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ORIGINAL ARTICLE

Prostate Cancer

# Extended lymph node dissection in robot-assisted radical prostatectomy: lymph node yield and distribution of metastases

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**In this study, we reported our experience performing robotic extended lymph node dissection (eLND) in patients with prostate cancer. A total of 147 patients with intermediate and high-risk prostate cancer who underwent robotic eLND from May 2008 to December 2011 were included in this analysis. The dissection template extended to the ureter crossing the iliac vessels. We assessed lymph node yield, lymph node positivity, and perioperative outcomes. Lymph node positivity was also evaluated according to the number of lymph nodes (LNs) removed (<22 *vs* ≥22). The median number of LNs removed was 22 (11–51), and 97 positive LNs were found in 24 patients (16.3%). While the obturator fossa was the most common site for LN metastases (42.3%, 41/97), the internal iliac area was the most common area for a single positive LN packet (20.8%, 5/24). Eight patients (33.3%, 8/24) had positive LNs at the common iliac area. The incidence of positive LNs did not differ according to the number of LNs removed. Complications associated with eLND occurred in 21 patients (14.3%) and symptomatic lymphocele was found in five patients (3.4%). In conclusion, robotic eLND can be performed with minimal morbidity. Furthermore, LN yield and the node positive rate achieved using this robotic technique are comparable to those of open series. In addition, the extent of dissection is more important than the absolute number of LNs removed in eLND, and the robotic technique is not a prohibitive factor for performing eLND.**

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**Keywords:** lymph node excision; prostatectomy; prostatic neoplasm; robotics

## INTRODUCTION

Radical prostatectomy is a mainstay treatment for men with localized prostate cancer. Following the first descriptions of the robot-assisted laparoscopic technique,[1] the use of surgical robots for treating prostate cancer has diffused rapidly over the past decade. Although there has been no large randomized clinical trial comparing robotic and open radical prostatectomy, robot-assisted radical prostatectomy (RARP) seems to offer oncologic outcomes comparable to those of open surgery even in patients with high-risk prostate cancer.[2] Case volume, rather than surgical modality, is often considered a primary contributor to surgical outcome.[3] However, there has recently been a statistically significant decline in the use of lymph node dissection (LND). Furthermore, LND is 5 times less likely in minimally invasive surgery than in open surgery even after controlling for tumor characteristics.[4] This trend is particularly worrisome because surgical modality should not be a factor in deciding whether or not to perform LND.

Although the advent of prostate specific antigen (PSA) has resulted in stage migration with decreased incidence of LN metastases, the presence of LN metastases remain an adverse prognostic factor. Unfortunately, recent sophisticated imaging procedures have limited ability for nodal staging.[5,6] In addition, most well-known nomograms might be imprecise as a result of differing extents of LND.[7,8] Currently, LND is the gold standard for determining nodal staging.[9]

Debates about the indication and extent of LND are ongoing. Despite the benefits of staging accuracy and its possible therapeutic role in eliminating microscopic metastases, LND is also associated with several disadvantages, such as increased morbidity, longer operation time, and higher cost.[9,10] Therefore, current guidelines do not recommend performing LND in all patients; however, extended LND (eLND) should be performed in patients with a risk of LN metastases.[11–13] Until date, several studies have reported the experiences and outcomes of eLND using robotic systems.[14–16] With the growing use of RARP even in patients with high-risk of prostate cancer, it is valuable to share robotic eLND experiences as the role of LND should not be ignored in RARP. The objective of the current study is to present our robotic eLND experiences in prostate cancer surgery.

## MATERIALS AND METHODS

From May 2008 to December 2011, a total of 234 patients with intermediate or high-risk prostate cancer underwent RARP with eLND. A single surgeon performed all procedures and the patient database was collected prospectively after obtaining Institutional Review Board Approval (1-2012-0024). Of the 234 patients, 47 with neoadjuvant hormonal treatment and 40 with incomplete LN information (including location or number) were excluded from the analysis. Thus, 147 patients were finally included in this study. Risk stratification was

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based on D'Amico risk criteria.[17] All patients underwent preoperative staging with computed tomography or magnetic resonance imaging and bone scan, which confirmed the absence of metastatic disease.

All procedures, including eLND, were conducted through a transperitoneal approach using the daVinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). The port configuration is described in detail in our previous report.[18] The eLND template consisted of the external iliac, obturator, internal iliac, and common iliac up to the ureteric crossing. In addition, the lymphofatty tissue of the periprostatic area was sent separately to pathology. All eLNDs were performed prior to radical prostatectomy. The peritoneal incisions commenced from the lateral to medial umbilical ligament. After the bladder was lowered, fatty tissues covering the vesicoprostatic junction and periprostatic area were removed. The peritoneal incision proceeded proximally up to the ureteric crossing over the iliac vessel, and the lymphatic tissue covering the common iliac artery was removed. Dissection of the external iliac packet was limited by the lateral border of the external iliac artery and inferiorly by the node of Cloquet. After dissecting the tissues around the common iliac artery and its bifurcation area, the internal iliac artery was identified and nodal tissues around the internal iliac were removed. Lymphatic tissues within the obturator fossa were also removed, sparing the obturator nerve. The LNs were retrieved by laparoscopic forceps through a 12 mm assistant trocar site. LN specimens from each packet were sent separately for pathological analysis.

Next, LN specimens were fixed in 10% neural buffered formalin and embedded in a paraffin block. Slides were then stained with hematoxylin and eosin and examined microscopically. Harvested nodes were identified by a pathologist and all LN specimens were examined by a single genitourinary pathologist with >15 years of experience. The total number of LNs removed and the number of positive LNs for each anatomical location were recorded. Packets without any nodal tissue were regarded as containing zero LNs.

Clinicopathologic characteristics and perioperative outcomes were evaluated. Complications that were presumably associated with eLND were also recorded and defined according to the Clavien classification system.[19] Quantitative variables were compared using the Mann–Whitney U-test and qualitative variables were compared using the Chi-squared test or Fisher exact test. Uni- and multi-variate logistic regression analyses were conducted to identify preoperative variables that predict LN invasion after eLND. The Statistical Package for Social Science for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. $P < 0.05$ was considered as significant, and all $P$ values were two-sided.

## RESULTS

Robotic eLND was performed in 147 patients; patient characteristics are summarized in **Table 1**. Mean age at surgery was 65.3 years and median PSA was 10.7 ng ml$^{-1}$. A total of 108 patients (73.5%) were classified in the D'Amico high-risk group. The median operation time for eLND was 47 min (interquartile range (IQR): 35–56, range 24–100). The median estimated blood loss from RARP with eLND was 250 ml, and no patient received a blood transfusion. Of the 147 patients, 24 (16.3%) had LN metastases. The incidence of LN metastases was correlated with Gleason score and tumor stage. A total of 97 positive LNs were found, and the median number of positive LNs in patients with LN metastases was two (IQR 1–5, range 1–21).

Overall, a median of 22 LNs (IQR 18–26, range 11–57) were removed from all patients. The mean number of LNs per patient in each packet is illustrated in **Figure 1**. There was no difference in the median number of LNs removed between the right and left sides (10 *vs* 11, respectively, $P = 0.558$). Periprostatic fat tissues overlying the prostate and vesicoprostatic junction were also removed. Twelve patients (8.2%) had LNs in the periprostatic area. In these patients, the median number of LNs removed was one and the range was from 1 to 5.

The obturator fossa was the most common site for LN metastases. The number of positive LNs removed from this area consisted of 42.3% of all positive LNs (41/97) and 50% of patients

**Table 1: Clinicopathological characteristics of all patients**

| | *All (n=147)* | *LN (–) (n=123)* | *LN (+) (n=24)* | *P* |
|---|---|---|---|---|
| Age (year) | | | | |
| Mean±s.d. | 65.3±7.0 | 65.3±6.4 | 66.4±7.2 | 0.468 |
| Median, IQR | 66, 62–70 | 66, 62–70 | 66, 62–70 | |
| BMI (kg m$^{-2}$) | | | | |
| Mean±s.d. | 24.2±2.3 | 24.2±2.2 | 24.0±2.8 | 0.704 |
| Median, IQR | 24.2, 22.4–25.6 | 24.2, 22.5–25.6 | 24.3, 21.4–25.8 | |
| PSA (ng ml$^{-1}$) | | | | |
| Mean±s.d. | 15.6±17.9 | 13.2±11.6 | 28.1±33.9 | 0.043 |
| Median, IQR | 10.7, 6.5–17.4 | 10.1, 6.1–15.7 | 16.7, 10.1–25.8 | |
| Biopsy Gleason score, *n* (%) | | | | |
| 6 | 19 (12.9) | 18 (14.6) | 1 (4.2) | 0.007 |
| 7 | 57 (38.8) | 52 (42.3) | 5 (20.8) | |
| 8–10 | 71 (48.3) | 53 (43.1) | 18 (75.0) | |
| Total biopsied cores | | | | |
| Mean±s.d. | 11.6±3.5 | 11.5±3.4 | 11.9±3.5 | 0.653 |
| Median, IQR | 12, 10–12 | 12, 10–12 | 12, 10–12 | |
| Number positive cores | | | | |
| Mean±s.d. | 4.2±2.9 | 3.8±2.5 | 6.2±3.6 | 0.004 |
| Median, IQR | 3, 2–6 | 3, 2–5 | 5, 3–9 | |
| Percentage of positive cores | | | | |
| Mean±s.d. | 37.9±25.2 | 34.6±22.8 | 54.3±30.3 | 0.005 |
| Median, IQR | 33, 17–50 | 30, 16–50 | 51, 25–81 | |
| Clinical T stage, *n* (%) | | | | |
| T1 | 80 (54.4) | 75 (61.0) | 5 (20.8) | <0.001 |
| T2 | 44 (29.9) | 37 (30.1) | 7 (29.2) | |
| T3 | 23 (15.7) | 11 (8.9) | 12 (50.0) | |
| D'Amico risk group, *n* (%) | | | | |
| Intermediate | 39 (26.5) | 37 (30.1) | 2 (8.3) | 0.040 |
| High | 108 (73.5) | 86 (69.9) | 22 (91.7) | |
| Number LNs removed | | | | |
| Mean±s.d. | 22.5±7.18 | 22.2±6.5 | 23.8±9.9 | 0.328 |
| Median, range | 22, 18–26 | 22, 18–26 | 21, 16–26 | |
| Pathologic Gleason score, *n* (%) | | | | |
| 6 | 15 (10.2) | 14 (11.4) | 1 (4.2) | 0.007 |
| 7 | 78 (53.1) | 70 (56.9) | 8 (33.3) | |
| 8–10 | 54 (36.7) | 39 (31.7) | 15 (62.5) | |
| Pathologic T stage, *n* (%) | | | | |
| T2 | 82 (55.8) | 77 (62.6) | 5 (20.8) | <0.001 |
| T3a | 39 (26.5) | 35 (28.5) | 4 (16.7) | |
| T3b | 26 (17.7) | 11 (8.9) | 15 (62.5) | |

IQR: interquartile range; s.d.: standard deviation; BMI: body mass index; PSA: prostate-specific antigen; LNs: lymph nodes with LN metastases (12/24) had a positive LN in the obturator fossa (**Figure 2**). However, only four patients (16.7%, 4/24) had a single positive LN packet in the obturator fossa. The internal iliac area was the most common area to find a single positive LN packet (20.8%, 5/24). Eight patients (33.3%, 8/24) had positive LNs at the common iliac area, and three of these patients (12.5%, 3/24) had no intrapelvic LN involvement. Of the 12 patients who had LNs in the periprostatic area, only one had positive LNs. This patient had 14 positive LNs in both the pelvic and common iliac area. The rate of LN positivity did not differ between groups when patients were stratified by the median number of LNs removed (<22 *vs* ≥ 22; **Table 2**). On univariate logistic regression analysis, PSA, clinical stage, biopsy Gleason score, and percentage of positive cores were significantly associated with LN metastases. On multivariate analysis, PSA ($P$ = 0.021) and clinical stage ($P$ = 0.017) were independent predictors of LN metastases, while biopsy Gleason score and percentage of positive cores lost statistical significance after controlling for other variables (**Table 3**).

Complications associated with LND occurred in 21 patients (14.3%). Clavien Grade 3 complications were observed in three patients (2.0%) who underwent percutaneous drainage for symptomatic lymphocele. Symptomatic lymphocele was found in five patients (3.4%) and two patients were treated conservatively. Of the five patients with symptomatic lymphocele, one was diagnosed 3 months after surgery owing to spiking fever, while the others were diagnosed during their postoperative hospital stay. Lymphedema was observed in 15 patients (10.2%), which resolved after physical treatment in most patients. Only three patients (2.0%) showed mild persistent symptoms. Neuropraxia was observed in one patient (0.7%), which resolved spontaneously 3 months after surgery.

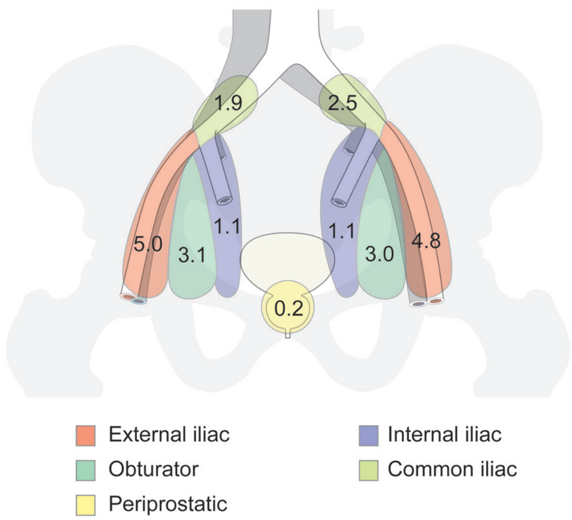


**Figure 1:** Mean number of lymph nodes removed from each anatomic location.

**Table 2: Clinicopathological characteristics of patients according to the number of LNs removed**

| | *LNs removed<22 (n=73)* | *LNs removed≥22 (n=74)* | *P* |
|---|---|---|---|
| Mean age (year)±s.d. | 65.5±6.8 | 65.5±6.2 | 0.995 |
| Mean BMI (kg $m^{-2}$)±s.d. | 24.3±2.2 | 24.0±2.4 | 0.442 |
| Mean PSA (ng $ml^{-1}$)±s.d. | 14.0±13.2 | 17.3±21.7 | 0.267 |
| Pathologic Gleason score, *n* (%) | | | |
| 6 | 8 (11.0) | 7 (9.5) | 0.722 |
| 7 | 39 (53.4) | 39 (52.7) | |
| 8–10 | 26 (35.6) | 28 (37.8) | |
| Pathologic T stage, *n* (%) | | | |
| T2 | 41 (56.2) | 41 (55.4) | 0.967 |
| T3a | 19 (26.0) | 20 (27.0) | |
| T3b | 13 (17.8) | 13 (17.6) | |
| LN metastases, *n* (%) | 12 (16.4) | 12 (16.2) | 0.971 |
| Mean number LN removed±s.d. (median, IQR) | 17.1±3.0 (18, 15–20) | 27.8±6.0 (26, 24–31) | <0.001 |

s.d.: standard deviation; BMI: body mass index; PSA: prostate-specific antigen; IQR: interquartile range; LNs: lymph nodes

**Table 3: Uni- and multi-variate logistic regression analysis for prediction of LN metastases**

| | *Univariate* | | *Multivariate* | |
|---|---|---|---|---|
| | *OR (95% CI)* | *P* | *OR (95% CI)* | *P* |
| PSA | 1.04 (1.01–1.07) | 0.005 | 1.04 (1.00–1.07) | 0.021 |
| Clinical stage (≥T2 *vs* T1) | 5.93 (2.07–16.9) | 0.001 | 3.93 (1.27–12.1) | 0.017 |
| Biopsy Gleason score | | 0.024 | | 0.070 |
| ≤6 | 1 | | 1 | |
| 7 | 1.73 (0.18–15.8) | 0.627 | 1.95 (0.14–26.5) | 0.614 |
| ≥1 | 6.11 (0.76–49.1) | 0.089 | 6.68 (0.55–80.9) | 0.135 |
| Percentage positive cores | 1.02 (1.01–1.04) | 0.001 | 1.01 (0.99–1.03) | 0.072 |

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

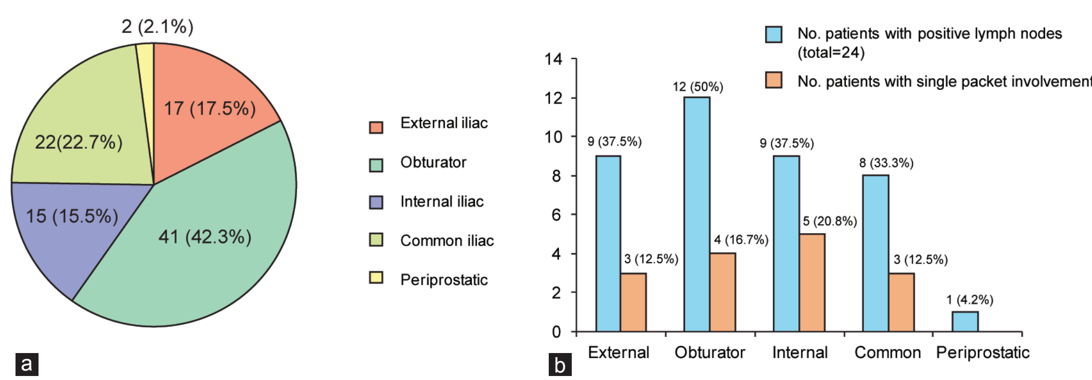


**Figure 2: (a)** Anatomical distribution of 97 positive lymph nodes (LNs) in 24 patients with LN metastases, (**b**) and the number of patients with positive LNs and a single positive LN packet from each anatomic location.

## DISCUSSION

The definition and extent of eLND vary between studies.[14,20,21] Some authors have suggested that the total number of LNs removed contributes to staging accuracy and LN count was thus a determining factor for eLND.[10,22] However, the number of LNs can vary among patients according to the way the specimen were handled by pathologists or the method by which the LN specimens were submitted to pathology.[23] In the current study, we found no significant difference in the incidence of LN metastases according to the number of LNs removed. Furthermore, the LND template seems to be more important than the number of LNs removed.

While eLND is commonly considered to be the removal of lymphatic tissues in the intrapelvic area (external iliac, obturator, internal iliac), in this study we also removed common iliac nodes up to the ureteric crossing and periprostatic lymphofatty tissues. This template that includes the common iliac area is based on the results of a multimodality mapping study.[21] The mapping study demonstrated that extending the template up to the ureteric crossing removes approximately 75% of all prostate primary lymphatic landing sites, while only 63% are located in the intrapelvic area. In this study, we observed that 22.7% of positive LNs were found in the common iliac area, and three patients (12.5%, 3/24) had positive LNs exclusively in this area without intrapelvic involvement.

While no consistent conclusion has been reached regarding the extent of LND, it is generally agreed that the LNs in the internal iliac area should be removed. Many researchers have demonstrated that up to 50% of positive LNs are found in the internal iliac area.[9,24,25] Even though the mean number of LNs in the internal iliac area was almost one-fifth of those in the external iliac area in this study, the number of positive LNs was not significantly different between the external iliac and internal iliac areas (17 and 15 positive LNs, respectively). While a portion of the internal iliac LNs can be sent as obturator LNs, meticulous dissection of the internal iliac area should be recommended and emphasized to all robotic surgeons.

We routinely removed fatty tissue in the periprostatic area. In RARP, surgeons commonly remove the periprostatic fatty tissue to clearly expose the apex of the prostate and vesicoprostatic junction. It was previously reported that approximately 15% of patients had LNs in the periprostatic area and LN involvement was exclusively found in the periprostatic area in some of these patients.[26] In our study, cohort of patients with intermediate and high-risk prostate cancer, 12 patients (8.2%) had LNs in the periprostatic area, and positive LNs were found in one patient who had multiple LN metastases. In addition, we found that another patient had up to five LNs in the periprostatic area. Thus, we believe that meticulous removal of periprostatic tissue might improve LND staging accuracy.

The therapeutic role of LND is one of the main contentious issues in prostate cancer treatment to date. Some authors have suggested that LND may improve prostate cancer outcome by eliminating micrometastatic disease that might otherwise progress and subsequently disseminate systemically. Recently, the first randomized controlled study to assess the impact of LND extent on biochemical outcome was published. While the biochemical outcome in the aforementioned study did not differ according to LND extent in low-risk patients, eLND positively affected biochemical outcomes in intermediate and high-risk patients.[27] Moreover, long-term oncologic outcomes of patients with LN metastases were favorable, and some remained free of biochemical recurrence after LND.[28,29] Although there is no level 1 evidence demonstrating improved cancer specific survival by LND, increasing evidence suggests that LND may confer a survival benefit.

A recent study that analyzed data from the Surveillance, Epidemiology, and End Results cancer registry reported that there was a significant decline in the use of LND with the increased prevalence of RARP.[4] This trend is attributable to a surgeon's concern with functional outcomes over oncologic outcomes, and the omission of LND during early segments of the learning curve. Regardless of surgical modality, eLND is still recommended in patients with a risk of LN metastases and RARP should not be a determining factor for not performing LND.[4,11,13] The technical feasibility of eLND has been reported in previous studies,[14–16] and we have also demonstrated that LN yield and LN positive rate achieved using robotic techniques are comparable to those achieved in open series.[25,30]

This study has several limitations. Although data were collected prospectively, patients with missing data due to undefined locations from which the pathological specimens were obtained were excluded from the analysis. With respect to pathological examination, additional analyses of LN specimens, such as immunohistochemical staining or real-time polymerase chain reaction, were not performed even though they are known to increase the detection rate of LN metastases when conventional histopathology is negative.[31,32] Finally, data on nerve sparing or postoperative erectile function were not included in the analysis owing to incomplete information. Thus, we could not evaluate the impact of eLND on postoperative erectile function. Despite these limitations, the strengths of our study include the fact that the surgeries were all performed by a single, experienced surgeon, that LND was performed using a consistent technique and template during the study period, and that all patients adhering to a uniform protocol. In this study, we assessed the technical feasibility of robotic eLND and evaluated LN yield and metastasis distribution. Further studies are needed to evaluate the oncologic outcome of LND with different dissection templates and longer-term follow-up.

## CONCLUSIONS

Robotic eLND is technically feasible and can be performed with minimal morbidity. Furthermore, the LN yield and node positive rate achieved using the robotic technique is comparable to those of open series. Rates of LN metastases were not influenced by the number of LNs removed when a consistent extended template and dissection technique were applied. The robotic technique is not a prohibitive factor for performing eLND.

## AUTHOR CONTRIBUTIONS

KHK conceived study design, performed statistical analysis and drafted the manuscript. SKL and KCK helped to draft the manuscript. WKH and SJH provided critical revision of the manuscript for important intellectual content. KHR conceived study design and supervised writing of the manuscript.

## COMPETING INTERESTS

All authors declare no competing interests.

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