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Preoperative Predictors of Lymph Node Invasion and Biochemical Recurrence in High-risk Prostate Cancer

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Abstract. *Aim: To evaluate the preoperative predictors of pathological lymph node (LN) metastasis and prognostic factors for postoperative biochemical recurrence (BCR) in robot-assisted radical prostatectomy with extended pelvic LN dissection in patients with D'Amico high-risk prostate cancer (PCa). Patients and Methods: Overall, 107 patients with D'Amico high-risk PCa underwent robot-assisted radical prostatectomy with extended pelvic LN dissection without neoadjuvant or adjuvant therapy. BCR was defined as a prostate-specific antigen (PSA) level ≥0.2 ng/ml. Moreover, BCR-free survival rates were determined using Kaplan-Meier analysis. Logistic regression analysis was used to evaluate preoperative predictors of pathological LN metastasis. Cox regression analysis was used to evaluate the effects of preoperative and pathologic variables on BCR. Results: The median follow-up was 21 months, and the 5-year BCR-free survival rate was 59.8%. The positive LN rate was 21.5%. In multivariate analysis, the percentage of positive cores was a significant preoperative predictor of positive LNs. Patients with >50% positive cores (p=0.004) and PSA density (PSAD) >0.5 ng/ml/cc (p=0.005) had a high risk of having ≥3 positive LNs. In multivariate analysis, PSAD >0.5% was a significant preoperative predictor of BCR. Among the postoperative predictors, the number of positive LNs was significantly associated with BCR. Patients with ≥3 positive LNs (n=7) had significantly lower BCR-free survival rates than patients with one or two positive LNs (n=16) (p<0.001). Patients with >50% positive cores and PSAD >0.5 ng/ml/cc had a risk for a high number of positive LNs (≥3) that was strongly associated with shorter BCR-free survival (p<0.001). Conclusion: The percentage of positive cores may be useful as a preoperative predictor of pathological LN metastasis in patients with high-risk PCa. Patients with >50% positive cores and PSAD >0.5 ng/ml/cc were found to have a high risk for ≥3 positive LNs and shorter BCR-free survival.*

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Key Words: Extended pelvic lymph node dissection, robot-assisted radical prostatectomy, percent positive cores.

In the current era of robotic surgery era, extended pelvic lymph node dissection (ePLND) is recommended for patients who are at high-risk for prostate cancer (PCa) according to several guidelines on PCa (1, 2). In general, ePLND includes the area between the external iliac vein and above the obturator nerve (limited PLND), the area below the obturator nerve up to the internal iliac vessels, and the proximal common iliac vessel area under the ureter (3). However, the therapeutic benefit of ePLND remains controversial, and no consensus has been reached. Patients with PCa and pathologically positive lymph nodes (LNs) are considered to have a worse prognosis than those with negative LNs (4-6). However, in patients with locally advanced PCa, pathologically positive LNs have been reported not to be a predictor of biochemical recurrence (BCR) after radical prostatectomy, including robot-assisted radical prostatectomy (RARP). Indeed, some patients with PCa have pathologically positive LNs without BCR and additional adjuvant therapy. One report suggests that patients with PCa that have few pathologically positive LNs have a lower risk of BCR (7).

The aim of this study was to evaluate the preoperative predictors of LN metastasis and prognostic factors for postoperative BCR in RARP with ePLND for patients in the high-risk group of the D'Amico PCa risk classification (8).

Patients and Methods

We retrospectively analysed 503 consecutive patients with PCa who underwent RARP between September 2014 and October 2020 at our

hospital. All surgeries were performed using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). One hundred and forty-five patients who were classified as being in the high-risk group of the D'Amico PCa risk classification underwent ePLND. Among these patients, 36 received neoadjuvant hormonal therapy, while two patients received adjuvant ADT after surgery. In the present study, we analysed 107 patients who were classified as being at high-risk under the D'Amico PCa risk classification and underwent RARP with ePLND without neoadjuvant or adjuvant therapy. The research protocol was approved by the institutional review board of Nagasaki University Hospital (No. 16052318).

Preoperative prostate volume was estimated using magnetic resonance imaging to calculate the prostate-specific antigen density (PSAD). The ePLND consisted of the excision of fibrofatty tissue along the external iliac vein, obturator nerve, internal iliac vessels, and proximal common iliac vessel area under the ureter (3). Furthermore, all fibrofatty tissue within the obturator fossa was removed to completely expose the obturator nerve. Fat tissue containing LNs were fixed in 10% neutral buffered formalin, embedded in paraffin blocks, and stained with haematoxylin and eosin. Pathologists at our Institution diagnosed pathologically positive LNs. The number of nodes, size of the largest node, and any gross features were described. BCR was defined as PSA levels ≥0.2 ng/ml with second confirmatory increase at least 6 weeks after surgery. BCR-free survival rates were determined by Kaplan–Meier analysis. Logistic regression analysis was used to evaluate the preoperative predictors of LN metastasis. Cox regression analysis was used to evaluate the effects of preoperative factors and pathologic variables on BCR. JMP® Pro 15 for Windows (SAS Institute Japan, Tokyo, Japan) was used for statistical analyses. A value of $p<0.05$ (two sided) was considered significant.

Results

Six urologists at our hospital performed ePLND, and this study included the initial cases for each surgeon. Among these, three surgeons performed ≥20 ePLNDs, while others performed <20 operations. These three surgeons who performed ≥20 operations removed a median of 18 LNs (range=5-36). Table I shows the patients' clinical characteristics in this study. The median follow-up time was 21 months (range=2-63 months). The median age at surgery was 69 years (range=49-76 years). Table II shows the patients' pathological outcomes after RARP. The median number of removed LNs was 17 (range=5-36) in the pN0 cohorts and 20 (range=8-31) in pN1 cohort ($p=0.538$). Twenty-three patients (21.5%) had pathologically positive LNs [≥3 pathologically positive LNs: n=7 (30.4%); two pathologically positive LNs: n=6 (26.1%); one pathologically positive LN: n=10 (43.5%)]. Table III lists the clinicopathological factors that may predict positive LNs. Among the preoperative factors, >50% positive cores and PSAD >0.5 were significantly associated with positive LNs in univariate analysis. In multivariate analysis, >50% positive cores [odds ratio (OR)=3.366, 95% confidence intervaI (CI)=1.240-9.133; $p=0.017$] was a significant predictor of positive LNs. Regarding postoperative factors, pathological Gleason score, pathological T stage, extraprostatic extension,

Table I. *Clinical characteristics of patients who underwent robot-assisted radical prostatectomy with extended pelvic lymph node dissection.*

Characteristic	Patients with pN0, (n=84)	Patients with pN1, (n=23)
Age, years		
Median (range)	69 (56-81)	72 (50-83)
PSA, ng/ml		
Median (range)	8.58 (1.37-79.32)	11.40 (3.48-40.52)
Biopsy Gleason score, n (%)		
6	3 (3.6)	0 (0)
7	11 (13.1)	6 (26.1)
8	52 (61.9)	9 (39.1)
9	17 (20.2)	7 (30.4)
10	1 (1.2)	1 (4.3)
Clinical T stage, n (%)		
T1	43 (51.2)	9 (39.1)
T2a	10 (11.9)	3 (13.0)
T2b	7 (8.3)	2 (8.7)
T2c	13 (15.5)	6 (26.1)
T3a	8 (9.5)	2 (8.7)
T3b	1 (1.2)	1 (4.3)
Tx	2 (2.4)	0 (0)
Positive cores, %		
Median (range)	33 (8-100)	58 (8-100)
PSAD, ng/ml/cc		
Median (range)	0.30 (0.06-1.92)	0.41 (0.07-1.73)

PSA: Prostate-specific antigen; PSAD: PSA density.

Table II. *Pathological outcomes of patients who underwent robot-assisted radical prostatectomy with extended pelvic lymph node dissection.*

	Patients with pN0, (n=84)	Patients with pN1, (n=23)
Pathological Gleason score, n (%)		
6	2 (2.4)	0 (0)
7	55 (65.5)	8 (34.5)
8	10 (11.9)	4 (17.4)
9	17 (20.2)	11 (47.8)
10	0 (0)	0 (0)
Pathological T stage, n (%)		
T2a	5 (6.0)	0 (0)
T2b	8 (9.5)	0 (0)
T2c	44 (52.4)	6 (26.1)
T3a	19 (22.6)	5 (21.7)
T3b	6 (7.1)	12 (52.2)
Tx	2 (2.4)	0 (0)
Extension, n (%)		
Extraprostatic	23 (27.4)	16 (69.6)
Surgical margin, n (%)		
Positive	13 (15.5)	11 (47.8)
LNs removed		
Median (range)	17 (5-36)	20 (8-31)
Number of positive LNs		
Median (range)	0 (0)	2 (1-11)

LNs: Lymph nodes.

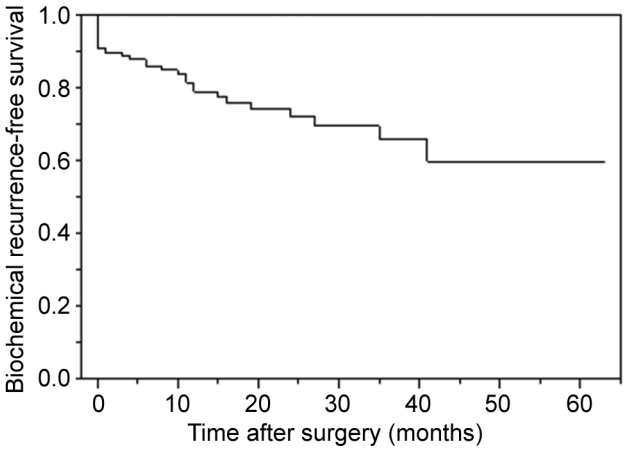

Figure 1. *Kaplan–Meier curve for biochemical recurrence-free survival considering the whole cohort.*

and positive surgical margins were significantly associated with positive LNs in the univariate analysis. In multivariate analysis, positive surgical margins (OR=5.245, 95% CI=1.774-15.506; p=0.003) were significantly associated with positive LNs. We confirmed that 28 patients (26.2%) had BCR after RARP during follow-up. A PSA nadir of >0.2 ng/ml after surgery was found in 10 patients (9.3%). The median postoperative follow-up duration after RARP was 21 months, and the 2-, 3-, and 5-year BCR-free survival rates were 72.2%, 65.8%, and 59.8%, respectively (Figure 1). Table IV shows the clinicopathological predictors of BCR after RARP. Among the preoperative factors, PSAD >0.5 ng/ml/cc was a significant predictor of BCR (hazard ratio=2.482, 95% CI=1.150-5.354; p=0.021) in multivariate analysis. In the postoperative factors, ≥3 pathological positive LNs was a significant predictor of BCR (hazard ratio=4.837, 95% CI=1.705-13.722; p=0.003). Moreover, patients with ≥3 positive LNs (n=8) had significantly lower BCR-free survival rates than patients with one or two positive LNs (n=16) (Figure 2, log-rank test, p<0.001). Based on these results, we classified the entire cohort into two groups using the percentage of positive cores and PSAD. Patients with both >50% positive cores and PSAD >0.5 ng/ml/cc had a high risk for ≥3 positive LNs (Table V) and significantly shorter BCR-free survival (Figure 3, log-rank test, p<0.001).

Discussion

Robotic surgery has facilitated surgical procedures that were difficult in the past. In the robotic surgery era, ePLND is recommended for patients with higher-risk PCa in several guidelines (1, 2). Briganti *et al*. reported that the estimated risk for positive LNs in high-risk patients was 15-40% (9). Therefore, ePLND is recommended for all patients with high-risk PCa according to the 2017 European Association of Urology guidelines (2). However, the necessity for ePLND remains controversial, and no consensus has been reached. One of the accepted roles of an appropriately performed ePLND is to provide accurate nodal staging in patients with PCa (3). For accurate PCa staging, an autopsy series suggested the removal of 20 nodes (10). However, the ideal number of LNs to be removed for adequate PCa staging remains controversial. Furthermore, the oncological benefit of ePLND remains unclear (6). Although LN dissection is a time-consuming and complicated procedure, ePLND remains justified because it enables accurate assessment of PCa staging (11).

To avoid unnecessary ePLND, the European Association of Urology guidelines recommend ePLND in patients with a more than 5% risk of LN invasion according to several available validated nomograms (9, 12, 13). These nomograms consist of preoperative factors including preoperative serum PSA, clinical T stage, biopsy Gleason score, and percentage age of positive cores. Among these preoperative factors, the percentage of positive cores has been regarded as an essential factor in predicting LN invasion (9). Furthermore, recent studies suggest that the percentage of positive cores may be a significant predictor of BCR. Nagao *et al*. reported that Gleason score at biopsy of ≥8 and ≥30% positive cores were independent predictors of biochemical progression (14). Hamada *et al*. reported preoperative factors predicting BCR after radical prostatectomy for D'Amico high-risk PCa. They concluded PSAD ≥0.4 ng/ml/cc and ≥70% positive cores from the dominant side may be significant predictors of biochemical progression after RP (15). Thus, several reports have shown the importance of the percentage of positive cores as a predictive factor for both LN invasion and BCR. In the present study, we showed that >50% positive cores and PSAD >0.5 ng/ml/cc were significant predictors of positive LNs and BCR, respectively. This may help to eliminate unnecessary ePLND in patients with D'Amico high-risk PCa. Considering that the percentage of positive cores reflects the volume of the tumour and PSAD reflects the degree of destruction of the glandular ducts of the prostate, these indices are consistent as indicators for determining the progression and malignancy of PCa.

The clinical course of PCa with positive LNs is diverse. It is not always lethal, and it may not progress even in the absence of adjuvant hormone therapy (16). Regardless of tumour characteristics, ePLND with at least 20 LNs reportedly provides correct LN staging in 90% of cases (17). In our RARP series, a median of 18 LNs (range=5-36) were removed, and 23 patients (21.5%) had pathologically positive LNs. The total number of resected LNs was 20 or more in 47 patients, <20 in 55 patients, and unknown in five patients. However, the rate of detection of positive LNs was not

Table III. *Predictors of positive lymph nodes*.

Variable	Comparison	Univariate *p*-value	Multivariate		
			OR	95% CI	*p*-Value
Pre-operative factors					
PSA	>20 *vs*. ≤20 ng/ml	0.106			
Biopsy Gleason score	≥8 *vs*. <8	0.366			
Clinical T stage	≥T2c *vs*. <T2c	0.306			
Positive cores	>50% *vs*. ≤50%	0.007	3.366	1.240-9.133	0.017
PSAD	>0.5 *vs*. ≤0.5 ng/ml/cc	0.034	2.505	0.914-6.867	0.074
Post-operative factors					
Pathological Gleason score	≥8 *vs*. <8	0.007	4.333	1.494-12.564	0.007
Pathological T stage	≥T3a *vs*. <T3a	<0.001			
Extraprostatic extension	Yes *vs*. no	<0.001			
Positive surgical margin	Yes *vs*. no	0.002	5.245	1.774-15.506	0.003

CI: Confidence intervaI; OR: odds ratio; PSA: prostate-specific antigen; PSAD: PSA density.

Table IV. *Predictors of biochemical recurrence after robot-assisted radical prostatectomy.*

Variable	Comparison	Univariate *p*-Value	Multivariate		
			HR	95% CI	*p*-Value
Pre-operative factors					
PSA	>20 *vs*. ≤20 ng/ml	0.264			
Biopsy Gleason score	≥8 *vs*. <8	0.895			
Clinical T stage	≥T2c *vs*. <T2c	0.077			
Positive cores	>50% *vs*. ≤50%	0.012	1.874	0.865-4.059	0.111
PSAD	>0.5 *vs*. ≤0.5 ng/ml/cc	0.013	2.482	1.150-5.354	0.021
Post-operative factors					
Pathological Gleason score	≥8 *vs*. <8	0.024			
Pathological T stage	≥T3a *vs*. <T3a	<0.001			
Extraprostatic extension	Yes *vs*. no	<0.001			
Positive surgical margin	Yes *vs*. no	<0.001	3.117	1.309-7.420	0.010
Positive lymph nodes	≥3 *vs*. <3	<0.001	4.837	1.705-13.723	0.003

CI: Confidence intervaI; OR: odds ratio; PSA: prostate-specific antigen; PSAD: PSA density.

significantly different between the groups (27.7% *vs*. 18.8%, p=0.254). Morizane *et al*. reported that patients with 1-2 positive LNs had significantly higher BCR-free survival rates than those with ≥3 positive LNs. They concluded that some patients with 1-2 pathologically positive LNs can be cured by RARP with ePLND (7). Compared to their previous report, our patients with 1-2 positive LNs had significantly higher BCR-free survival rates than those with ≥3 positive LNs. None of the patients died of PCa during the follow-up period. The combination of >50% positive cores and PSAD >0.5 ng/ml/cc was a predictor of ≥3 positive LNs, which was significantly associated with shorter BCR-free survival.

Briganti *et al*. reported that the biochemical progression-free survival rate at 5 years after radical prostatectomy was 55.2% in patients with surgically treated D'Amico high-risk PCa (18). In our study, the BCR-free survival rate was similar (59.8%). However, our study has several limitations. Firstly, it was a single-institution retrospective study, and the sample population was too small. Moreover, the incidence of pN1 might have affected the statistical results. Secondly, this was not a single-surgeon series. Thirdly, our median follow-up period (21 months) was too short to assess the long-term BCR rate or to analyse overall survival. However, we believe that information and discussion of the present study are important in managing patients who are high-risk for D'Amico PCa.

In conclusion, we confirmed that patients who are at D'Amico high-risk for PCa with >50% positive cores and PSAD >0.5 ng/ml/cc had an increased risk for positive LNs and shorter BCR-free survival. Considering that ePLND may not have oncological benefits and may increase adverse

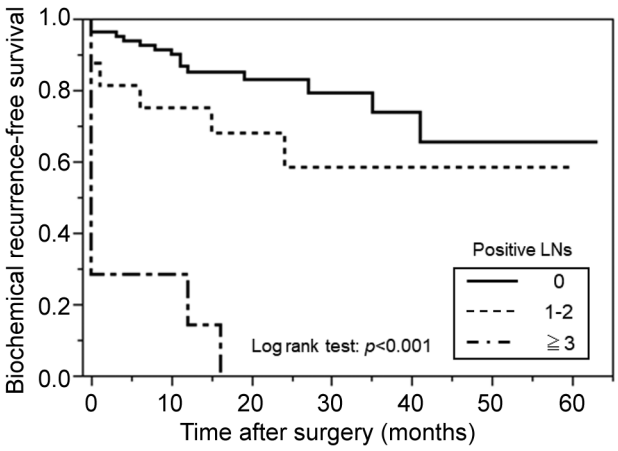

Figure 2. *Kaplan–Meier curves for biochemical recurrence-free survival by number of positive lymph nodes (LNs).*

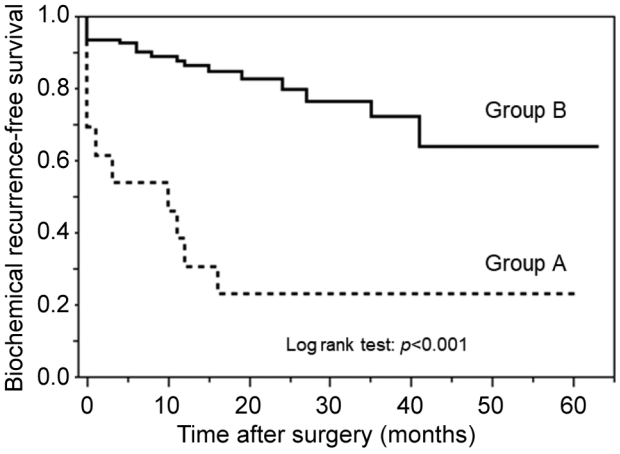

Figure 3. *Kaplan–Meier curves for biochemical recurrence-free survival among patients classified according to the percentage of positive cores and prostate-specific antigen density. Two groups were defined, group A: patients with >50% positive cores and prostate-specific antigen density >50 ng/ml/cc; group B: all other patients.*

Table V. *Preoperative factors predictive for ≥3 positive lymph nodes.*

Variable	Comparison	Univariate *p*-Value	Multivariate		
			OR	95% CI	*p*-Value
PSA (ng/ml)	>20 *vs.* ≤20 ng/ml	0.001			
Biopsy Gleason score	≥8 *vs.* <8	0.488			
Clinical T stage	≥T2c *vs.* <T2c	0.013			
Positive cores	>50% *vs.* ≤50%	<0.001	11.395	1.166-111.132	0.036
PSAD	>0.5 *vs.* ≤0.5 ng/ml/cc	<0.001	11.608	1.152-117.011	0.038

CI: Confidence intervaI; OR: odds ratio; PSA: prostate-specific antigen; PSAD: PSA density.

events, the necessity for ePLND will remain a controversial issue for some time to come.

Conflicts of Interest

None.

Authors' Contributions

YS: Surgery, data collection, data analysis and writing of the manuscript. TH: surgery, data collection and data analysis. KM, TM and KO: surgery. YM and HS: supervision.

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