Dokkyo Medical Journal
1(1): 39-48, 2022

Original

Extended Pelvic Lymph Node Dissection during Robotic Prostate Surgery for Intermediate- to High-risk Prostate Cancer: A Propensity Score-matched Analysis for Biochemical Recurrence-free Survival

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Summary

Background: There are pros and cons regarding the benefit of extended pelvic lymph node dissection (PLND) during surgery for prostate cancer (PCa). A randomized controlled trial failed to demonstrate any survival benefits, and the therapeutic role of PLND remains unclear. We evaluated early survival outcome using a propensity score (PS)-matched analysis.

Methods: Three hundred ninety-nine patients with intermediate- to high-risk PCa were enrolled. They were determined to have a lymph node (LN) invasion probability of greater than 7% on the established nomogram. The National Comprehensive Cancer Network classification was used as risk stratification. Biochemical recurrence (BCR)-free survival was compared between the two groups divided by the threshold of the LN yield set at 15.

Results: The mean LN yield was 23.7 and 3.4 in the sufficient (n = 217) and insufficient (n = 182) LN yield groups, respectively. In the unmatched cohort, the advantage of the 3-year BCR-free survival for sufficient LN yield remained at 10.0% (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.43-1.07; p = 0.098). In the PS-matched cohort with 133 patients in each group, the difference in the 3-year BCR-free survival rate widened to 15.8% (HR 0.54, 95% CI 0.31-0.93; p = 0.027). A Cox regression multivariate analysis performed on the model with postoperative pathological factors showed an independent predictive value of LN yield.

Conclusions: The results demonstrate the therapeutic role of PLND in intermediate- to high-risk PCa. The benefit of PLND depends on the surgeon adhering to the template and removing a sufficient number of LNs in patients with an optimal risk-range.

Key Words: biochemical recurrence-free survival, extended pelvic lymph node dissection, high-risk prostate cancer, intermediate-risk prostate cancer, propensity score-matched analysis

Background

The widespread use of prostate-specific antigen (PSA) screening and multiple core biopsy protocol has resulted in early detection of prostate cancer (PCa) at a curable stage in North America and Europe[1)]. The national cancer data in Japan also revealed a similar stage migration of PCa, and the incidence of localized

Received October 5, 2021; accepted October 15, 2021
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cancer increased markedly between 2000 and 2003 with an annual percent change of 29.7%[2]. Currently, PCa has become the most prevalent malignant disease and was categorized as the sixth leading cause of death in Japanese men. In addition, radical prostatectomy is a first-line therapy, while robotics has become a standard surgical method for patients with localized PCa.

The early detection of PCa and new surgical approach consequently raises the new issue of whether it is necessary to perform pelvic lymph node dissection (PLND) in conjunction with prostatectomy. In the early era of minimally invasive prostatectomy performed by robotics, the rate of the PLND procedure was drastically reduced compared to the era of open prostatectomy, and the trend was observed in both surgical approaches. The reasons were speculated to be affected by academic status of institutions, surgeon volume, economic issues, and regional differences[3,4]. When viewed at a national level, this trend is still observed in Japan and in the United States[5]. In a recent analysis using the National Cancer Data Base of United states, nearly 40% of patients with unfavorable risk disease did not receive PLND[6].

The safety and feasibility of the PLND procedure appear to have improved in proportion to the surgical volume, and PLND has become the gold standard for providing accurate nodal staging for PCa[7,8]. However, there are pros and cons in systematic reviews regarding the direct benefit of PLND on survival outcomes[9-12], and expanding the template consistently results in more complications[13]. A randomized controlled trial (RCT) did not demonstrate better survival outcomes for extended PLND during radical prostatectomy, despite suggesting the potential benefits of biochemical recurrence (BCR)-free survival in high-grade PCa[14]. Thus, the therapeutic role of PLND has remained unclear for more than a decade.

PLND cannot be accepted as a standard procedure if the survival benefits do not outweigh the negative impacts. This study focused on BCR-free survival as an endpoint, and the therapeutic impact of extended PLND during robotic prostatectomy was evaluated in contemporary patients with intermediate- to high-risk PCa at Dokkyo Medical University Hospital using a propensity score (PS)-matched analysis.

Methods

Patient enrollment

A total of 1020 patients underwent robot-assisted radical prostatectomy (RARP) between October 2012 and October 2021 at our prostate center. Of these patients, 399 with intermediate- to high-risk PCa who were determined to have an LN involvement probability of greater than 7% on the Briganti 2012 nomogram were enrolled in the study[15]. The National Comprehensive Cancer Network (NCCN) classification was used as the risk stratification. The clinical stage was determined by assessing the results of a digital rectal examination (DRE) and multiparametric magnetic resonance imaging (MRI) findings, and the appropriate staging was used for risk stratification and nomogram. Patients treated before May 2015, those with a short follow-up period; i.e., less than 6 months, and those diagnosed with clinically positive LN (cN1) or with a total biopsy number less than 10 were excluded, while those who received neoadjuvant androgen-ablation therapy were not excluded.

Robotic prostatectomy and pelvic lymph node dissection

RARP followed by PLND was carried out using an intraperitoneal anterior approach by six surgeons, and the extended PLND template was applied from 2015. The extended PLND template included the bilateral intrapelvic regions, such as obturator, external iliac, internal iliac, and common iliac up to the ureter crossing. Tissues in the Marcille triangle as the obturator region and lateral vesical fat tissue as the internal iliac region were included from February 2018. Prostatectomy specimens and LNs separated by regions were submitted for pathological evaluation.

Postoperative follow-up

After robotic surgery, patients who received neoadjuvant androgen-ablation therapy did not continue any hormonal therapy. PSA levels combined with general blood test and physical status were examined every three months, and adjuvant treatment such as radiotherapy or androgen-ablation therapy was not performed until a judgment of BCR, although the pathological results show positive surgically resected mar-

gins or LN metastases. BCR was defined as a PSA level greater than 0.2 ng/mL with a subsequent increase.

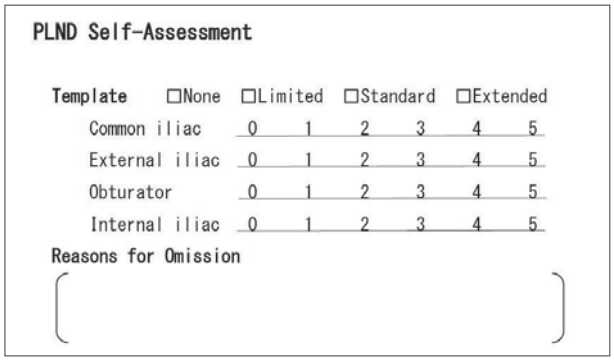
Patient characteristics of entire cohort

The endpoint for the entire cohort was BCR-free survival as an early oncological outcome. Our retrospective analysis found that the lower limit for the LN number was around 15 in high quality PLND as determined by our surgeons' self-assessment, which consisted of the degree of LN dissection in each part in the template and the reason when omitted (Fig. 1). Accordingly, we tentatively set a threshold of a sufficient LN number at 15, and compared estimated BCR-free survival between extended PLND with a sufficient LN yield group (sufficient LN yield group, n = 217) and other (insufficient LN yield group, n = 182) in the entire cohort (Table 1). The "LN yield" means the number of lymph nodes obtained by PLND. The insufficient LN yield group included patients that underwent standard-, limited-, unilateral-, and omitted-PLND with various reasons.

The covariate factors used in the PS-matching were age, body mass index, PSA, MRI measured prostate volume, clinical T-stage, number of biopsy cores, number of positive cores, biopsy grade groups proposed by the 2014 International Society of Urological Pathology (ISUP)[16], NCCN risk, neoadjuvant androgen-ablation, and Briganti LN involvement probability. In this study, the findings for multiparametric MRI were read by specialists in urologic radiology to determine whether or not there were typical suspicious lesions for malignancy, and histopathologies were evaluated by specialists in urologic pathology.

Statistical analyses

The quantitative and qualitative data were compared using Student's t-test and a chi-squared test or Fisher's exact test, respectively. The covariate factors for the PS-matched analysis included the previously identified preoperative variables. Survival was estimated using Kaplan-Meier analysis, and differences were compared with the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox regression analysis, which was also used for multivariate analyses.


PLND Self-Assessment

Template ☐None ☐Limited ☐Standard ☐Extended

Common iliac	0	1	2	3	4	5
External iliac	0	1	2	3	4	5
Obturator	0	1	2	3	4	5
Internal iliac	0	1	2	3	4	5

Reasons for Omission

Figure 1 Self-assessment sheet for surgeons performing robot-assisted radical prostatectomy with extended pelvic lymph node dissection.

All statistical analyses were performed with EZR, which is a graphical user interface for R (2020 The R Foundation for Statistical Computing, version 4.0.3). All statistical tests were two-sided, with a p-value of less than 0.05 was considered as statistically significant.

Ethics and patient consents

This study was conducted in accordance with the Helsinki Declaration and was approved by the institutional ethical review boards at Dokkyo Medical University Hospital (i.e., approval number #28010, including the responsibility to report the results of this study for further clinical evaluation). In addition, each patient signed a consent form regarding the storage of their information for the purpose of research and acknowledged that the results of this study did not affect the subsequent clinical course.

Results

Pathological outcomes in entire cohort

The mean (median) LN yield and the number (%) of patients with a positive LN were 23.7 (22) and 39 (18.0%), respectively, in the sufficient LN yield group. The photo shows the gross appearance of the left-side pelvis after the extended and sufficient PLND (Fig. 2). No distribution bias was observed in the pathological T-stage and the positive resection margin rate. The ISUP grading in patients who received neoadjuvant therapy remains for reference (Table 2). The LN yield in patients who received neoadjuvant therapy was lower than in hormone naïve patients (20.5 versus 24.1, p = 0.010).

Table 1 Preoperative patient characteristics of unmatched and matched cohort

	Unmatched cohort			Propensity score-matched cohort		
	LN yield ≥ 15 (n = 217)	LN yield < 15 (n = 182)	p	LN yield ≥ 15 (n = 133)	LN yield < 15 (n = 133)	p
Mean age, years (SD)	67.4 (6.2)	68.4 (6.2)	0.112	68.1 (5.6)	67.8 (6.2)	0.748
Mean BMI, kg/m^2 (SD)	24.8 (2.7)	24.6 (3.0)	0.636	24.9 (2.8)	24.7 (3.0)	0.578
Mean PSA, ng/mL (SD)	11.0 (8.4)	11.1 (9.8)	0.970	11.6 (8.6)	10.5 (9.2)	0.327
Mean PV, mL (SD)	39.2 (12.9)	44.3 (22.1)	0.004	42.0 (13.8)	40.3 (15.7)	0.327
Clinical T-stage, n (%)			0.279			0.145
T1c	22 (10.1)	19 (10.4)		15 (11.3)	12 (9.0)	
T2a-c	149 (68.7)	137 (75.3)		86 (64.7)	101 (75.9)	
T3a-b	45 (20.7)	25 (13.7)		31 (23.3)	20 (15.0)	
T4	1 (0.5)	1 (0.5)		1 (0.8)	0 (0.0)	
Mean biopsy cores (SD)	15.4 (2.3)	16.3 (2.6)	< 0.001	16.1 (2.2)	16.0 (2.6)	0.586
Mean positive cores (SD)	5.9 (3.1)	4.8 (3.0)	0.001	5.3 (3.1)	5.1 (3.2)	0.530
ISUP grade group, n (%)			0.058			0.661
1-2	10 (4.6)	11 (6.0)		7 (5.3)	9 (6.8)	
3	54 (24.9)	64 (35.2)		34 (25.6)	39 (29.3)	
4	115 (53.0)	87 (47.8)		67 (50.4)	67 (50.4)	
5	38 (17.5)	20 (11.0)		25 (18.8)	18 (13.5)	
NCCN classification, n (%)			0.023			0.397
Intermediate-risk	47 (21.7)	58 (31.9)		30 (22.6)	37 (27.8)	
High-risk	170 (78.3)	124 (68.1)		103 (77.4)	96 (72.2)	
Neoadjuvant hormone, n (%)			0.776			0.256
Received	33 (15.2)	25 (13.7)		27 (20.3)	19 (14.3)	
Not received	184 (84.8)	157 (86.3)		106 (79.7)	114 (85.7)	
Mean Briganti LNI, % (SD)	21.3 (18.0)	16.6 (16.1)	0.007	20.7 (17.7)	17.3 (16.0)	0.101

LN = lymph node; SD = standard deviation; BMI = body mass index; PSA = prostate-specific antigen; PV = prostate volume; ISUP = International Society of Urological Pathology; NCCN = National Comprehensive Cancer Network; LNI = lymph node involvement

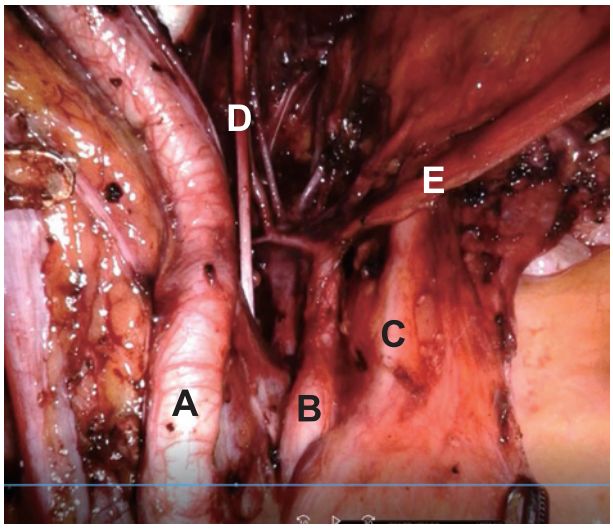


Figure 2 Gross appearance of the left-side pelvis after extended and sufficient pelvic lymph node dissection. A = external iliac artery; B = internal iliac artery; C = ureter; D = obturator nerve; E = umbilical artery.

BCR-free survival in entire and each NCCN risk cohort

Twenty-six (6.5%) patients were interpreted as BCR on the first PSA checkup after surgery. After a mean follow-up of 30.0 months in the unmatched cohort, BCR was observed in 32 (14.7%) and 45 (24.7%) patients in the sufficient and insufficient LN yield group, respectively. The median value is usually indicated by the Kaplan-Meier method, but in this study, a 3-year BCR was used instead due to the low recurrence rate of patients. The estimated curve did not reach the median, and the advantage of 3-year BCR-free survival for sufficient LN yield remained at 10.0% (HR 0.68, 95% CI 0.43-1.07; p = 0.098) (Fig. 3A).

There were differences in preoperative factors associated with prostate volume, biopsy-related parameters, risk distribution, ISUP grade group, and neoadjuvant therapy. PS-matching was adjusted for these background differences and converged each LN yield

Table 2 Pathological outcomes in unmatched and matched cohort

	Unmatched cohort			Propensity score-matched cohort		
	LN yield ≥ 15 (n = 217)	LN yield < 15 (n = 182)	p	LN yield ≥ 15 (n = 133)	LN yield < 15 (n = 133)	p
Pathological T-stage, n (%)			0.293			0.312
T0	2 (0.9)	1 (0.5)		2 (1.5)	0 (0.0)	
T2a-c	117 (53.9)	111 (61.0)		72 (54.1)	79 (59.4)	
T3a-b	98 (45.2)	69 (37.9)		59 (44.4)	53 (39.8)	
T4	0 (0.0)	1 (0.5)		0 (0.0)	1 (0.8)	
ISUP grade group*, n (%)			0.707			0.704
NA	2 (0.9)	0 (0.0)		2 (1.5)	0 (0.0)	
1-2	40 (18.4)	39 (21.5)		23 (17.3)	30 (22.6)	
3	80 (36.9)	73 (40.3)		49 (36.8)	51 (38.3)	
4	50 (23.0)	34 (18.8)		31 (23.3)	27 (20.3)	
5	45 (20.7)	35 (19.3)		28 (21.1)	25 (18.8)	
Mean LN yield, n (SD)	23.7 (7.4)	3.4 (4.3)	< 0.001	24.1 (7.9)	3.7 (4.3)	< 0.001
LN metastases, n (%)	39 (18.0)	3 (1.6)	< 0.001	20 (15.0)	3 (2.3)	< 0.001
Positive resection margin, n (%)	76 (35.0)	56 (30.8)	0.394	41 (30.8)	42 (32.3)	0.895

LN = lymph node; NA = not available; SD = standard deviation; ISUP = International Society of Urological Pathology

* The grading in patients received neoadjuvant therapy remains for reference.

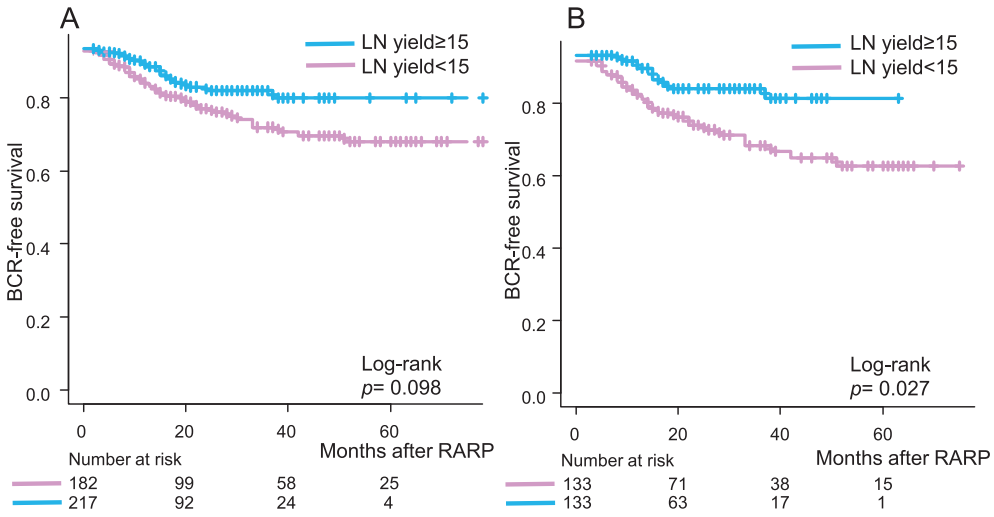


Figure 3 Kaplan-Meier estimates biochemical recurrence-free survival stratified by lymph node yield in unmatched cohort **(A)** and propensity score-matched cohort **(B)**.

group to 133 patients (Table 1). The inequality of postoperative factors other than the results related to lymph nodes was resolved with an adjustment of preoperative factors (Table 2). The difference in the 3-year BCR-free survival widened to 15.8% (HR 0.54, 95% CI 0.31-0.93; p = 0.027) (Fig. 3B).

The PS-matched cohort was further stratified by NCCN risk group; no arms reached the median, and the high-risk PCa contributed more to statistical differences than the intermediate-risk PCa. The 3-year BCR-free survival for intermediate-risk and high-risk PCa with sufficient versus insufficient LN yield were 100.0% versus 94.6% and 79.5% versus 58.5%, respectively (Fig. 4).

Predictive factors for BCR in Cox proportional hazard model

Conventional multivariate analysis was also performed on the model with LN yield and postoperative pathological factors. All known unfavorable pathological features, such as T3-4, N1, ISUP grade group 4-5, large index tumor volume, and positive resection mar-

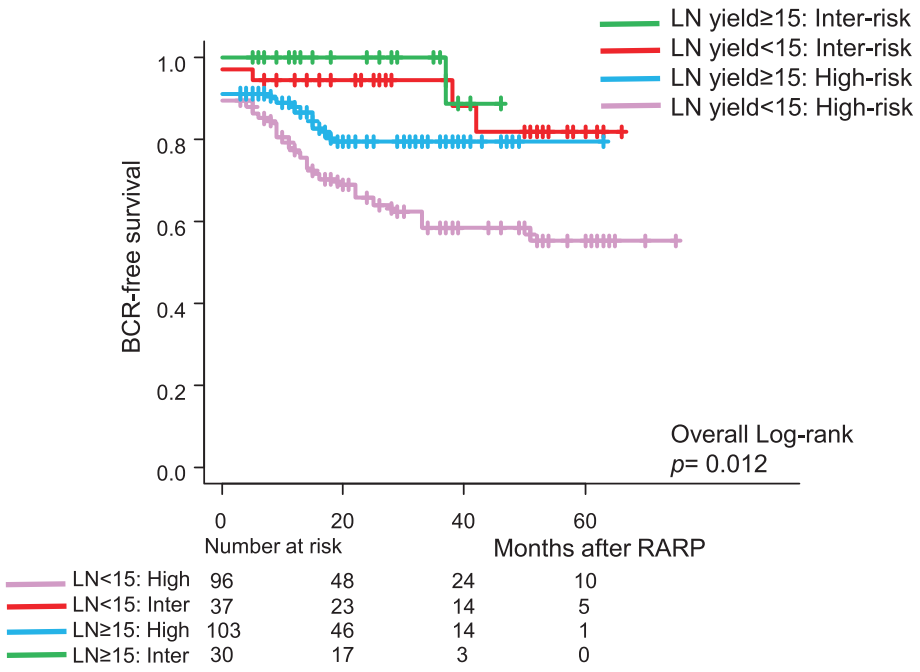


Figure 4 Kaplan-Meier estimates biochemical recurrence-free survival stratified by National Comprehensive Cancer Network classification risk group and lymph node yield in propensity score-matched cohort.

Table 3 Predictive factors for biochemical recurrence in Cox proportional hazard model

	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
LN yield ≥ 15 (*n* = 217) vs. < 15 (*n* = 182)	0.68	0.43-1.07	0.098	0.30	0.17-0.51	< 0.001
Pathological T stage ≥ 3 (*n* = 167) vs. < 3 (*n* = 232)	4.35	2.65-7.14	< 0.001	2.41	1.54-3.79	0.002
Pathological N stage 1 (*n* = 42) vs. 0 (*n* = 357)	4.76	2.86-7.92	< 0.001	4.59	2.41-8.75	< 0.001
ISUP grade group* ≥ 4 (*n* = 171) vs. < 4 (*n* = 228)	3.36	2.08-5.42	< 0.001	2.59	1.67-4.02	< 0.001
Index volume, mL ≥3.27 (*n* = 137) vs. < 3.27 (*n* = 259)	2.78	1.76-4.37	< 0.001	1.70	1.09-2.64	0.047
Resection margin 1 (*n* = 132) vs. 0 (*n* = 267)	2.52	1.61-3.95	< 0.001	1.29	0.78-2.13	0.323

HR = hazard ratio; CI = confidence interval; LN = lymph node; ISUP = International Society of Urological Pathology
* The grading in patients received neoadjuvant therapy remains for reference.

gin, were statistically significant predictors for BCR in the univariate analysis, and the LN yield remained at the statistical approach. In the multivariate analysis, the LN yield showed an independent predictive value, while the positive resection margin lost the independency (Table 3).

Surgical parameters and complications

The mean operating time on the robotic console was 53 minutes longer (184 versus 131 minutes, $p < 0.001$), while the mean blood loss including urine (215 ml versus 216 mL, $p = 0.934$) did not increase due to the LN yield procedure.

There were no postoperative complications classified as Clavien-Dindo grade IV or V and no statistical difference in frequency of grade III complications. There were some adhesive ileus, paralytic ileus, or infectious lymphocele that required radiographic intervention or surgery in each LN yield group, and a bleeding over 7,000 ml occurred 12 hours after surgery in one patient in the sufficient LN yield group.

Discussion

The PS-matching followed by survival analysis using preoperative factors showed a statistically significant value of extended PLND for BCR-free survival with a promising hazard ratio, despite the statistics remaining at an equivocal trend in the unmatched entire cohort.

The Cox regression multivariate analysis using postoperative factors also showed its independent predictive value. These results clearly indicate the superiority of extended PLND for BCR-free survival in patients with intermediate- to high-risk PCa. In addition, the risk-range setting in the study was considered appropriate because of the enrolled patients with estimated LN involvement of 19.2% on average. At least in our prostate center, PLND can be accepted as a standard procedure based on the survival benefits outweighing the adverse effects.

Under the circumstances that the extended PLND provides accurate nodal staging while establishing safety and feasibility[7,8], but without distinct evidence of the survival benefits, the practice guidelines from both the American Urological Association and European Association of Urology (EAU) recommend PLND with an extended template in patients with intermediate- and high-risk PCa as an expert opinion[17,18]. Some systematic reviews and meta-analyses have referred to survival outcomes, but most consisted of reports with low levels of evidence. Furthermore, there are considerable variations in the LN yield and the positive rate of metastasis[9-12]. However, recent reports have found a possible superiority for PLND regarding the effects of BCR-free survival with hazard risks of approximately 0.6-0.7[10,11].

Unfortunately, the long-awaited RCT could not demonstrate better survival outcomes of extended PLND, despite the study being precisely designed to expect a 15% advantage in BCR-free survival[14]. The report must be an important reference, but an incorrect patient selection regarding the risk-range setting was identified; there was a favorable cancer profile characterized by more than one-third of patients having an ISUP grade group 1 and an estimated risk of LN involvement of 11% to 12% that reduced the effect of extended PLND[19]. On the contrary, a recent RCT to determine the role of prophylactic pelvic irradiation for high-risk, locally advanced PCa successfully showed improved disease-free survival[20]. Although one cannot compare the different treatment modalities on the same basis, the crucial difference is that the enrolled patients had a higher risk PCa in the latter RCT, and the estimated risk of LN involvement was more than 20%. Prior to this study, we analyzed the survival outcomes of patients with different LN invasion probabilities at different risk PCa, and the difference in outcome measurements widened in the higher risk subgroup[21]. These precedents indicated that the selection of patients and risk-range setting is essential when evaluating the therapeutic role of PLND.

Introducing an attractive report regarding molecular LN staging may alter patient risk stratification and affect PLND application or efficient adjuvant therapy. Molecular LN status is determined by prostate-specific expression of Kallikrein 3 (KLK3) using a quantitative polymerase chain reaction that detects LN metastases with a higher sensitivity and the risk of BCR than histopathological diagnosis. Interestingly, patients with pN0/molecular N1 were observed at the same proportion as those with pN1/N1[22]. The study group later proposed a combined KLK3/transmembrane serine protease 2 panel as a diagnostic and prognostic tool for molecular LN analysis[23]. These studies imply that the role of PLND removes LN micrometastases unrecognized by histopathology.

The results of this study point to unique characteristics and limitations. The study enrolled PCa patients whose clinical stage was determined by a combination of DRE and multiparametric MRI. In general, MRI shows higher sensitivity and lower specificity than DRE, and the use of an MRI finding leads to the upstaging of clinical T-stage and risk grouping and further affects treatment intensification in approximately 30% of patients[24]. MRI staging has possible advantages to determine a locally advanced high-risk group in the EAU risk group and to improve model performance at both Memorial Sloan Kettering Cancer Centre 2018 and Briganti 2012 nomograms[25,26]. In our cohort, the risk migration to a higher risk group remained at only 3.5% (14/399 patients). This is probably because the staging did not rely solely on MRI, and the NCCN classification with T3 or higher as one of the high-risk criteria but not D'Amico was used in the risk stratification. Nevertheless, the measured values of BCR-free survival cannot simply be compared to those in other reports since the Will Rogers phenomenon arising from the risk migration has often occurred[27].

Secondly, most previous studies have excluded patients who received neoadjuvant treatment, although the current study did not. It is well acknowledged that

neoadjuvant hormonal therapy has no significant effect on BCR-free survival[28], and recent findings have shown no significant effect even on resection margin positivity[29]. These are the rationale for deciding which patients to enroll in this study, and the rate of neoadjuvant therapy was adjusted in the PS-matching. In real-world practices, considerable neoadjuvant hormonal manipulation is still performed, and the rate increases at higher disease stages, expecting a delay in cancer progression until surgery. We considered that multiple biases in patient selection or background confounding were unavoidable, whether these patients were included or excluded.

A new statistical approach using the rigorous application of a causal inference framework and the concept of causal mediation analysis has attracted attention. One recent report indicated that the impact of extended PLND was not restricted to a staging benefit, but also involved a therapeutic benefit of reducing BCR or second-line therapy experience at approximately 30%. This method clearly quantifies the direct effect mediated through the removal of occult micro metastases, which has not mediated indirect effect through the detection of nodal disease and potential adjuvant therapy[30]. When a well-designed RCT is not feasible due to ethical issues, such methodology may resolve the analytical challenges of PLND for survival benefits.

Although the PS-matching adjusted the differences in known background factors, several limitations would restrict the oncological impact and quality of the results, including the study design being a retrospective analysis, outcomes by multiple surgeons, study at a single institution, the comparison of patients receiving various degrees of PLND, the short follow-up periods, and the relatively small number of patients. Despite such limitations, this report should serve as an important reference indicating the positive therapeutic role of PLND.

In conclusion, there should be PCa patient benefit from PLND. Our study clearly demonstrates the therapeutic role of PLND in intermediate- and high-risk PCa that may harbor both recognizable and unrecognizable metastases. The benefit of PLND depends on the study design, selection of patients with an optimal risk-range, and the surgeon complying with the extended template and removing a sufficient number of LNs.

Acknowledgments

The authors are special thanks to Toshimi Sairenchi, Chief director of Center for Research Collaboration and Support in Comprehensive Research Facilities for Advanced Medical Science at Dokkyo Medical University for his statistical advice in conducting this study.

Competing Interests

The authors declare that they have no competing interests.

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