BCR). In addition, approximately 20% of patients had prostate-specific antigen (PSA) persistence, but they did not receive immediate treatment in the control arm. Therefore, the evidence obtained from the study by Messing et al. may not fit the current status of the management for prostate cancer with LNI.

The favorable impact of adjuvant radiotherapy (RT) on survival in patients with LNI compared with adjuvant ADT alone and salvage RT was suggested in retrospective studies.[6-10] However, the survival benefit of adjuvant RT may be achieved in a limited population with moderate risk, and patient selection may be important.[11-13]

Recently, PSA persistence in prostate cancer with LNI has been recognized to be robustly associated with unfavorable outcomes including survival, and most patients with persistent PSA should be managed with immediate intensive treatment.[14-16] However, to our knowledge, there is no evidence of the therapeutic impact of adding RT to ADT for PSA persistence in patients with LNI. Meanwhile, a subset of patients with LNI does not experience recurrence or require additional treatment. Therefore, adjuvant treatment for all patients with LNI may result in overtreatment and increase the physiological and economic burden. Accordingly, the European Association of Urology (EAU) guideline recommends the use of adjuvant ADT with or without RT or observation if a patient has only one or two positive lymph nodes and no PSA persistence (PSA < 0.1 ng/ml) after RP with extended PLND.[3] However, the strength of this recommendation is weak, and the treatment strategy for patients with LNI has not been well established. Therefore, we aimed to reveal the outcomes of various management strategies among patients with LNI in a Japanese multi-institutional retrospective study.

2 | MATERIALS AND METHODS

2.1 | Patients

This study retrospectively enrolled patients who were pathologically diagnosed with LNI after PLND during RP conducted between 2006 and 2019 at 33 institutions participating in the Japanese Urological Oncology Group. The study was approved by the institutional review board of each institute. Patients at least 20 years old were included. Patients with a prior history of treatment for prostate cancer before RP, evidence of distant metastasis, or no performance of RP were excluded. Of 572 eligible patients, we excluded 11 patients for whom (i) the pathological diagnosis using the RP specimen was non-adenocarcinoma and/or (ii) their PSA level was not examined after RP (Figure 1). Finally, the data of 561 patients were analyzed.

2.2 | Methods

Clinicopathological and survival data were obtained from patients' medical records. Clinical staging was determined using the unified TNM criteria.[17] International Society of Urological Pathology (ISUP) grade groups were categorized as follows: <3 + 4 = 7 (I); 3 + 4 (II); 4 + 3 (III); 4 + 4 (IV); or 9-10 (V). Gleason scores 3 + 5 and 5 + 3 were included in category IV according to a previous report.[18]

The indication and extent of PLND were determined at the physician's discretion. The patients were stratified by the presence or absence of persistent PSA (≥0.1 ng/ml at the initial assessment of PSA levels after RP).[16] The timing of postoperative PSA measurement was determined at the physician's discretion (median, 34 days; interquartile range [IQR] = 29-45 days).

2.3 | Treatment

All treatments were performed at the physician's discretion. Adjuvant and salvage treatments were defined as treatments provided before and after postoperative disease recurrence, respectively. When patients had PSA persistence after RP, any treatment was defined as salvage treatment. ADT consisted of castration alone, antiandrogen monotherapy, or combined

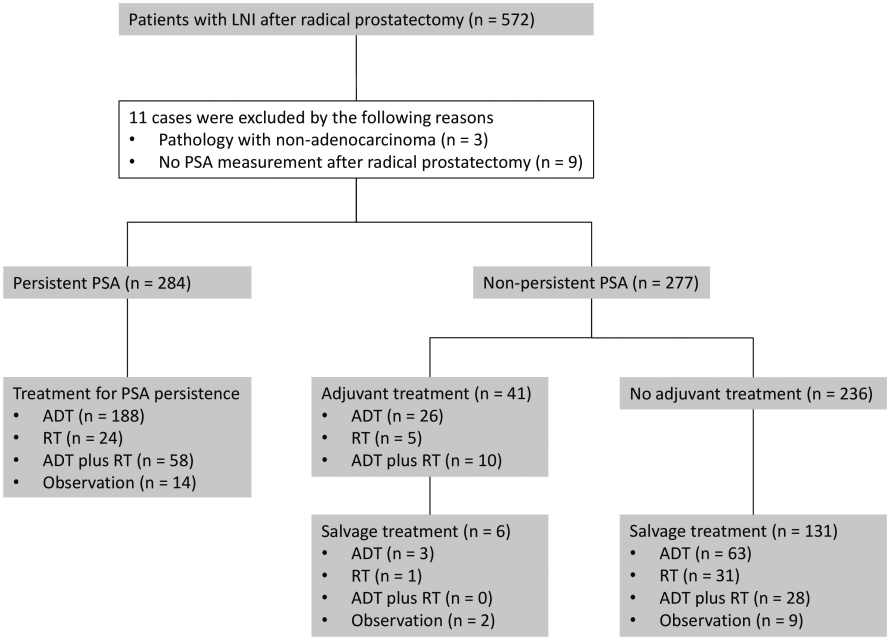

FIGURE 1 CONSORT diagram illustrating the distribution of patients and their management. The analyzed patients were stratified by prostate-specific antigen (PSA) persistence and adjuvant treatment in patients without PSA persistence. ADT, androgen deprivation therapy; LNI, lymph node involvement; RT, radiotherapy

androgen blockade (CAB; surgical or medical castration plus an antiandrogen). Radiotherapy was administered to the prostate and seminal vesicle bed with or without pelvic lymph node area. Three-dimensional conformal RT or intensity-modulated RT using linear accelerators with high-energy photon beams was performed, and 50-76 Gy were delivered at 1.8-2.0 Gy per fraction. Median 66 Gy (IQR, 64.8-70 Gy) was irradiated to the prostate bed alone (20.1%) or prostate bed with pelvis (79.9%).

2.4 | Follow-up

Biochemical recurrence was defined as PSA ≥0.2 ng/ml after RP with or without adjuvant treatment. Biochemical recurrence after salvage treatment was defined as PSA ≥0.2 ng/ml if PSA declined by <0.2 ng/mL. If PSA did not decline by <0.2 ng/ml after salvage treatment, the starting date of salvage treatment was defined as the date of BCR. Disease recurrence was determined by BCR, radiographic recurrence, or physician's judgment. Castration resistance was defined as an increase of PSA levels of 25% and 1.0 ng/ml, radiographic progression by RECIST version 1.1, or by physician's judgment.[19] Metastasis was detected by imaging modalities such as computed tomography and bone scan.

To analyze disease-free survival (DFS), castration resistance–free survival (CRFS), and metastasis-free survival (MFS), disease recurrence, castration resistance, and the presence of metastasis in addition to death attributable to any cause were defined as the end events, respectively. To analyze CSS and OS, deaths attributable to prostate cancer and all-cause mortality were defined as the end events, respectively. Patients with none of these events were censored at the last follow-up visit. Follow-up started on the date of RP and ended on the date of last follow-up or the date of the event. Metastasis-free survival was set as primary outcome because it has been identified as a robust surrogate marker for OS in prostate cancer.[20-22]

2.5 | Statistical analysis

All analyses were performed using JMP16 software (SAS Institute). Continuous and categorical data were described as the median with IQR and numbers with percentages, respectively. Continuous and categorical data were analyzed using Wilcoxon's rank sum and Pearson's chi-squared tests, respectively. Survival analyses were conducted using the Kaplan-Meier method and log-rank test. A Cox proportional hazards model was used to estimate hazard ratios (HRs). The propensity score, which reflects the probability of survival, was calculated using a logistic regression model in which potential confounders such as the percentage of positive biopsy core, clinical N-stage, ISUP grade group at RP specimen, pathological T-stage, and number of positive lymph nodes were used as independent variables and treatment method was used as the dependent variable. One-to-one propensity score–matched pairs were selected from the two groups by nearest neighbor matching. All P values were two-sided, and $p < 0.05$ was considered significant.

3 | RESULTS

Patients' characteristics are presented in Table 1. As expected, the PSA level at diagnosis, percentage of positive biopsy core, ISUP grade group at biopsy and RP specimens, clinical and pathological T-stages, and rate of positive resection margin were high. Concerning the surgical approach, 181 (32.3%), 46 (8.2%), and 334 patients (59.5%) were treated with open, laparoscopic, and robot-assisted RP, respectively. The median numbers of positive lymph nodes and excised lymph nodes were 1 and 14, respectively. During a median follow-up of 4.8 years (IQR, 2.6-8.0 years), castration resistance, local recurrence, regional lymph node metastasis, distant metastasis, mortality from prostate cancer, and mortality from other causes were observed in 81 (14.4%), 10 (1.8%), 7 (1.2%), 50 (8.9%), 21 (3.7%), and 12 patients (2.1%), respectively. Among 50 patients who presented with distant metastasis, the sites of metastasis were non-regional lymph node in 17 patients, bone in 39 patients, lungs in 7 patients, liver in 2 patients, and other sites in 4 patients. The CRFS, MFS, CSS, and OS rates were 86.8%, 89.9%, 97.7%, and 96.7%, respectively, at 5 years and 75.3%, 79.5%, 91.4%, and 88.5%, respectively, at 10 years (Figure S1). When the prognostic factors for MFS were analyzed, the percentage of positive biopsy core, clinical N-stage, ISUP grade group at RP specimen, pathological T-stage, and number of positive lymph nodes, and PSA persistence after RP were prognostic for MFS (Table 2).

Of the 561 patients analyzed, 284 (50.6%) had PSA persistence, whereas 277 (49.4%) did not have PSA persistence. When patient characteristics were compared between patients with and without PSA persistence, the PSA level at diagnosis, percentage of positive biopsy cores, ISUP grade group at RP, pathological T-stage, and resection margin status were more adverse in patients with PSA persistence (Table 1). In addition, the number of positive lymph nodes and the number of excised lymph nodes were higher and lower, respectively, in patients with persistent PSA (Table 1). The survival rates were prominently worse among patients with persistent PSA than among those without persistent PSA (5 and 10 years: CRFS, 81.0% and 62.2% vs 92.8% and 88.9%; MFS, 86.2% and 69.2% vs 93.8% and 90.4%; CSS, 97.1% and 85.8% vs 98.4% and 97.5%; and OS, 96.8% and 81.8% vs 96.7% and 95.8%; Figure 2).

When the prognostic factors for MFS were analyzed among patients with persistent PSA, clinical N-stage, ISUP grade group at RP specimen, pathological T-stage, and the number of positive lymph nodes were prognostic for MFS (Table 2). Among 284 patients with persistent PSA, 188, 24, and 58 were treated with ADT, RT, and ADT plus RT, respectively. Radiotherapy was associated with inferior DFS than ADT (HR, 3.54; 95% confidence interval [CI], 2.02-6.21; $p < 0.0001$), whereas ADT plus RT was linked to better DFS than ADT alone, albeit without statistical significance (HR, 0.63; 95% CI, 0.35-1.12; $p = 0.11$; Figure 3A). Castration resistance–free survival,

TABLE 1 Patient characteristics stratified by PSA persistence or adjuvant treatment for patients without PSA persistence

Variable	All ($n = 561$)	PSA persistence			Adjuvant treatment in no PSA persistence		
		Presence ($n = 284$)	Absence ($n = 277$)	*P* value	Performed ($n = 41$)	Not performed ($n = 236$)	*P* value
Age at diagnosis, years (IQR)	68 (64–72)	68 (63–72)	68 (65–71)	0.16	68 (65–72)	68 (65–71)	0.70
NA	0	0	0		0	0	
PSA value at diagnosis, ng/ml (IQR)	13.5 (8.4–22.6)	16.2 (9.3–27.5)	11.5 (7.6–17.9)	<0.0001*	10.4 (6.6–15.6)	11.5 (7.8–18.5)	0.16
NA	0	0	0		0	0	
Percentage of positive biopsy core, % (IQR)	50 (33–69)	50 (33–75)	50 (30–62)	0.018*	50 (38–70)	50 (29–60)	0.17
NA	1	1	0		0	0	
Biopsy ISUP grade group, *n* (%)							
Group I	12 (2.1%)	5 (1.8%)	7 (2.5%)		2 (4.9%)	5 (2.1%)	
Group II	46 (8.2%)	21 (7.4%)	25 (9.0%)		5 (12.2%)	20 (8.5%)	
Group III	102 (18.2%)	42 (14.9%)	60 (21.7%)		7 (17.1%)	53 (22.5%)	
Group IV	162 (29.0%)	86 (30.5%)	76 (27.4%)		10 (24.4%)	66 (28.0%)	
Group V	237 (42.4%)	128 (45.4%)	109 (39.4%)	0.20	17 (41.5%)	92 (39.0%)	0.69
NA	2	2	0		0	0	
Clinical T-stage, *n* (%)							
T1	113 (20.2%)	51 (18.0%)	62 (22.4%)		9 (22.0%)	53 (22.5%)	
T2a	297 (53.0%)	155 (54.8%)	142 (51.3%)		23 (56.1%)	119 (50.4%)	
T2b	5 (0.9%)	2 (0.7%)	3 (1.1%)		0 (0%)	3 (1.3%)	
T2c	15 (2.7%)	4 (1.4%)	11 (4.0%)		1 (2.4%)	10 (4.2%)	
T3/4	130 (23.2%)	71 (25.1%)	59 (21.3%)	0.19	8 (19.5%)	51 (21.6%)	0.89
NA	1	1	0		0	0	
Clinical N-stage, *n* (%)							
N0	526 (94.8%)	264 (94.3%)	262 (95.3%)		37 (92.5%)	225 (95.7%)	
N1	29 (5.2%)	16 (5.7%)	13 (4.7%)	0.27	3 (7.5%)	10 (4.3%)	0.37
NA	6	4	2		1	1	
Year of operation, *n* (%)							
2006-2012	187 (33.3%)	97 (34.2%)	90 (32.5%)		23 (56.1%)	67 (28.4%)	
2013-2019	374 (66.7%)	187 (65.8%)	187 (67.5%)	0.68	18 (43.9%)	169 (71.6%)	0.0005*
NA	0	0	0		0	0	

TABLE 1 (Continued)

Variable	All ($n = 561$)	PSA persistence			Adjuvant treatment in no PSA persistence		
		Presence ($n = 284$)	Absence ($n = 277$)	*P* value	Performed ($n = 41$)	Not performed ($n = 236$)	*P* value
Operation approach, *n* (%)							
Open RP	181 (32.3%)	97 (34.2%)	84 (30.3%)		22 (53.7%)	62 (26.3%)	
Laparoscopic RP	46 (8.2%)	27 (9.5%)	19 (6.9%)		4 (9.8%)	15 (6.4%)	
Robot-assisted RP	334 (59.5%)	160 (56.3%)	174 (62.8%)	0.24	15 (36.6%)	159 (67.4%)	0.0007*
NA	0	0	0		0	0	
RP ISUP grade group, *n* (%)							
Group I	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Group II	48 (8.6%)	14 (4.9%)	34 (12.4%)		4 (9.8%)	30 (12.8%)	
Group III	131 (23.4%)	56 (19.8%)	75 (27.3%)		11 (26.8%)	64 (27.4%)	
Group IV	78 (14.0%)	48 (17.0%)	30 (10.9%)		3 (7.3%)	27 (11.5%)	
Group V	301 (53.8%)	165 (58.3%)	136 (49.5%)	0.0005*	23 (56.1%)	113 (48.3%)	0.74
NA	3	1	2		0	2	
Pathological T-stage, *n* (%)							
T2	91 (16.3%)	27 (9.5%)	64 (23.2%)		6 (14.6%)	58 (24.7%)	
T3a	175 (31.3%)	81 (28.6%)	94 (34.1%)		11 (26.8%)	83 (35.3%)	
T3b	282 (50.4%)	167 (59.0%)	115 (41.7%)		22 (53.7%)	93 (39.6%)	
T4	11 (2.0%)	8 (2.8%)	3 (1.1%)	<0.0001*	2 (4.9%)	1 (0.4%)	0.016*
NA	2	1	1		0	1	
Resection margin, *n* (%)							
Negative	252 (45.2%)	107 (37.8%)	145 (52.7%)		17 (41.5%)	128 (54.7%)	
Positive	306 (54.8%)	176 (62.2%)	130 (47.3%)	0.0004*	24 (58.5%)	106 (45.3%)	0.12
NA	3	1	2		0	2	
Number of positive lymph nodes (IQR)	1 (1–2)	1 (1–3)	1 (1–2)	<0.0001*	1 (1–2)	1 (1–2)	0.057
NA	0	0	0		0	0	
Number of removed lymph nodes (IQR)	14 (9–21)	13 (9–19)	15 (9–23)	0.0075*	10 (7–17)	17 (10–25)	0.0011*
NA	0	0	0		0	0	

Abbreviations: IQR, interquartile range; ISUP, International Society of Urological Pathology; NA, not available; PSA, prostate-specific antigen; RP, radical prostatectomy.

*Statistically significant.

TABLE 2 Univariate analysis of the associations between clinicopathological parameters and metastasis-free survival

	All ($n = 561$)			PSA persistence ($n = 284$)			No PSA persistence ($n = 277$)		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P*– value
Age at diagnosis,									
<60 years	ref	–	–	ref	–	–	ref	–	–
60–69 years	0.91	0.45–1.83	0.79	0.93	0.40–2.12	0.85	1.03	0.28–3.83	0.96
≥70 years	1.13	0.56–2.29	0.73	1.65	0.73–3.71	0.23	0.91	0.14–2.62	0.51
PSA value at diagnosis									
<10 ng/ml	ref	–	–	ref	–	–	ref	–	–
≥10, <20 ng/ml	0.72	0.39–1.32	0.29	0.57	0.28–1.15	0.12	0.65	0.19–2.23	0.49
≥20 ng/ml	1.23	0.71–2.15	0.46	0.63	0.32–1.24	0.18	2.32	0.84–6.40	0.11
Percentage of positive biopsy core									
<50%	ref	–	–	ref	–	–	ref	–	–
≥50%	2.40	1.40–4.11	0.0014*	1.75	0.97–3.18	0.065	7.61	1.75–33.0	0.0067*
Clinical T-stage									
T1	ref	–	–	ref	–	–	ref	–	–
T2	1.30	0.68–2.49	0.43	0.91	0.45–1.85	0.80	6.02	0.78–46.4	0.085
T3/4	1.41	0.68–2.93	0.35	1.03	0.46–2.31	0.93	5.32	0.62–45.6	0.13
Clinical N-stage									
N0	ref	–	–	ref	–	–	ref	–	–
N1	4.49	2.21–9.13	<0.0001*	4.40	1.84–10.5	0.0008*	4.84	1.39–16.9	0.013*
Year of operation									
2006-2012	ref	–	–	ref	–	–	ref	–	–
2013-2019	1.28	0.74–2.22	0.38	1.07	0.56–2.04	0.83	2.34	0.73–7.48	0.15
Operation approach									
Open RP	ref	–	–	ref	–	–	ref	–	–
Laparoscopic RP	0.47	0.14–1.53	0.21	0.19	0.025–1.38	0.10	1.79	0.36–8.84	0.48
Robot-assisted RP	1.15	0.66–1.99	0.62	1.06	0.56–2.02	0.85	1.77	0.57–5.51	0.32
RP ISUP grade group									
Group ≤III	ref	–	–	ref	–	–	ref	–	–
Group IV	3.02	1.25–7.29	0.014*	2.02	0.68–6.01	0.21	4.45	0.99–20.1	0.052
Group V	3.63	1.78–7.40	0.0004*	3.30	1.39–7.82	0.0068*	3.28	0.92–11.6	0.066
Pathological T-stage									
T2/3a	ref	–	–	ref	–	–	ref	–	–
T3b	2.81	1.60–4.97	0.0004*	2.20	1.12–4.35	0.023*	3.16	1.12–8.92	0.029*
T4	14.3	5.55–37.1	<0.0001*	9.00	3.09–26.2	<0.0001*	23.8	2.72–209	0.0042*
Resection margin									
Negative	ref	–	–	ref	–	–	ref	–	–
Positive	1.61	0.98–2.66	0.062	1.48	0.81–2.70	0.21	1.37	0.55–3.40	0.50
Number of positive lymph nodes									
1	ref	–	–	ref	–	–	ref	–	–
2	1.29	0.68–2.46	0.44	1.04	0.93	0.44	1.21	0.33–4.42	0.77
≥3	3.25	1.90–5.56	<0.0001*	1.97	1.05–3.70	0.034*	5.66	2.02–15.8	0.0010*
Number of removed lymph nodes									
<10	ref	–	–	ref	–	–	ref	–	–
≥10, <20	1.32	0.74–2.38	0.35	1.82	0.93–3.55	0.081	0.54	0.15–2.03	0.36
≥20	1.58	0.84–2.98	0.16	1.70	0.76–3.84	0.20	1.91	0.64–5.65	0.24

TABLE 2 (Continued)

	All (n = 561)			PSA persistence (n = 284)			No PSA persistence (n = 277)		
Variable	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P– value
PSA persistence									
Absence	ref	–	–	–	–	–	–	–	–
Presence	2.71	1.60–4.59	0.0002*	–	–	–	–	–	–

Abbreviations: CI, confidence interval; HR, hazard ratio; ISUP, International Society of Urological Pathology; PSA, prostate-specific antigen; RP, radical prostatectomy.

*Statistically significant.

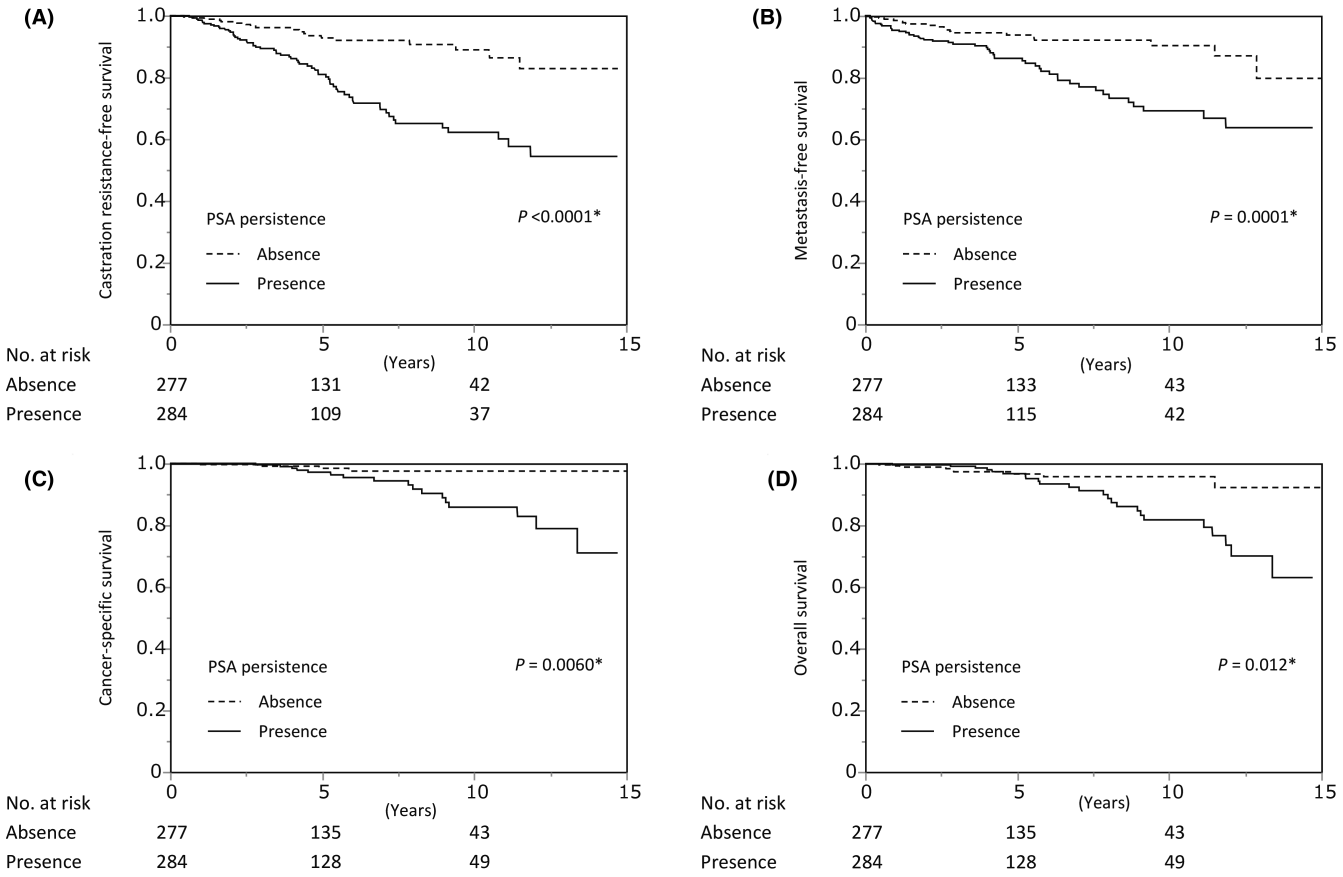

FIGURE 2 Kaplan-Meier analysis of prognosis stratified by prostate-specific antigen (PSA) persistence. Castration resistance–free survival (A), metastasis-free survival (B), cancer-specific survival (C), and overall survival (D) stratified by PSA persistence

MFS (Figure 3B), CSS, and OS were similar among the treatments for PSA persistence in univariate analysis (Figure S2A). However, when adjusted by prognostic factors for MFS including clinical N-stage, ISUP grade group at RP specimen, pathological T-stage, and the number of positive lymph nodes, ADT plus RT was associated with significantly better MFS than ADT alone (HR, 0.37; 95% CI, 0.15-0.93; p = 0.034; Table 3). However, ADT plus RT was more frequently administered to patients with younger age, treated with minimum-invasive surgery, and positive resection margin (Table S1). Then, propensity score matching was performed to adjust for the imbalanced backgrounds between the groups as much as possible. Excluding the year of operation and surgical approach, background characteristics were balanced after propensity score matching (Table S2). When the prognosis of patients was compared between the ADT and ADT plus RT groups, DFS (Figure 3C), MFS (Figure 3D), and OS (Figure S2B) were significantly better in the ADT plus RT group, whereas statistical significance was not reached for CRFS and CSS (Figure S2B).

Among 277 patients without PSA persistence, 41 and 236 patients were treated with and without adjuvant treatment, respectively (Figure 1). When the prognostic factors for MFS were analyzed among patients without PSA persistence, the percentage of positive biopsy core, clinical N-stage, pathological T-stage, and number of positive lymph nodes were prognostic for MFS (Table 2). The assessment of patient characteristics indicated that more patients with operation in former years, open RP, high pathological

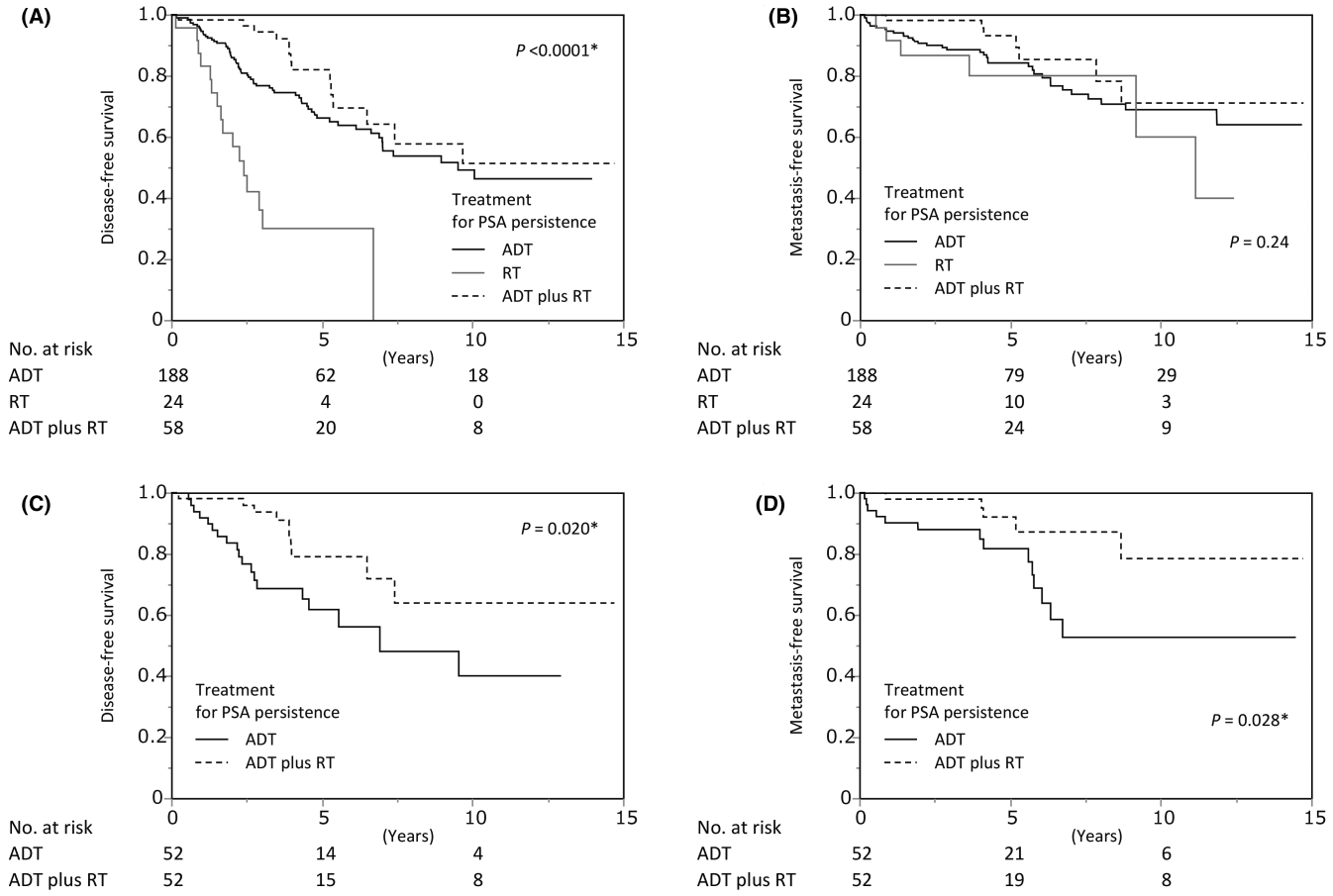

FIGURE 3 Kaplan-Meier analysis of prognosis among patients with prostate-specific antigen (PSA) persistence. Disease-free survival (A) and metastasis-free survival (B) stratified by treatment for PSA persistence. Disease-free survival (C) and metastasis-free survival (D) stratified by treatment for PSA persistence after propensity score matching. ADT, androgen deprivation therapy; RT, radiotherapy

T-stage, and a small number of excised lymph nodes were treated with adjuvant treatment (Table 1). Disease-free survival was better among patients treated with adjuvant treatment than among those assigned to observation (Figure S3). Meanwhile, CRFS, MFS, CSS, and OS were comparable between adjuvant treatment and observation (Figure S3). When adjusted by prognostic factors for MFS including the percentage of positive biopsy core, clinical N-stage, pathological T-stage, and number of positive lymph nodes, MFS was inferior for observation than for adjuvant treatment, although statistical significance was not reached (HR, 3.03; 95% CI, 0.48-19.1; $p = 0.24$; Table S3).

4 | DISCUSSION

In data from the US National Cancer Data Base, approximately 63% of patients with LNI after RP were initially managed with observation, whereas approximately 20%, 5%, and 13% were treated with ADT alone, RT alone, and ADT plus RT, respectively.[23] Similarly, 42% of patients were initially managed with observation in this study, whereas 38%, 5%, and 12% were initially treated with ADT alone, RT alone, and ADT plus RT, respectively. The lower percentage of patients assigned to observation may be attributable to the high rate of PSA persistence in this study, although data on PSA persistence are unavailable in the US National Cancer Data Base.[23]

When the PSA level after RP does not decline to <0.1 ng/mL, almost all patients will experience BCR. Therefore, the immediate initiation of additional treatment is recommended for such patients.[14] Based on the study by Messing et al., add-on ADT is a standard treatment for patients with LNI after RP. However, as revealed in this study, the prognoses of such patients were not satisfactory, and improvement of oncological outcomes is required. Previously, adjuvant RT for LNI after RP was reported to be associated with improved OS compared with adjuvant ADT alone and salvage RT in retrospective studies.[6-10] Consistently, adding RT to ADT was associated with better DFS, MFS, and OS after RP even for patients with prostate cancer with LNI and PSA persistence. Addition of RT is thought to eradicate or decrease residual tumor in prostate and pelvis after operation, leading to improved outcomes. Actually, the patients with positive resection margin were more frequently treated with ADT plus RT in this study, consistently with a previous study.[7] To the best of our knowledge, this is the first study to demonstrate benefits including improved survival for adding RT to ADT in patients with LNI and PSA persistence after RP. Previously, a subgroup of

TABLE 3 Multivariate analysis of the associations between clinicopathological parameters and metastasis-free survival among patients with PSA persistence

Variable	HR	95% CI	*P* value
Treatment for PSA persistence			
ADT	ref	-	-
RT	1.67	0.67–4.16	0.27
ADT plus RT	0.37	0.15–0.93	0.034*
Clinical N-stage			
N0	ref	-	-
N1	5.09	2.04–12.7	0.0005*
RP ISUP grade group			
Group ≤III	ref	-	-
Group IV	2.65	0.82–8.62	0.10
Group V	3.30	1.26–8.63	0.015*
Pathological T-stage			
T2/3a	ref	-	-
T3b	1.94	0.96–3.92	0.066
T4	11.6	3.33–40.2	0.0001*
Number of positive lymph nodes			
1	ref	-	-
2	0.90	0.42–1.95	0.79
≥3	1.19	0.58–2.41	0.64

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; ISUP, International Society of Urological Pathology; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy.

*Statistically significant.

patients with LNI was suggested to have benefited from adjuvant RT.[11-13] Based on the finding in this study, patients with PSA persistence are also candidates for adjuvant RT in addition to ADT even though their clinicopathological features do not fit the criteria for adjuvant RT. PSA persistence can be recognized before physicians recommend adjuvant treatment. Thus, this finding is important in clinical decision-making for selecting adjuvant ADT with RT, indicating the need for prospective studies comparing outcomes between ADT alone and ADT plus RT.

Contrary to the findings for patients with PSA persistence, the prognoses among most patients without PSA persistence were favorable. Meanwhile, high-risk patients might benefit from adjuvant treatment, as supported by the favorable HR for adjuvant treatment among patients without PSA persistence. However, definitive finding was not obtained because of the limited statistical power of the study. Then, as recommended by the EAU guideline, adjuvant ADT with or without RT or observation is considered appropriate if patients have one or two positive lymph nodes and PSA <0.1 ng/ml after RP with extended PLND.[3]

The present study had several limitations. The study design was retrospective, and the study cohort consisted mostly of Japanese patients. Although this study enrolled patients from multiple institutions to increase the number of cases with the relatively rare entity of LNI after RP, the number of cases was not sufficient in some subgroups, such as ADT plus RT for patients with PSA persistence. Also, an analysis by dividing into subcategories is statistically less powerful. The pathological diagnosis was assessed in each institution, and central review was not performed. The features of the follow-up protocol, such as the test interval and modality, including PSA and imaging, and the treatment protocol, including the strategy for PLND, differed among patients. Detailed information on the imaging performed for each patient and toxicity related to treatment was unavailable.

In conclusion, the results of this study indicated that PSA persistence in patients with prostate cancer with LNI carries a high risk of poor prognosis, and it should be managed by intensive treatment, as adding RT to ADT might improve survival. Thus, this study warrants further investigation on the role of ADT plus RT for patients with prostate cancer with LNI and PSA persistence.

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DISCLOSURE

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ORCID

Masaki Shiota https://orcid.org/0000-0002-3306-4858
Makito Miyake https://orcid.org/0000-0001-9503-7356
Shintaro Narita https://orcid.org/0000-0003-2988-1860
Hiroaki Matsumoto https://orcid.org/0000-0003-0568-1258
Shinichi Sakamoto https://orcid.org/0000-0002-7508-7521
Hideki Enokida https://orcid.org/0000-0002-3050-9700
Shigetaka Suekane https://orcid.org/0000-0003-1150-2893

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SUPPORTING INFORMATION

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