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Indication for and Extension of Pelvic Lymph Node Dissection During Robot-assisted Radical Prostatectomy: An Analysis of Five European Institutions

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Abstract

Background: Several reports have shown that patients who undergo minimally invasive radical prostatectomy have a lower chance of undergoing pelvic lymph node dissection (PLND), irrespective of the disease characteristics.
Objective: We evaluated the rate and extension of PLND in patients who underwent robot-assisted radical prostatectomy (RARP). We tested the adherence of the indication for PLND to the European Association of Urology (EAU) guidelines.
Design, setting, and participants: Our study was a multi-institutional retrospective analysis of prospectively collected data on 2985 consecutive patients who underwent RARP at five high-volume European institutions. Patients were stratified according to preoperative cancer risk group.
Intervention: RARP.
Outcome measurements and statistical analysis: The rate and extent of PLND across different institutions were analyzed. Univariable and multivariable logistic regression models evaluated the association between preoperative variables and the probability of receiving PLND, as well as the presence of lymph node invasion (LNI). Finally, the probability of LNI was calculated for each patient, and the indication for PLND was compared with the EAU guidelines' indications.
Results and limitations: A lymph node dissection was performed in 1777 patients (59.7%; 34.5% of low-risk patients, 64.9% of intermediate-risk patients, and 91.2% of high-risk patients). These rates were different across institutions: 5.0–41.4% in low-risk patients ($p < 0.001$), 31.3–81.4% in intermediate-risk patients ($p < 0.001$), and 84.6–96.4% in high-risk patients ($p = 0.06$). The mean and median number of nodes removed was 10.8, and 122 patients (4.1%) had nodal metastases. At multivariable analysis, the institution

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represented an independent predictor of PLND ($p < 0.001$). Of patients with current indication for PLND (EAU guidelines), 77.8% actually received the procedure. Limitations were the retrospective study design with different pathologic assessment and lack of follow-up data.

Conclusions: PLND is performed in a high proportion of patients undergoing RARP in high-volume centers in Europe for whom the procedure is indicated by the EAU guidelines, but significant differences exist among institutions. An effort toward a more rigorous standardization of PLND is advocated.

Patient summary: In this paper, we investigated the indication for and extension of pelvic lymph node dissection (PLND) in different institutions in Europe. Despite PLND being widely performed, significant variations with regard to PLND do exist among different institutions. Therefore, a thrust toward more rigorous attention to PLND is advocated.

1. Introduction

Pelvic lymph node dissection (PLND) represents the most accurate staging procedure for patients diagnosed with organ-confined prostate cancer (PCa) who undergo radical prostatectomy (RP) [1]. Several predicting tools are available to quantify the risk of lymph node invasion (LNI) [2–4]. The European Association of Urology (EAU) guidelines on PCa recommend omitting PLND when the risk of LNI is ≤5%, while they do recommend performing PLND for all other patients [1]. To date, there are few real-world data about the current management of PCa patients who underwent RP with regard to the indication for and the extension of PLND in both open and robotic approaches. It has been demonstrated that patients who undergo minimally invasive RP have a lower chance of receiving PLND as compared with their counterparts who undergo open RP, bringing into question the oncologic role of minimally invasive RP [5,6]. Finally, several studies of patients who underwent robot-assisted RP (RARP) and PLND have shown that the number of nodes routinely removed is very low [7,8]. However, to date, RARP has been used increasingly in the setting of organ-confined PCa [9]. Proper planning and execution of PLND are crucial in patients treated with RARP and are even more important because it has been suggested that RARP may also represent an effective treatment for high-risk patients [10]. It is therefore of utmost importance to establish whether an appropriate PLND is actually routinely performed during RARP, since several studies showed that an extended PLND is feasible during RARP [11–15], but no population-based European study is available to demonstrate this issue.

The objective of the study was to examine the rate and the extension of lymph node dissection (LND) according to preoperative risk groups in a large population of patients who underwent RARP in five high-volume European institutions and to test whether the indication for PLND actually adheres to the EAU guidelines.

2. Materials and methods

2.1. Patient population

For the purpose of the study, we merged the databases, including prospectively collected data on 3058 consecutive patients not previously treated with androgen deprivation therapy and/or radiation therapy who underwent RARP at five high-volume European institutions between 2005 and 2012. Patients with missing clinical and/or pathologic data were excluded ($n = 73$; 2.3%), resulting in 2985 patients with complete preoperative information (age, prostate-specific antigen [PSA], clinical stage, biopsy Gleason score, and percentage of positive biopsy cores) and complete pathologic information regarding the occurrence of LNI, the number of lymph nodes removed, and the number of positive lymph nodes. All surgeries were performed with the da Vinci system.

2.2. Statistical analyses

For the purpose of the analyses, patients were stratified according to preoperative risk groups as follows: low risk (PSA <10 ng/ml, clinical stage T1c, and Gleason score ≤6), high risk (PSA >20 ng/ml, clinical stage T3, or Gleason score 8–10), or intermediate risk (all remaining patients).

First, descriptive statistics were used to analyze the rate of LND in the overall population and in each risk group category by χ^2 analyses. Second, the student t test and analysis of variance were used to measure and compare the number of nodes removed during LND in each risk group category. Third, univariable analysis (UVA) and multivariable analysis (MVA) logistic regression models predicting the probability of receiving an LND were fitted. Covariates consisted of preoperative PSA, clinical stage (categorized as cT1c, cT2, and cT3), biopsy Gleason score, percentage of positive biopsy cores (defined as the number of positive cores over the number of total cores taken), and institution (coded as a nonordinal categorical variable). Fourth, UVA and MVA logistic regression analyses were used to predict the presence of LNI. Covariates consisted of preoperative PSA, clinical stage, biopsy Gleason score, percentage of positive biopsy cores, and number of nodes removed (coded as continuous variable). The same analysis was conducted after stratifying the population according to risk categories. Finally, the LNI probability according to the nomogram of Briganti et al. [16] was calculated for each patient. The EAU guidelines cut-off for the indication for PLND was tested in the overall population as well as according to each institution.

All statistical analyses were performed using SPSS v.18.0 (IBM Corp., Armonk NY, USA). All tests were two-sided, with a significance level set at 0.05.

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Table 1 – Descriptive statistics for preoperative variables of 2985 patients treated with robot-assisted radical prostatectomy in five European institutions

Variable	Overall	Institution 1	Institution 2	Institution 3	Institution 4	Institution 5
Patients, no. (%)	2985	99 (3.3)	917 (30.7)	882 (29.5)	828 (27.7)	259 (8.7)
Age, yr						
Mean (median)	62.4 (63)	60.4 (60)	62.6 (63)	63.5 (64)	61.3 (62)	62.67 (63)
Range	37–80	45–73	39–80	37–80	37–76	40–80
PSA, ng/ml						
Mean (median)	9.2 (7)	10.2 (7.5)	7.1 (6.0)	8.8 (6.6)	10.7 (8.2)	12.3 (9.8)
Range	0.3–254.0	3.2–53.0	1–55.0	0.3–180.0	1.2–254.0	1.2–102.0
Clinical stage, no. (%)						
T1	1816 (60.8)	44 (44.4)	680 (74.2)	747 (84.7)	242 (29.2)	103 (39.8)
T2	1409 (35.2)	52 (52.5)	218 (23.8)	134 (15.2)	489 (59.1)	156 (60.2)
T3	120 (4.0)	3 (3.0)	19 (2.1)	1 (0.1)	97 (11.7)	None
Biopsy Gleason sum, no. (%)						
2–6	1742 (58.4)	46 (46.5)	654 (71.3)	437 (49.5)	495 (59.8)	110 (42.5)
7	981 (32.9)	44 (44.4)	235 (25.6)	370 (42.0)	255 (30.8)	77 (29.7)
8–10	262 (8.7)	9 (9.1)	28 (3.1)	75 (8.5)	78 (9.4)	72 (27.8)

PSA = prostate-specific antigen.

3. Results

Table 1 reports the descriptive statistics for preoperative parameters in the overall population, as well as according to the institution of origin. In the overall population, the mean and median PSA values at surgery were 9.18 ng/ml and 7.0 ng/ml, respectively. The clinical stage was T1, T2, and T3 in 60.8%, 35.2%, and 4.0% of the patients, respectively. The biopsy Gleason sum was 2–6, 7, and 8–10 in 58.4%, 32.9%, and 8.7% of patients, respectively. The overall population fitted the risk categories as follows: 31.6% low-risk patients, 52.4% intermediate-risk patients, and 16.0% high-risk patients. As listed in Table 1, several differences among the institutions were noted in terms of preoperative variables.

Table 2 shows the parameters related to the LND. PLND was performed in 1777 patients (59.5%), and the median number of nodes removed was 10. LNI was found in 122 patients (4.1%). LNI was found in 3 (0.9%), 50 (4.9%), and 69 (15.8%) of the low-, intermediate-, and high-risk patients who underwent PLND, respectively. Of patients for whom there was no indication for PLND according to the EAU guidelines, 67 patients (4.9%), 39 patients (2.8%), and 26 patients (1.9%) had extracapsular extension, seminal vesicle invasion, and Gleason score 8–10 at pathology, respectively. Of patients who had no indication for PLND according to the EAU guidelines and for whom PLND was actually performed, 7 patients (0.5%) had LNI at pathology.

Figure 1A shows the different rate of LND performed at each institution. The indication for PLND ranged from 35.4% to 68.7% according to the institution of origin ($p < 0.001$). The same analysis was repeated according to each risk group category (Fig. 1B). In the overall population, PLND was performed in 34.5% of low-risk patients, 64.9% of intermediate-risk patients, and 91.2% of high-risk patients ($p < 0.001$).

Figure 2 shows the percentages of PLND according to preoperative risk group at different institutions. These rates were different across institutions in low-risk patients (5.0–41.4%; $p < 0.001$) and in intermediate-risk patients

Table 2 – Descriptive statistics of lymph node dissection in patients treated with robot-assisted radical prostatectomy and consensual lymph node dissection in five European institutions

Variable	Overall	Institution 1	Institution 2	Institution 3	Institution 4	Institution 5
Patients, no. (%)	2985	99 (3.3)	917 (30.7)	882 (29.5)	828 (27.7)	259 (8.7)
LND performed, no. (%)						
Yes	1777 (59.5)	35 (35.4)	576 (62.8)	606 (68.7)	386 (46.6)	174 (67.2)
No	1208 (40.5)	64 (64.6)	341 (37.2)	276 (31.3)	442 (53.4)	84 (32.4)
Nodes removed, no.						
Mean (median)	10.85 (10)	9.91 (9)	10.31 (9)	9.82 (8)	12.67 (12)	12.43 (11)
Range	1–57	6–17	1–57	1–48	6–30	1–53
Positive nodes, no.						
Mean (median)	0.16 (0)	0.02 (0)	0.14 (0)	0.09 (0)	0.13 (0)	0.56 (0)
Range	0–17	0–1	0–8	0–17	0–4	0–16
Nodal stage, no. (%)						
pN0	1655 (55.4)	34 (34.3)	546 (59.5)	579 (65.6)	365 (43.0)	141 (54.4)
pN1	122 (4.1)	1 (1.0)	30 (3.3)	27 (3.1)	30 (3.6)	34 (13.1)
pNx	1208 (40.5)	64 (64.6)	341 (37.2)	276 (31.3)	442 (53.4)	84 (32.4)

LND = lymph node dissection.

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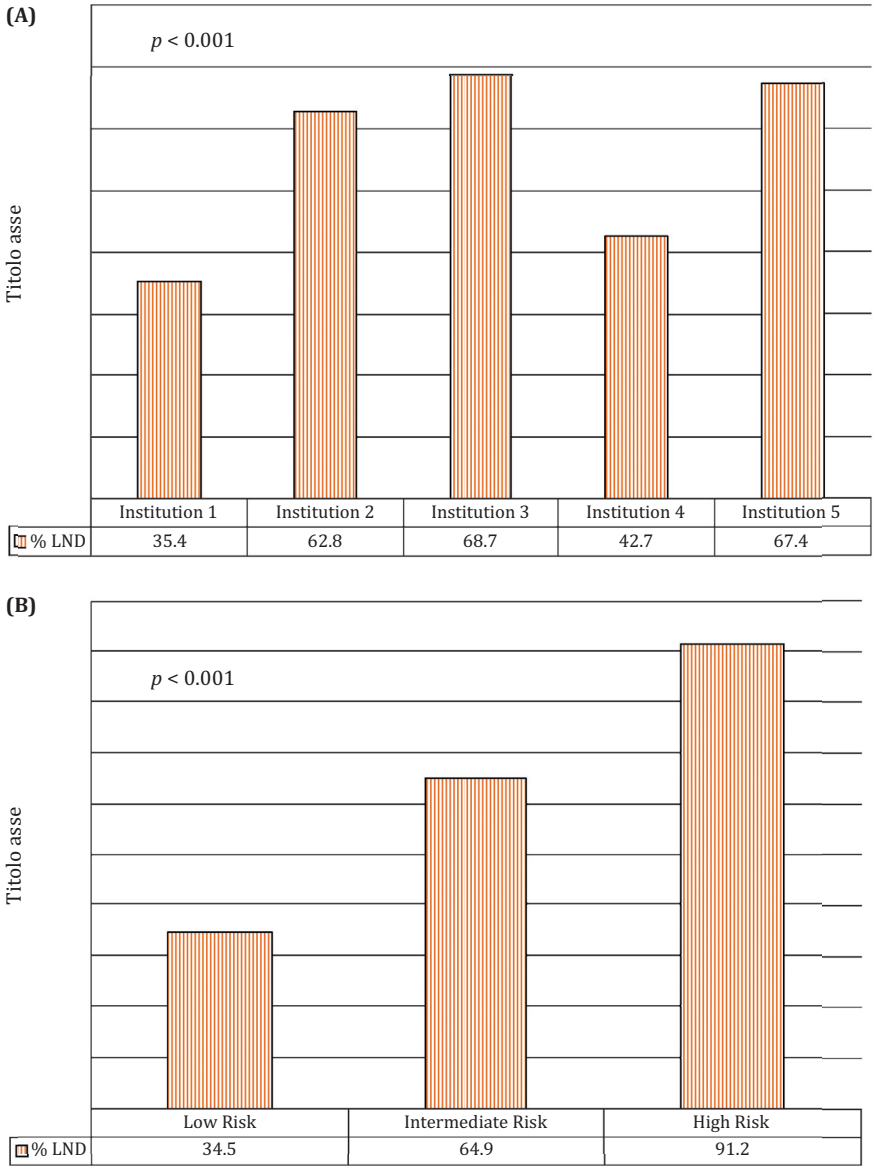

Fig. 1 – Percentage of lymph node dissections (LNDs) performed (A) at five different European centers and (B) by preoperative risk categories.

(31.2–81.4%; $p < 0.001$) but were not significantly different in high-risk patients (84.6–96.4%; $p = 0.06$).

Figure 3 shows the mean number of nodes removed at each institution according to preoperative risk group category. These figures were 9.3 (8.9–12.2; $p = 0.61$), 10.2 (9.1–12.4; $p < 0.001$) and 13.4 (9.8–14.9; $p = 0.18$) nodes for low-, intermediate-, and high-risk patients, respectively. It is interesting to acknowledge that a significant variability was found in the intermediate-risk category of patients, while not in either low- and high-risk patients, despite small differences among institutions.

Table 3 shows the results of the univariable and multivariable logistic regression analyses testing the association between preoperative variables and the probability of receiving PLND in the overall population. At both UVA and MVA, all predictors were significantly associated with the probability of receiving PLND (all $p < 0.001$). It is noteworthy that the institution of origin represented an independent predictor of receiving PLND at MVA ($p < 0.001$).

Table 4 shows the results of the univariable and multivariable logistic regression analyses testing the association between preoperative variables and nodal status at final pathology in the overall population. At UVA, all predictors were significantly associated with LNI (all $p < 0.001$). At MVA, the PSA, clinical stage, primary biopsy Gleason, percentage of positive cores, and number of nodes removed achieved an independent predictor status (all $p < 0.005$). It is noteworthy that the number of nodes removed represented one of the most significant predictors of LNI (odds ratio [OR]: 1.07; $p < 0.001$).

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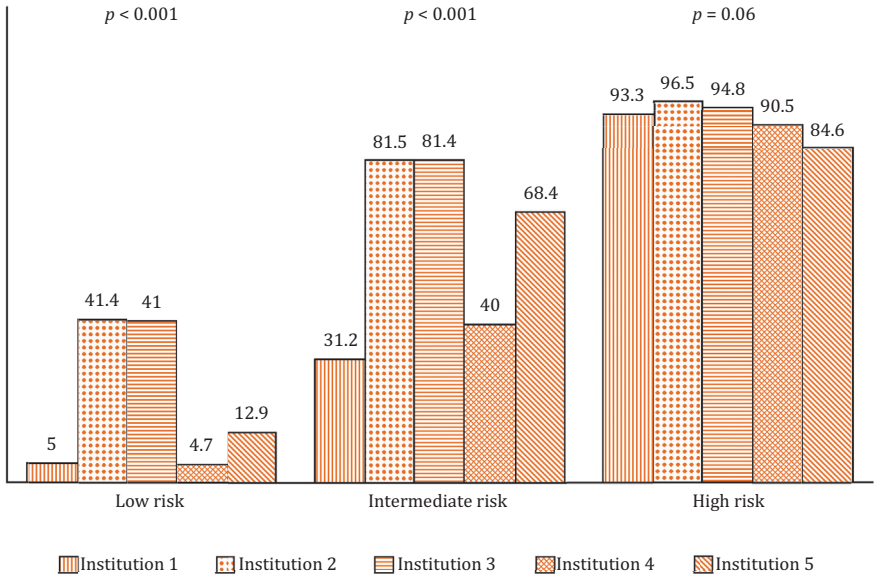

Fig. 2 – Percentage of pelvic lymph node dissections performed at five different European centers by preoperative risk group.

Table 5 shows the results of the univariable and multivariable logistic regression analyses testing the association between preoperative variables and nodal status at final pathology in low-, intermediate-, and high-risk patients. It is interesting to note that the number of nodes removed represented an independent predictor of LNI in high-risk patients (OR: 1.06; $p < 0.001$) and in intermediate-risk patients (OR: 1.07; $p < 0.001$), while the number of nodes removed did not achieve independent predictor status in low-risk patients ($p = 0.23$).

Finally, when we tested the EAU guidelines cut-off for the indication for PLND, we found that 77.8% of patients with an LNI risk >5% actually received PLND, ranging from 45.6% to 90.8% in the five institutions.

4. Discussion

PLND represents the most effective method to detect lymph node metastases in PCa and should be planned on the basis of the disease characteristics only, regardless of surgical

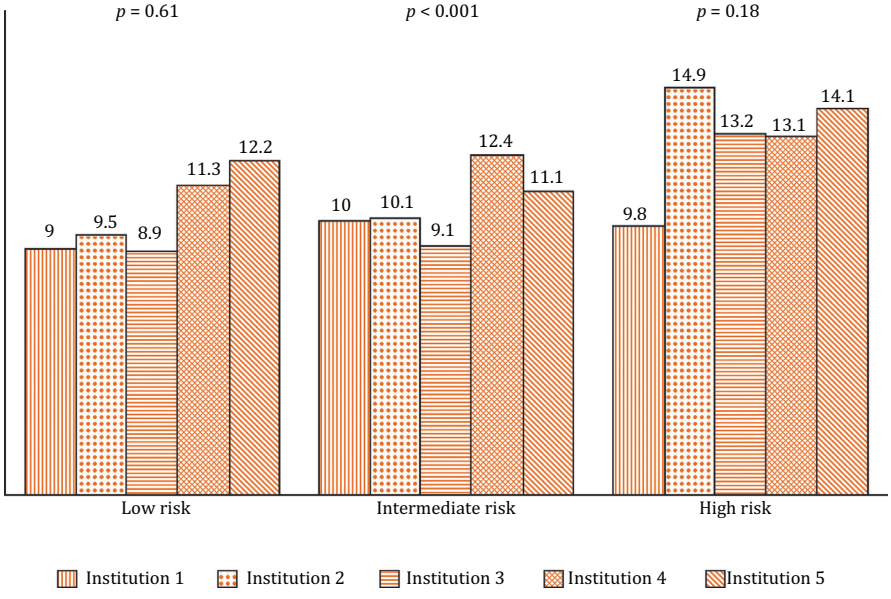

Fig. 3 – Mean number of lymph nodes removed at five different European centers by preoperative risk group.

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Table 3 – Univariable and multivariable logistic regression analyses predicting the probability of receiving a lymph node dissection in 2985 patients treated with robotic-assisted radical prostatectomy in five European institutions

Predictor	Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
PSA	1.114 (1.094–1.134)	<0.001	1.160 (1.13–1.19)	<0.001
Clinical stage	–	<0.001	–	<0.001
cT2 vs cT1	1.267 (1.084–1.479)	0.003	1.16 (1.24–2.12)	<0.001
cT3 vs cT1	6.409 (3.577–11.482)	<0.001	6.010 (2.27–12.16)	<0.001
Primary Gleason grade ≥4 vs ≤3	10.857 (7.590–15.529)	<0.001	13.85 (8.84–21.72)	<0.001
Secondary Gleason grade ≥4 vs ≤3	6.433 (5.274–7.845)	<0.001	7.89 (6.08–10.25)	<0.001
Percentage of positive biopsy cores	9.889 (6.756–14.474)	<0.001	5.5 (3.41–8.89)	<0.001
Institution	–*	<0.001	–*	<0.001

CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen.
* Not shown (categorical nonordinal variable).

technique. However, there are studies showing that patients who undergo minimally invasive RP have a lower chance of undergoing a consensual PLND, independently by preoperative disease characteristics [5,6].

A Surveillance Epidemiology and End Results–Medicare–based analysis showed that a patient treated with RARP has a five times lower chance of receiving PLND when compared with patients treated with RP, claiming an approach-dependent disparity in PCa management [5]. Of the North America uro-oncologists interviewed by a survey, 19% reported that the indications for and extent of PLND differ based on approach [17], but the significance of this result is weakened by the lack of a population-based validation on real data. Nonetheless, it has also been shown that a baseline patient selection phenomenon makes unbalanced the comparison of RARP- and RP-treated cohorts [18]. Finally, several studies have shown that an extended PLND during RARP is feasible and that the procedure can retrieve a number of nodes perfectly comparable to that achieved with an extended open approach [10,12,19,20]. Therefore, whether or not the robotic approach could be a limitation in performing an adequate LND. both in terms of indications and extension. is still a matter of debate.

Our study represents the first report about the indications for and extension of PLND in a large, multi-institutional European population of patients who underwent RARP, and several results may be of interest. First, our data show that PLND during RARP is widely performed in Europe. PLND is routinely performed in 35–68% of patients undergoing RARP. More precisely, PLND is routinely performed in virtually all high-risk patients (91.2%) and in the majority of intermediate-risk patients (64.9%), despite substantial differences among institutions. PLND during RARP is also performed in a significant percentage of patients with low-risk disease (34.5%).

Second, the indications for PLND significantly vary according to institutional guidelines, despite the current availability of highly accurate predicting tools for LNI and of the EAU guidelines. In our population, 77.8% of patients deserving PLND according to the EAU guidelines actually received it; the percentage ranged from 45.6% to 90.8% in the different institutions. There might be two different explanations for the scarce adherence to the guidelines: Individual surgeons are not aware of the guidelines, or perhaps they do not subscribe to the rationale for performing PLND. Unfortunately, we do not have the data to demonstrate which of the two reasons might be more influential. In any case, it must be stated that during our study period, the EAU guidelines were not yet indicating the >5% cut-off of LNI probability as a major indication for PLND. Nonetheless, the vast majority of patients for whom PLND has been later indicated actually already received PLND. The MVA showed that the institution of origin represents an independent predictor of the

Table 4 – Univariable and multivariable analyses predicting the probability of pN1 in 1777 patients treated with robot-assisted radical prostatectomy and consensual lymph node dissection in five European institutions

Predictor	Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
PSA	1.034 (1.020–1.048)	<0.001	1.020 (1.006–1.034)	0.004
Clinical stage	–	<0.001	–	0.001
cT2 vs cT1	3.633 (2.389–5.524)	<0.001	2.173 (1.331–3.545)	0.002
cT3 vs cT1	10.482 (5.823–18.870)	<0.001	3.375 (1.690–6.738)	0.001
Primary Gleason grade ≥4 vs ≤3	6.909 (4.761–10.026)	<0.001	2.637 (1.675–4.152)	<0.001
Secondary Gleason grade ≥4 vs ≤3	2.989 (2.066–4.324)	<0.001	1.579 (1.006–2.477)	0.047
Percentage of positive biopsy cores	30.750 (15.194–62.233)	<0.001	10.654 (4.767–23.815)	<0.001
Number of nodes removed	1.100 (1.078–1.122)	<0.001	1.072 (1.045–1.100)	<0.001

PSA = prostate-specific antigen; OR = odds ratio; CI = confidence interval.

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Table 5 – (a) Univariable and (b) multivariable logistic regression analyses predicting the probability of pN1 in 1777 patients treated with robot-assisted radical prostatectomy and consensual lymph node dissection in five European institutions by preoperative risk category

(a)

Variable	Overall	Institution 1	Institution 2	Institution 3	Institution 4	Institution 5
Patients, no. (%)	2985	99 (3.3)	917 (30.7)	882 (29.5)	828 (27.7)	259 (8.7)
Age, yr						
Mean (median)	62.4 (63)	60.4 (60)	62.6 (63)	63.5 (64)	61.3 (62)	62.67 (63)
Range	37–80	45–73	39–80	37–80	37–76	40–80
PSA, ng/ml						
Mean (median)	9.2 (7)	10.2 (7.5)	7.1 (6.0)	8.8 (6.6)	10.7 (8.2)	12.3 (9.8)
Range	0.3–254.0	3.2–53.0	1–55.0	0.3–180.0	1.2–254.0	1.2–102.0
Clinical stage, no. (%)						
T1	1816 (60.8)	44 (44.4)	680 (74.2)	747 (84.7)	242 (29.2)	103 (39.8)
T2	1409 (35.1)	52 (52.5)	218 (23.8)	134 (15.2)	489 (59.1)	156 (60.2)
T3	120 (4.0)	3 (3.0)	19 (2.1)	1 (0.1)	97 (11.7)	None
Biopsy Gleason sum, no. (%)						
2–6	1742 (58.4)	46 (46.5)	654 (71.3)	437 (49.5)	495 (59.8)	110 (42.5)
7	981 (32.9)	44 (44.4)	235 (25.6)	370 (42.0)	255 (30.8)	77 (29.7)
8–10	262 (8.8)	9 (9.1)	28 (3.1)	75 (8.5)	78 (9.4)	72 (27.8)
Prostate volume, ml						
Mean (median)	46.1 (41)	43 (42)	51 (47)	41 (38)	47 (41)	40 (36)
Range	11–180	15–107	15–155	20–160	28–180	11–113
Risk group, no. (%)						
Low	944 (31.6)	20 (20.2)	449 (49.0)	315 (35.7)	129 (15.6)	31 (12.0)
Intermediate	1563 (52.4)	64 (64.6)	411 (44.8)	451 (51.1)	500 (60.4)	137 (52.9)
High	478 (16.0)	15 (15.2)	57 (6.2)	116 (13.2)	199 (24.0)	91 (35.1)

(b)

	Predictor	Univariable		Multivariable	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value
Low-risk patients (*n* = 326)	PSA	1.39 (0.73–2.67)	0.317	0.96 (0.32–2.9)	0.948
	Percentage of positive biopsy cores	0.74 (0.17–3.15)	0.688	0.64 (0.12–3.25)	0.587
	Number of nodes removed	1.13 (0.99–1.29)	0.057	1.14 (0.92–1.42)	0.23
Intermediate-risk patients (*n* = 1016)	PSA	1.12 (1.05–1.2)	<0.001	1.09 (1.01–1.18)	0.02
	Clinical stage cT2 vs cT1	1.79 (0.98–3.27)	0.06	1.787 (0.9–3.55)	0.09
	Primary Gleason grade ≥4 vs ≤3	5.82 (3.268–10.35)	<0.001	4.69 (1.73–12.71)	0.002
	Secondary Gleason grade ≥4 vs ≤3	1.35 (0.746–2.45)	0.32	1.86 (0.7–4.98)	0.21
	Percentage of positive biopsy cores	1.19 (1.11–1.28)	<0.001	5.79 (1.65–20.25)	0.006
	Number of nodes removed	1.09 (1.06)–1.13	<0.001	1.07 (1.03–1.12)	<0.001
High-risk patients (*n* = 436)	PSA	1.01 (0.99–1.02)	<0.001	1.012 (0.99–1.03)	0.1
	Clinical stage	-	0.06	-	0.25
	cT2 vs cT1	2.11 (1.1–4.03)	0.02	1.82 (0.87–3.79)	0.11
	cT3 vs cT1	1.99 (0.97–4.06)	0.06	1.75 (0.75–4.08)	0.19
	Primary Gleason grade ≥4 vs ≤3	1.48 (0.88–2.5)	0.14	1.25 (0.67–2.33)	0.48
	Secondary Gleason grade ≥4 vs ≤3	1.64 (0.98–3.02)	0.112	1.27 (0.63–2.56)	0.49
	Percentage of positive biopsy cores	1.26 (1.15–1.38)	<0.001	14.63 (4.92–43.5)	<0.001
	Number of nodes removed	1.06 (1.03–1.09)	<0.001	1.06 (1.03–1.1)	<0.001

PSA = prostate-specific antigen; OR = odds ratio; CI = confidence interval.

occurrence of PLND. This phenomenon reflects the variability of surgeons' attitudes toward PLND and could be interpreted as worrisome, representing the need for a more meticulous preoperative patient evaluation. However, after stratification of the study population into risk groups, the different indications for PLND were confirmed in low- and intermediate-risk patients, while in the high-risk group PLND is performed in virtually all patients regardless of the treating surgeon.

The third result of interest is regarding the adequacy of the anatomic template. It has been shown that an extended PLN is feasible during RARP [10,12,19,21], and the EAU guidelines clearly state that whenever extended PLND is performed, the PLND should be extended [1]. Our study shows the median number of lymph nodes removed as 10.85, ranging from 9.8 to 14.1 according to the institution. These numbers must be interpreted with caution, since they reflect the results of different centers with different pathologists. It should be recognized that the number of nodes does not invariably reflect the extension of PLND, since the number of nodes may be highly variable within the same template. However, to date, the number of nodes still represents the most reliable measure of the accuracy of PLND and the most widely used definition of PLND. The removal of nodes in separate or single packages might have influenced the number of nodes reflected by our data, since it has been clearly shown that submitting lymph nodes in distinct

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packages significantly enhances the number of nodes available for histologic examination [22]. In contrast, the most meticulous studies show that the mean number of nodes removed with an extended template may be ≥20 [2,10,12,23], which is highly comparable to the number achieved with open surgery in high-volume centers [16,17]. Our numbers are quite far from these figures. However, if we consider only high-risk patients, our number of nodes is much higher, reflecting an effort toward more meticulous PLND in this category of patients.

Finally, it is not surprising that the number of lymph nodes removed emerged as a significant predictor of LNI in high-risk as well as intermediate-risk patients but not in low-risk patients. This finding represents a confirmation of other studies from open surgery [2,23], but it has never been demonstrated in robotic prostatectomy. This message should push surgeons toward more extended PLND in intermediate- and high-risk PCa patients, while it could justify the omission of PLND in low-risk patients. The finding underlines the evidence that as previously demonstrated in RP cohorts [24], even in patients treated with RARP, a correct nodal staging relies on an adequate anatomic extension of the LND template. Our study may show the current limits of RARP and PLND, but unfortunately there are no similar studies performed in patients undergoing open RP for comparison.

Despite several strengths, the present study is not without limitations. First, the anatomic templates of PLND could not be retrieved for all patients since several surgeons were involved in the study, and this information could not be used in our analyses. However, this limitation might be considered a point of robustness, since it clearly reflects the different approaches in the different institutions. It is difficult to define the exact limits of PLND in our patient cohorts, since this trial was not a prospective one and the definition of the exact template of PLND is not available. However, this limitation might also represent a strength of our study, since no indication for the PLND template was used, and therefore our data truly represent the real dedication of our surgeons to PLND.

Second, as previously mentioned, the lack of a centralized pathologist represents an important bias that applies to all multi-institutional studies on PLND and must be considered when interpreting our results.

Third, despite the inclusion of five centers in Europe, our data do not represent all the European centers, in which different guidelines toward PLND might be applied.

Fourth, our data may reflect a learning curve bias, since our population included the first patients who were treated with RARP in each institution, and it may be hypothesized that nodal retrieval and indication for PLND both increase during the learning curve of RARP (although this idea has never been clearly demonstrated). Detailed information regarding the number and experience of all surgeons was not available in our database.

Fifth, the lack of a control group of patients treated with open RRP and PLND clearly reduces the validity of our findings when addressing the limits of PLND at RARP. It will be interesting to perform a similar study on these patients.

Despite these limitations, our study represents a large picture of the attitudes toward LND in patients who underwent RARP in Europe during the study period. We strongly believe that the analyses of our data may help robot-assisted surgeons to improve their attention toward PLND. More important, the lack of follow-up data represents the main limitation of the study, since evidence that more extended PLND is related to better survival has not been demonstrated in PCa.

5. Conclusions

PLND is widely performed in patients undergoing RARP in high-volume centers in Europe for whom the procedure is currently indicated by the EAU guidelines. The rate and extension of PLND vary significantly among institutions, especially in low- and intermediate-risk patients. An effort toward a more rigorous standardization of LND in terms of both indication and extension is advocated.

Author contributions: Nazareno Suardi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Suardi, Van Der Poel, Walz, Haese, Buffi, Rocco, Ficarra, Briganti, Govorov.
Acquisition of data: Suardi, Haese, Steuber, Ficarra, Borghesi, Mottrie, Govorov, Pushkar, Buffi, Guazzoni, Montorsi, Briganti, Van Der Poel.
Analysis and interpretation of data: Suardi, Larcher, Haese, Govorov, Ficarra, Walz, Montorsi, Van Der Poel.
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