Prostate International 12 (2024) 117–127

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Review Article

# Current status and therapeutic value of extended pelvic lymph node dissection during radical prostatectomy for prostate cancer

Shuichi Morizane*, Atsushi Takenaka

*Division of Urology, Department of Surgery, Faculty of Medicine, Tottori University, Yonago, Tottori, Japan*

ARTICLE INFO

*Article history:*
Received 2 February 2024
Received in revised form
8 March 2024
Accepted 14 March 2024
Available online 17 March 2024

*Keywords:*
Pelvic lymph node dissection
Pelvic lymphadenectomy
Prostate cancer
Therapeutic value

ABSTRACT

Pelvic lymph node dissection (PLND) is important for accurate staging and prognosis of prostate cancer. Several guidelines recommend extended pelvic lymph node dissection (ePLND) for patients with non-low-risk prostate cancer. However, the therapeutic benefits of ePLND are unclear. Therefore, we reviewed the literature regarding the therapeutic value of PLND for prostate cancer. Although some reports showed that ePLND improves postoperative biochemical recurrence and postoperative overall survival compared with limited lymph node dissection, other reports show no benefits. Overall, the current evidence supporting ePLND is poor. The extent of PLND varied among studies concerning the therapeutic value of ePLND, and study design issues such as patient background and length of follow-up period were different. Some reports demonstrated potential therapeutic value for ePLND when adjusting for patient background. Focusing on patients with high-grade prostate cancer may be important in demonstrating the therapeutic benefits of ePLND. Although the incidence of major adverse events related to ePLND was low, the possibility of adverse events such as lymphedema and lymphocele formation should be considered. In the future, we hope that evidence for optimal selection criteria for ePLND and the extent of ePLND will become more definitive and evidence for the therapeutic value of ePLND will be developed.


## 1. Introduction

Prostate cancer has been on the rise in recent years, accounting for 21% of all new cancer cases and 10% of cancer deaths in men.[1] Prostate cancer usually progresses slowly, although some cases progress rapidly. With the widespread use of prostate-specific antigen (PSA) screening since the 1990s, the incidence of prostate cancer has rapidly increased worldwide.[2] Radical prostatectomy (RP) and external-beam radiation therapy (RT) are the gold standard for treating localized prostate cancer. In addition, several recent guidelines recommend extended pelvic lymph node dissection (ePLND) during RP for localized prostate cancer in intermediate- to high-risk patients, with diagnostic rather than therapeutic intent.[3,4] Performing ePLND during RP may have therapeutic value in some patients if micrometastases are excised.[5] However, the incidence of pelvic lymph node metastases is increasing coincident with a decline in the detection of localized disease.[6] Definitive evidence supporting ePLND during RP, including oncological outcomes such as biochemical recurrence (BCR), cancer-specific survival (CCS), and overall survival (OS), is lacking. The purpose of this review is to clarify the status and the advantages and disadvantages of ePLND and summarize current evidence supporting the therapeutic value of ePLND for prostate cancer in the robotic surgery era.

## 2. Selection criteria for ePLND in localized prostate cancer patients

Most urologists use the D'Amico or National Comprehensive Cancer Network (NCCN) risk classification when selecting treatments for patients with prostate cancer.[4,7] The consensus is that PLND is unnecessary for patients with low-risk prostate cancer.[3,4,8–13] For prostate cancer, the diagnostic accuracy of imaging tests, such as computerized tomography and magnetic resonance imaging (MRI), is inadequate; the reported sensitivity and specificity of imaging tests are 40% and 80%, respectively.[14,15] In recent years, the advent of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scan has shown promise in improving the accuracy of preoperative staging of prostate cancer.[16]

* Corresponding author. Division of Urology, Department of Surgery, Faculty of Medicine, Tottori University, 86 Nishi-cho, Yonago, Tottori 683-8503, Japan.
*E-mail address:* morizane@tottori-u.ac.jp (S. Morizane).

https://doi.org/10.1016/j.prnil.2024.03.002

In a meta-analysis, Wang et al reported a trend of higher sensitivity and diagnostic accuracy of 68Ga-PSMA-11 PET/CT than of multiparametric MRI for the detection of lymph node metastases in patients with prostate cancer, although PSMA PET/CT missed as many as 29% of the lymph nodal involvements (LNIs) identified by PLND.[17] Therefore, many guidelines recommend ePLND at the time of RP for intermediate- to high-risk prostate cancer patients for diagnostic purposes.[3,4,10]

The NCCN guidelines and the European Association of Urology guidelines recommend performing ePLND during RP for prostate cancer patients who were diagnosed preoperatively as having a high likelihood of LNI using Briganti nomograms or other methods.[3,4,10,18–20] However, some studies suggest that an LNI cutoff of 5% may be too low to demonstrate the therapeutic benefits of ePLND.[21] Nomograms have continued to improve, and a nomogram that includes MRI fusion prostate biopsy results has recently been proposed.[20] Panaiyadiyan et al summarized the various nomograms, which have been reported to predict the pathologic stage and LNI after RP for localized prostate cancer.[22] Currently, PLNDs are performed according to a variety of selection criteria, including the Briganti nomogram, Memorial Sloan Kettering Cancer Center nomogram, D'Amico classification, NCCN classification, and Partin tables (Table 1).[7,10,18,20,23-31] However, no definitive selection criteria have been established.[32,33]

## 3. Current status of PLND during RP in clinical practice

In a study of 2,985 consecutive patients who underwent robot-assisted radical prostatectomies between 2005 and 2012, Suardi et al. reported that PLNDs were performed in 34.5%, 64.9%, and 91.2% of low-, intermediate-, and high-risk prostate cancer patients, respectively.[34] However, the number of removed lymph nodes (NRN) was approximately 10, and we suspect that ePLND was not performed sufficiently in most cases. In a study by Leyh-Bannurah et al., the PLND adherence rate was almost 69% for 49,358 patients from the Surveillance and End Results (SEER) database who underwent RP between 2010 and 2013.[10] Patients who did not undergo PLND despite elevated LNI risk had more favorable prostate cancer characteristics than the average patient, and patients who underwent PLND despite a low-risk had worse PCa characteristics than the average patient.[10] Thus, in actual clinical practice, each urologist may make subtle judgments based on patient conditions, even though various selection criteria for ePLND exist. The SEER database recently reported that PLND is performed in 89% of high-risk NCCN prostate cancer patients, 75% of intermediate unfavorable-risk patients, and 59% of intermediate favorable-risk patients, and adherence rates are increasing annually.[35]

## 4. Disadvantages of ePLND in localized prostate cancer patients

Performing ePLND has several disadvantages. Lymph node dissection inevitably prolongs the operative time; ePLND increases the operative time by 30 min, which is double the operative time increase for limited PLND (lPLND).[36-39] Our previous report showed a significant difference in the median intraoperative blood loss between lPLND and ePLND (80 mL (vs.) 100 mL, respectively, $P < 0.001$).[36] Conversely, another report found no significant difference in the median intraoperative blood loss between standard PLND (sPLND) and ePLND (200 mL for both, $P = 0.15$).[40] Systematic reviews on intraoperative blood loss were inconclusive and reported the absence and presence of PLND-related blood loss.[37,38]

**Table 1**
Summary of the selection criteria for lymph node dissection

| Study | Study period | Prediction model | Outcome measure | No of patients | Variables | Predictive accuracy |
|---|---|---|---|---|---|---|
| D'Amico et al. 1998 | 1989-1997 | Risk classification | Biochemical recurrence | 888 | PSA, clinical T stage, biopsy GS | NA |
| Mohler et al. 2010 | NA | Risk classification | NA | NA | PSA, clinical T stage, biopsy GS | NA |
| Partin et al. 1997 | 1982-1996 | Probability table | LNI | 4133 | Biopsy GS, clinical T stage, PSA | 82.9% |
| Makarov et al. 2007 | 2000-2005 | Probability table | LNI | 573 | Biopsy GS, clinical T stage, PSA | 90.6% |
| Cagiannos et al. 2003 | 1985-2000 | Probability nomogram | LNI | 5510 | PSA, clinical T stage, biopsy GS | 76% |
| Briganti et al. 2006 | 2002-2005 | Probability nomogram | LNI | 602 | PSA, clinical T stage, biopsy GS | 76% |
| Briganti et al. 2012 | 2006-2010 | Probability nomogram | LNI | 588 | PSA, clinical T stage, biopsy GS, percentage of positive cores | 87.6% |
| Gandaglia et al. 2019 | 2016-2018 | Probability nomogram | LNI | 497 | PSA, clinical T stage, grade group at MRI-targeted biopsy, maximum diameter of the index lesion at multiparametric MRI, percentage of positive cores with clinically significant prostate cancer at systematic biopsy | 86% |
| Milonas et al. 2021 | 2005-2017 | Probability nomogram | LNI | 679 | PSA, clinical T stage, biopsy GS, percentage of positive cores | 79% |

GS, Gleason score; LNI, lymph node invasion; MRI, magnetic resonance imaging; NA, not available; PSA, prostate-specific antigen.

The most common complications associated with ePLND include obturator nerve injury, symptomatic lymphocele formation, and lymphedema. In a systematic review by Ploussard et al., no differences in complications related to PLND between open, laparoscopic, and robotic surgery for RP were detected.[37] No major vascular injuries, blood transfusions, or open conversions due to PLND occurred in the study by Ploussard et al.[37] Symptomatic lymphocele formation is significantly more likely to occur in ePLND than in lPLND.[36,38,41] Some systematic reviews concluded that the complications are associated with ePLND, including thromboembolic events.[42,43] However, other reports demonstrate that ePLND does not significantly increase complications.[44,45] A recent randomized clinical trial (RCT) reported no significant differences between lPLND and ePLND for grade four and five major complications.[46]

## 5. Diagnostic value of performing ePLND in localized prostate cancer patients

Despite its aforementioned prolonged operative time and increased complication risks, ePLND is primarily performed because of the diagnostic value of LNI. LNI information obtained from ePLND during RP may aid in decision-making during postoperative follow-up and adjuvant androgen deprivation therapy (ADT).[47] In general, more lymph nodes are removed with ePLND than with lPLND or sPLND, and the LNI rate is usually higher.[12,25,36,48-51] The median NRN for lPLND and sPLND compared with ePLND was 7 (3–12) (vs.) 18 (14.6–21), and the median percentages of LNI were 1.4 (0.6%–5%) for lPLND and sPLND and 12.1 (3.2%–17%) for ePLND. In addition, several systematic reviews confirmed the diagnostic value of ePLND, particularly for lymph node metastasis.[37,42,44,52]

## 6. Therapeutic value of performing ePLND in localized prostate cancer patients

The therapeutic value of ePLND for intermediate- and high-risk prostate cancer is still under debate. The association between the NRN during ePLND and biochemical recurrence-free survival (BCRFS), CSS, metastasis-free survival (MFS), and OS after RP is unclear. Several reports indicate that BCR is less likely to occur in patients with some positive lymph nodes, even if LNIs were detected with PLND during RP.[19,49,53,54] Therefore, some prostate cancer patients can benefit from the diagnostic and therapeutic value of ePLND during RP. Patients with micrometastatic lesions, which cannot be detected with current imaging techniques, will benefit from the removal of the lesions by ePLND during RP.[5] Removal of periprostatic fat tissue is also important because patients may have metastatic disease in both the regional lymph nodes and the periprostatic fat tissue.[36,55]

Tables 2 and 3 comparatively summarize the RP studies that report the negative and positive oncological outcomes of varying extents of PLND. Several reports comparing ePLND with no PLND or ePLND with lPLND found no significant differences in oncological outcomes (Table 2).[12,21,41,46,56,57] In a study by Kim et al., a retrospective comparison of ePLND and sPLND in a matched cohort detected no significant differences in the 3-year BCRFS rates (77.8% (vs.) 73.5%, respectively; $P = 0.497$).[41] In their cohort, the median NRN in the sPLND group was 12, and the negative BCRFS results for ePLND may be due to the relatively large NRN in both groups. Chen et al. reported that a cutoff point of 5% probability of LNI using the Briganti nomogram might be too low to show survival benefits in patients undergoing PLND. Preisser et al. reported a median follow-up of 33.5 months, including 30.5 and 60.7 months in patients who did and did not undergo PLND during the RP, respectively.[57] This observation period was very short; moreover, the observation period for the ePLND group was about half that of the lPLND group. The follow-up period for prostate cancer, including BCR, should be long. In the study by Preisser et al., a longer observation period in the ePLND group may have increased the BCR rate. Hori et al. reported that the ePLND group included more high-risk patients than the lPLND group and the follow-up time was shorter in the ePLND group than in the lPLND group.[12] Thus, no definitive conclusions can be made from these reports. Touijer et al. reported no significant difference in postoperative BCR between lPLND and ePLND in an RCT.[46] Currently, only a few prospective studies compared ePLND and lPLND; therefore, the study by Touijer et al. is very useful. However, the median NRNs were 12 and 14 in the lPLND and ePLND groups, respectively. Thus, the negative therapeutic BCRFS results for ePLND may be due to the relatively high number of NRNs in the lPLND group.

As shown in Table 3, positive therapeutic results for ePLND have also been reported.[5,25,49-51,58-61] Joslyn and Konety investigated cancer-specific mortality in 13,020 prostate cancer patients undergoing RP over 127 months and concluded that more extensive lymphadenectomy (more than 10 NRN) was associated with a lower risk of prostate cancer death, even after restricting the analysis to patients with negative lymph nodes.[5] According to Joslyn and Konety, the association between NRN and cancer deaths may be due to the elimination by nodal resection of micrometastases, which were not detected by routine histologic examination.[5] In other studies, more NRN instead of the extent of PLND led to better oncological outcomes, including BCRFS, CSS, and OS.[58-61] In addition, several reports comparing lPLND and ePLND also demonstrated that ePLND led to better oncological outcomes, including MFS, CSS, and BCRFS.[25,49-51]

In a systematic review, Choo et al. concluded that ePLND provides oncological benefits for the prevention of biochemical recurrence in patients with moderate- to high-risk prostatic cancer.[62] However, other systematic reviews concluded that ePLNDs during RP provided no oncological benefits.[38,42,44] Overall, the therapeutic value of ePLND during RP remains unclear.

## 7. Why does the therapeutic value of ePLND for patients with localized prostate cancer remain controversial?

The difficulty in determining the therapeutic value of ePLND during RP for localized prostate cancer may be due to the lack of uniformity in the extent of PLND and the lack of consistent selection criteria for patients undergoing PLND. The extent of PLND has not yet been clearly defined and varies among reports.[37,38,63] Most urologists define the lPLND as the node between the external iliac vein and the obturator nerve, as reported by Ploussard et al. (referred to as the obturator lymph node) (Fig. 1A).[37] Furthermore, most urologists performing ePLND cover areas 1–4 in Fig. 1A. However, even in this well-known figure, the location of the internal iliac lymph node is unclear, and the removal of the internal iliac lymph node, which lies medial to the vesicohypogastric fascia, is unclear. The obturator lymph node occupying the range of I in Fig. 1B of the report by Fossati et al.[38] is similar to the standard dissection (sPLND) shown by Ploussard et al.[37] Therefore, the extent of dissection of the obturator lymph node varies widely among reports. Furthermore, Godoy et al. defined the obturator area as the area occupied by two in Fig. 1C.[63] Confirming the definition of the extent of dissection in each study is essential. Regarding the extent of PLND, removal of the internal iliac and common iliac lymph nodes and the anterior sacral lymph nodes is recommended to increase their diagnostic value.[44,62,64,65] Grouping by NRN may lead to simpler and more accurate results than grouping by the extent of PLND as definitions of the extent of PLND in previous studies were unclear.

**Table 2**
Summary of negative therapeutic results for extended pelvic lymph node dissection.

| Study | Study period | Extent of the PLND | Cohort size | Risk category | NRN (median) | Number of patients with positive nodes (*n*, %) | Positive margin rate (%) | Outcome measure | Follow-up (median months) | Oncological outcomes and conclusions |
|---|---|---|---|---|---|---|---|---|---|---|
| Kim et al. 2013 | 2006–2011, retrospective | sPLND | 141 | Intermediate (35.5%), High (64.5%) | 12 | 7, 5.0% | NA | BCRFS | 36 | In the matched cohort, the 3-year BCRFS rates were 77.8% and 73.5% in the ePLND and sPLND groups, respectively, which was not significant (hazard ratio: 0.85, $P = 0.497$). Robot-assisted ePLND increased the LN yield and detection rate of LN metastases; however, robotic ePLND did not alter biochemical outcomes on short-term follow-up. |
| | | ePLND | 141 | Intermediate (31.9%), High (68.1%) | 21 | 17, 12.1% | NA | | 36 | |
| Mandel et al. 2017 | 1998–2012, retrospective | PLND (NRN ≤13) | 376 | NA | 9 | NA | 47.2 | BCRFS MFS CSS | 47.8 | The number of removed LNs did not significantly influence oncologic outcomes (BCRFS, MFS, or CSS). |
| | | Extensive PLND (NRN >13) | 330 | NA | 20 | NA | 54.3 | | 47.8 | This study concluded that only the number of positive LNs and not the total number of removed LNs was a factor that adversely influenced the oncological outcomes in LN-positive cases that underwent RP. |
| Chen et al. 2019 | 2010–2015, retrospective | No PLND | 4,267 | Low (8.6%), Intermediate (62.3%), High (29.1%) | 0 | 0, 0% | NA | CSS OS | 32 | No significant difference in survival was detected between patients with and without PLND (5-year CSS rate: 99.4% (vs.) 99.7%, $P = 0.479$; 5-year OS rate: 97.3% (vs.) 97.8%, $P = 0.204$). The cut-off point of 5% probability of LNI according to 2012- Briganti nomogram might be too low to show benefits in survival in patients underwent PLND. |
| | | PLND | 4,267 | Low (8.5%), Intermediate (62.5%), High (29.0%) | 6 | 250, 5.9% | NA | | 32 | |
| Preisser et al. 2020 | 2000–2017, retrospective | No PLND | 707 | Intermediate (73.6%), High (26.4%) | 0 | 0, 0% | 29.8 | BCRFS MFS CSM | 60.7 | After propensity score matching 10-yr BCR-, MFS-, and CSM-free survival rates were 60.4% (vs.) 65.6% ($P = 0.07$), 87.0% (vs.) 90.0% ($P = 0.06$) and 95.2% (vs.) 96.4% ($P = 0.2$) for PLND (vs.) no PLND. Multivariate Cox regression models adjusted for postoperative and preoperative tumor characteristics revealed that PLND was not an independent predictor of BCRFS, MFS, or CSM (all $P \geq 0.1$). The therapeutic value of PLND remains unclear. |
| | | PLND | 9,035 | Intermediate (52.3%) High (47.7%) | 14 | 1714, 19% | 27.8 | | 30.5 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Touijer et al. 2021 | 2011–2017, RCT | lPLND | 700 | NA | 12 | 81, 12% | NA | BCRFS | 37 | ePLND did not improve BCRFS compared with lPLND in men with clinically localized prostate cancer ($P = 0.5$). There were smaller than expected differences in the nodal count and the rate of positive nodes between the two templates. A randomized trial comparing PLND and no node dissection is warranted. |
| | | ePLND | 740 | NA | 14 | 100, 14% | NA | | 37 | |
| Hori et al. 2023 | 2013–2019, retrospective | No PLND | 192 | Low (28.1%), Intermediate (66.2%), High (5.7%) | 0 | 1, 0.5% | 16.1 | BCRFS | 36 | Comparing patients who underwent lPLND ($n = 208$) versus ePLND ($n = 134$), the BCR-free rate was significantly lower in the ePLND group compared with the lPLND group ($P < 0.0001$). However, in the propensity score matching population, there was no significant difference in the BCR-free rates between the lPLND and ePLND groups ($n = 86$ for each group, $P = 0.53$). ePLND significantly improved diagnostic accuracy; however, no therapeutic benefit of PLND was observed. |
| | | lPLND | 208 | Low (1.4%), Intermediate (62.5%), High (36.1%) | 7 | 3, 1.4% | 21.2 | | 49 | |
| | | ePLND | 134 | Low (0%), Intermediate (37.3%), High (62.7%) | 18 | 18, 13.4% | 32.8 | | 36.5 | |
| | | ePLND | 150 | Intermediate (62.0%), High (38.0%) | 17 | 25, 17% | 44 | | 53.9 | |

BCRFS, biochemical recurrence-free survival; CSM, cancer-specific mortality; CSS, cancer-specific survival; ePLND, extended pelvic lymph node dissection; lPLND, limited pelvic lymph node dissection; LN, lymph node; LNI, lymph node invasion; MFS, metastasis-free survival; NA, not applicable; NRN, number of removed lymph nodes; OS, overall survival; PLND, pelvic lymph node dissection; RCT, randomized controlled trial; RP, radical prostatectomy; sPLND, standard pelvic lymph node dissection.

**Table 3**
Summary of positive therapeutic results for extended pelvic lymph node dissection.

| Study | Study period | Extent of the PLND | Cohort size | Risk category | NRN (median) | Number of patients with positive nodes (*n*, %) | Positive margin rate (%) | Outcome measure | Follow-up (median months) | Oncological outcomes and conclusions |
|---|---|---|---|---|---|---|---|---|---|---|
| Joslyn et al. 2006 | 1988–1991, retrospective | NA | 13,020 | NA | NA | NA | NA | CSM | 127 | Patients undergoing excision of at least four LNs (node-positive and node-negative patients) or more than 10 LNs (only node-negative patients) had a lower CSM at 10 years than patients who did not undergo PLND.<br>Performing more extensive PLND during RP could improve the accuracy of staging and reduce the risk of CSM in the long term. |
| Schiavina et al. 2011 | 1995–2009, retrospective | NA | 872 | Low (46.1%), Intermediate (39.8%), High (14.1%) | 10.9 | 49, 8.6% | 27.6 | BCRFS | 55.8 | Patients with ≥10 LNs removed had significantly better BCRFS in patients at intermediate and high risk of LNI.<br>More extensive PLND during RP positively affects the BCRFS regardless of the nodal status in intermediate- and high-risk prostate cancer. |
| Abdollah et al. 2015 | 2000–2012, retrospective | PLND, pN1 | 315 | Low (9.2%), Intermediate (30.8%), High (60.0%) | 19 | 315, 100% | 57.5 | CSM | 54 | At 10 years, the CSM-free survival rates were significantly higher for patients with ≥14 LNs compared with patients with <14 LNs ($P = 0.04$).<br>In prostate cancer patients with LNI, the removal of a higher number of LNs during RP was associated with improvement in CSM rate. |
| Preisser et al. 2018 | 2004–2014, retrospective | PLND (NRN <10) | 21,166 | Intermediate (67.9%), High (32.1%) | 4 | 0, 0% | NA | CSM | 31 | At 72 months after RP, CSM-free rates were 99.5 versus 98.1% for NRN ≥11 and NRN ≤10, respectively ($P = 0.01$).<br>More extensive PLND at RP provides improved staging information and consequently is associated with lower CSM in D'Amico intermediate- and high-risk prostate cancer patients without evidence of LNI. |
| | | Extensive PLND (NRN ≥11) | 6,981 | Intermediate (65.4%), High (34.6%) | 15 | 0, 0% | NA | | 28 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Bivalacqua et al. 2013 | 1992–2003, retrospective | lPLND | 1986 | NA | 11.4 | 21, 1.1% | 33.3 | BCRFS<br>MFS<br>CSS | 96 | 5-year BCRFS for lPLND and ePLND was 7.1% (vs.) 30.1% ($P = 0.018$). The 10-year MFS for lPLND and ePLND was 22.2% vs 62.2% ($P = 0.035$). 10-year CSS for lPLND and ePLND was 52.6% (vs.) 83.6% ($P = 0.199$). In addition to affording valuable staging information, ePLND may confer a therapeutic benefit to patients found to have positive LNs at the time of RP. |
| | | ePLND | 2,279 | NA | 14.6 | 73, 3.2% | 26.0 | | 120 | |
| Chenam et al. 2018 | 2008–2012, retrospective | lPLND | 326 | Intermediate (78.2%), High (21.2%) | 6 | 11, 3.4% | 28.5 | BCRFS | 54 | 3- and 5-year BCRFS for lPLND and ePLND was 75% and 85% ($P = 0.01$), and 67% and 76% ($P = 0.10$). ePLND was associated with higher 5-year BCRFS in node-negative patients (84% (vs.) 68%, $P = 0.0005$) and intermediate-risk patients (93% (vs.) 80%, $P = 0.0002$). ePLND improve LN yield and detection of positive LNs. This study suggests a reduced risk of BCR for robotic ePLND in intermediate risk and node-negative patients. |
| | | ePLND | 258 | Intermediate (70.9%), High (29.1%) | 20 | 39, 15.1% | 20.5 | | 46 | |
| Yang et al. 2021 | 2010–2015, retrospective | PLND (NRN <12) | 6,200 | NA | 5 | 353, 5.7% | NA | CSS<br>OS | 33 | NRN was not an independent predictor of OS ($P = 0.564$) and was not an independent predictor of CSS in any LNI risk subgroup (all $P > 0.05$). However, in patients with a probability of LNI ≥37 using the 2012 Briganti nomogram, multivariate analyses showed that increased NRN was associated with improved OS ($P = 0.002$). ePLND might be associated with improved survival in prostate cancer patients with a high risk of LNI, which supports the use of ePLND in highly selected prostate cancer patients. |
| | | Extensive PLND (NRN ≥12) | 6,200 | NA | 16 | 844, 13.6% | NA | | 33 | |
| Morizan et al. 2022 | 2010–2019, retrospective | lPLND | 161 | Intermediate (48.4%), High (39.1%) | 8 | 1, 0.6% | 20.5 | BCRFS | 67.2 | A significantly better BCRFS was observed in the ePLND group than in the lPLND group in the intermediate- or higher-risk groups ($P = 0.001$) using the D'Amico risk classification |
| | | ePLND | 217 | Intermediate (8.3%), High (91.7%) | 18 | 17, 7.8% | 16.6 | | 67.2 | |

(*continued on next page*)

**Table 3** (*continued*)

| Study | Study period | Extent of the PLND | Cohort size | Risk category | NRN (median) | Number of patients with positive nodes (*n*, %) | Positive margin rate (%) | Outcome measure | Follow-up (median months) | Oncological outcomes and conclusions |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | and the percentage of positive biopsy cores.<br>According to Tottori risk classification, BCR may be less likely to occur when ePLND is performed during robotic RP for patients with localized prostate cancer at intermediate risk or higher. |
| Lestingi et al. 2021 | 2012–2016, RCT | lPLND | 150 | Intermediate (63.0%), High (37.0%) | 3 | 5, 3.4% | 37 | BCRFS | 53.9 | Differences in early oncological outcomes were not demonstrated. However, median BCRFS was 12.34 months in the lPLND group and not reached in the ePLND group (HR: 0.48, 95% CI: 0.26–0.91; $P = 0.024$) in patients diagnosed with ISUP grade groups 3–5.<br>Subgroup analysis suggests ePLND provides a potential BCRFS benefit in patients diagnosed with ISUP grade groups 3–5. |
| | | ePLND | 150 | Intermediate (62.0%), High (38.0%) | 17 | 25, 17% | 44 | | 53.9 | |

BCR, biochemical recurrence; BCRFS, biochemical recurrence-free survival; CSM, cancer-specific mortality; CSS, cancer-specific survival; ePLND, extended pelvic lymph node dissection; ISUP, International Society of Urological Pathology; lPLND, limited pelvic lymph node dissection; LN, lymph node; LNI, lymph node invasion; MFS, metastasis-free survival; NA, not applicable; NRN, number of removed lymph nodes; OS, overall survival; PLND, pelvic lymph node dissection; RCT, randomized controlled trial; RP, radical prostatectomy; sPLND, standard pelvic lymph node dissection.

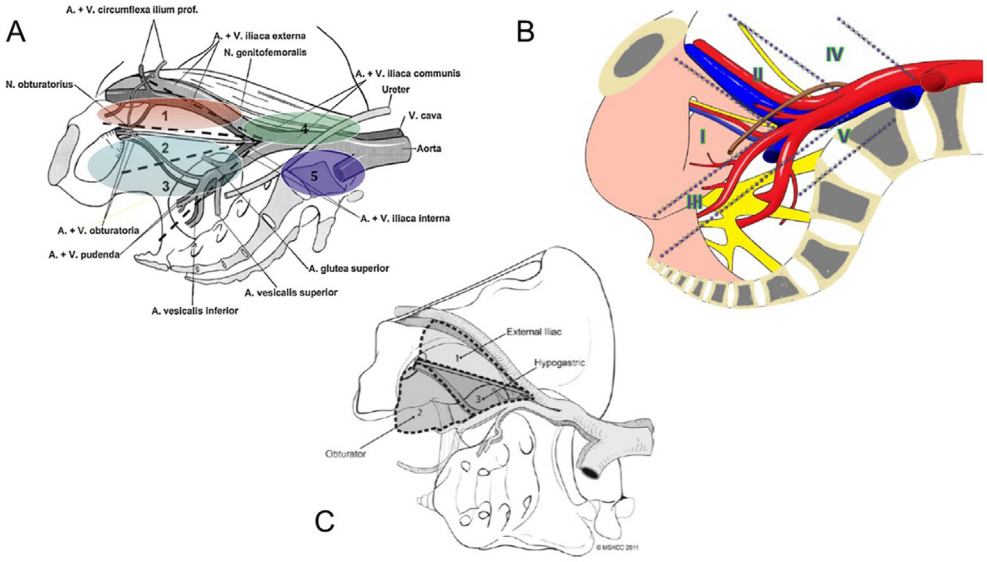


**Figure 1.** Typical extent of PLND reported previously.
The anatomic limits of PLND include area 1 (limited PLND), areas 1–3 (standard PLND), areas 1–4 (extended PLND), and areas 1–5 (superextended PLND) (Ploussard G, et al. Eur Urol 2014) (A). The anatomical areas to define the extent of dissection include I (obturator nodes), II (external iliac nodes), III (internal iliac nodes), IV (common iliac nodes), and V (presacral nodes) (Fassati N, et al. Eur Urol.2017) (B). (C) The anatomical boundaries of the lymph node packets include 1. external iliac area, extending from the external iliac vein ventral to obturator nerve and from the vein bifurcation to the pelvic floor at Cooper's ligament, including the ilioinguinal lymph node; 2. obturator area, which is below the obturator nerve medial to the obturator vessels between the bladder wall and the endopelvic fascia; and 3. Hypogastric area, which is also below the obturator nerve, was cephalad to the obturator packet and between the psoas muscle laterally and the hypogastric artery medially, including the tissue among the branches of the artery up to its origin at the bifurcation of the common iliac artery (Godoy G, et al. J Urol. 2012)
PLND, pelvic lymph node dissection.

Another important issue is the lack of clear selection criteria for patients who should undergo PLND during RP. Various risk classifications and nomograms have been proposed as patient selection criteria for PLND, and individual physicians decide which selection criteria to use.[3,4,7,18,19,26,66] The current standard is to perform ePLND during RP for patients with intermediate- to high-risk localized prostate cancer. However, the cohorts within this group that are expected to have beneficial oncological outcomes, including improved BCRFS, are unclear. We previously proposed the Tottori risk classification using the D'Amico risk classification and the percentage of positive biopsy cores for the evaluation of oncological outcomes using ePLND during RP.[25] In this study, no differences in the beneficial effects on BCRFS between ePLND and lPLND were detected in intermediate- to high-risk patients based on the D'Amico risk classification. However, a new classification of the same cohort, adding the percentage of positive biopsy cores to the D'Amico risk classification, confirmed the benefit of ePLND in reducing BCR. Similarly, Yang et al. showed that patients with a probability of LNI $\geq$ 37 based on the 2012-Briganti nomogram had better OS in the group with $\geq$ 12 NRNs than in the group with < 12 NRNs, although the difference was not significant for the overall cohort.[61] Furthermore, the RCT by Lestingi et al. showed no benefits of ePNLD on BCRFS in the overall cohort. However, a subanalysis of patients diagnosed with International Society of Urological Pathology grade 3–5 demonstrated significantly better BCRFS after ePLND than the benefits after lPLND.[51] Therefore, focusing on a relatively high-grade cohort is important for the efficacy of surgical therapy with ePLND alone.

## 8. Therapeutic value of performing ePLND in advanced prostate cancer patients

Shiota et al. reviewed prognoses in patients with pN1 prostate cancer and summarized the effects of adjuvant therapy on BCRFS, which varied from 28% to 61% at 5 years.[47] RFS and MFS were 55%–84% and 65%–80% at 10 years, and CSS and OS were approximately 80% and 70% at 10 years, respectively.[47] LNI has a strong unfavorable impact on the prognosis of patients with prostate cancer, including BCR and CSS.[5,6,25,39,53,54,59,64] However, RP and ePLND were performed aggressively in patients with advanced prostate cancers as part of a multimodal approach [67,68] because some patients with prostate cancer with LNI can experience a durable long-term MFS and CSS.[55,69] The efficacy of postoperative adjuvant ADT and RT has been demonstrated in several reports.[70-76] From these results, the addition of RT to immediate ADT may result in favorable disease control. When LNI is observed after RP with ePLND, many urologists may decide on additional treatment based on the recommendations of the European Association of Urology guidelines.[3] However, these recommendations are weak and are based on nodal involvement characteristics, as follows: (1) offer adjuvant ADT; (2) offer adjuvant ADT with additional RT; and (3) offer observation (expectant management) after ePLND and $\leq$ 2 nodes with microscopic involvement and a PSA value of <0.1 ng/mL and absence of extranodal extension.[3]

Mallikarjunappa et al. did not observe any patients with pN1 when they performed PLND in 42 patients with a preoperative diagnosis of advanced/high-grade prostate cancer.[77] Ghali et al. performed RP with PLND in 866 patients with a preoperative diagnosis of positive lymph nodes and approximately 18.4% of cases were pN0, suggesting the importance of RP with PLND for these patients.[78] Because preoperative diagnosis is not always accurate even with PMSA PET,[17,79] performing RP with ePLND, even for very-high-risk locally advanced prostate cancer patients, is reasonable. Although a gold standard treatment strategy for LNI in patients with prostate cancer has not been established, obtaining an accurate diagnosis of LNI by ePLND is important and allows for additional postoperative therapeutic options, which may be beneficial in the long postoperative life of patients with prostate cancer.

## 9. Conclusion

The most accurate method for diagnosing LNI is ePLND, and LNI is unfavorable for patients with prostate cancer who underwent RP. The decision to perform RP with ePLND should be carefully considered after informing the patient about the advantages and disadvantages of the procedure and the surgical and nonsurgical treatment options. Focusing on patients with prostate cancer who have relatively high-grade tumors may be important for determining the efficacy of surgical therapy with ePLND. The optimal patient selection criteria for performing PLND and the standard extent of PLND should be established in the future.

## Conflicts of interest

All authors declare no potential conflicts of interest to disclose.

## Funding/support and role of sponsor

None.

## Ethics statement

This study was conducted in accordance with the Declaration of Helsinki.

## Acknowledgments

None.

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