

# Extended lymph node dissection in robotic radical prostatectomy: Current status

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## ABSTRACT

**Introduction:** The role and extent of extended pelvic lymph node dissection (ePLND) during radical prostatectomy (RP) for prostate cancer patients remains unclear.

**Materials and Methods:** A PubMed literature search was performed for studies reporting on treatment regimens and outcomes in patients with prostate cancer treated by RP and extended lymph node dissection between 1999 and 2013.

**Results:** Studies have shown that RP can improve progression-free and overall survival in patients with lymph node-positive prostate cancer. While this finding requires further validation, it does allow urologists to question the former treatment paradigm of aborting surgery when lymph node invasion from prostate cancer occurred, especially in patients with limited lymph node tumor infiltration. Studies show that intermediate- and high-risk patients should undergo ePLND up to the common iliac arteries in order to improve nodal staging.

**Conclusions:** Evidence from the literature suggests that RP with ePLND improves survival in lymph node-positive prostate cancer. While studies have shown promising results, further improvements and understanding of the surgical technique and post-operative treatment are required to improve treatment for prostate cancer patients with lymph node involvement.

**Key words:** Lymph node-positive metastasis, pelvic lymph node dissection, prostate cancer, radical prostatectomy

## INTRODUCTION

The role of pelvic lymph node dissection (PLND) during radical prostatectomy (RP) for prostate cancer has evolved over time. Initially, PLND was used for staging purposes. If positive nodes were found intraoperatively, surgery was abandoned as it was felt that these patients had metastatic disease and therefore not curable with RP. However, the extent of PLND has long been called into debate even as a diagnostic purpose as one cannot truly conclude that there are no positive nodes if all potential nodal regions are not dissected.<sup>[1,2]</sup>

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While the diagnostic and prognostic role of PLND during RP is clear, its therapeutic benefit remains debatable.<sup>[3,4]</sup> Additionally, patients with high-risk, locally advanced prostate cancer or those felt to have clinical lymph node-positive disease were not offered RP and instead would receive primary androgen deprivation therapy (ADT).<sup>[5]</sup> Over the past couple of decades, studies have demonstrated improved survival in patients with positive lymph nodes who underwent RP and PLND over those just receiving ADT.<sup>[6-10]</sup> While this method of treatment was used, studies still investigated the role of extended pelvic lymph node dissection (ePLND) during RP for higher risk patients.<sup>[1,2,11]</sup> The extent of PLND is important as studies have demonstrated that it is associated with the detection rates of lymph nodes metastasis.<sup>[1,11,12]</sup> In addition, current guidelines including the EAU, AUA and NCCN recommend ePLND in patients at risk of lymph node metastasis.<sup>[13-15]</sup>

Some authors have demonstrated that the number of lymph nodes removed or the extent of PLND is associated with oncological outcomes, supporting the possible therapeutic benefits of PLND.<sup>[4,16-18]</sup> In contrast, several studies have been unable to find any evidence that ePLND has a beneficial impact on prostate cancer outcomes.<sup>[19-21]</sup> To further complicate matters, additional problems arise regarding the different extents of PLND and which is the

acceptable definition of ePLND.<sup>[22]</sup> Additionally, many different nomograms have been developed to help identify which patients require a PLND; however, there are many problems with these as most used only a standard template and therefore underestimate the incidence of lymph node disease.<sup>[23,24]</sup>

As the robotic approach to RP improved and exceeded the utilization of traditional open RP, the technique for PLND dissection also followed. Studies have demonstrated that robotic PLND can achieve similar nodal yield and oncologic outcomes to open RP.<sup>[25]</sup> Therefore, studies in the open RP literature can also be applied to the robotic technique. It does not appear that there are any increased complications with the robotic technique.

These findings have re-affirmed the difficulties in not only establishing the patient population that should undergo PLND but also the extent of acceptable lymph node dissection. Herein, we attempt to provide some clarity and evaluate the current status of ePLND in RP in patients with prostate cancer.

## MATERIALS AND METHODS

A systematic review of the literature through PubMed was performed to identify studies reporting on ePLND during RP for prostate cancer between 1996 and 2013. Medline was searched using one or several combinations of the following items: Extended, lymph node dissection, RP and robotic. Over 324 records were initially identified through database research. Further selection of studies followed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.<sup>[26]</sup> From these filtered studies, we then sought out studies that allowed us to compare these attributes among studies: Lymph node dissection, RP, extended lymph node dissection, prostate cancer and RP.

## EXTENT OF LYMPH NODE DISSECTION

A thorough PLND provides diagnostic and prognostic information for staging. It has been shown that the estimated number of lymph nodes necessary for optimal staging accuracy ranges between 20 and 28.<sup>[27]</sup> Abdollah and colleagues determined that the removal of 20 nodes resulted in accurate staging in 90% of their patients.<sup>[28]</sup> Actual data on nodal counts for the different dissection templates have been found. Allaf *et al.*<sup>[29]</sup> and Touijer *et al.*<sup>[30]</sup> found a significant difference in lymph nodes yielded between a standard PLND and ePLND to a limited PLND, and demonstrated that standard and ePLNDs yielded 11.6 and 12 positive lymph nodes, while the limited dissection yielded 8.9 and 10.1 positive lymph nodes, respectively. These studies show that more extensive dissections result in an increasing lymph node yield and

that an increasing nodal yield detects higher rates of lymph node involvement.

Lymphatic drainage from the prostate has been shown to extend to the external iliac nodes, the hypogastric and obturator nodes and up to the subaortic sacral nodes. However, there remains uncertainty regarding which of these nodal groups represents the primary landing site for metastatic prostate cancer and therefore which packets should be removed during RP.

Anatomic definitions of PLND define a limited/standard PLND as dissection of the lymphatics from the external iliac vein and obturator fossa. Throughout the literature, there are differing definitions for ePLND, causing much confusion when comparing studies. All include the external and internal iliac vessels with obturator fossa; however, they differ in their inclusion and extent of common iliacs and presacral nodes. Heidenreich *et al.* consider ePLND comprising dissection of the external and internal vessels up to the iliac bifurcation,<sup>[1]</sup> while Briganti *et al.* define ePLND as dissection up to the common iliac as well as the presacral lymph nodes.<sup>[31]</sup> The more common definition of ePLND includes the external iliac vein, obturator fossa, hypogastric vessels and common iliac up to the crossing of the ureter.<sup>[32-34]</sup> Some advocate removal of the subaortic and presacral nodes as part of an ePLND.<sup>[35,36]</sup>

While there are differences in defining ePLND, general agreement has been reached that should a PLND be indicated, it should be with an extended template and not with a limited/standard one.<sup>[14,37]</sup> The limited/standard dissection is associated with high false-negative rates in the detection of positive lymph nodes as it misses primary landing sites of disease.<sup>[1,11,27]</sup> Bader *et al.* conducted a study observing metastatic prostate cancer deposits in 88 high-risk men with lymph node + disease after RP and ePLND.<sup>[11]</sup> They found that the most common sites for metastasis were obturator fossa (60%), internal iliac (hypogastric) (58%) and external iliac nodal areas (36%). There were 19% who had metastasis in the hypogastric region alone. Godoy and colleagues also found that 37% of patients had positive nodes in the external iliac area above the obturator nerve.<sup>[38]</sup> This wide spread of lymphatic metastasis was also found in a recent prospective study of 19 very high-risk patients who were found to have lymph node + disease, with the most common affected nodes being the obturator (89%), external iliac (83%), common iliac (77%), internal iliac (44%) and presacral (33%) regions.<sup>[31]</sup> Heidenreich and colleagues conducted ePLND on 103 patients that comprised dissection up to the iliac bifurcation, and found that for high-risk patients (prostate-specific antigen [PSA] >10.5 ng/mL and biopsy Gleason 7 or greater), this definition of ePLND was able to detect metastasis in 26.2% of the patients.<sup>[1]</sup>

Lymph node mapping studies have found that ePLND should include the external and internal vessels including the oburator fossa and the common iliac up to the crossing of the ureter.<sup>[39]</sup> Heck *et al.*<sup>[39]</sup> and Mattei *et al.*<sup>[40]</sup> described a multimodality technique using a single-photon emission combined with computed tomography or magnetic resonance imaging to identify nodes potentially harboring disease. They found that a limited PLND resected only one-third of the primary lymphatic landing sites while an ePLND up to the ureteric crossing lead to the removal of approximately 75% of all nodes potentially harboring metastatic spread.<sup>[40]</sup> Addition of the presacral lymph nodes only added 8% additional nodal yield. Another study in 74 patients with localized prostate cancer scheduled to undergo RP and PLND first had patients obtain a technetium Tc 99m scintigraphy and single-photon emission computed tomography.<sup>[41]</sup> A guided PLND was followed by a very extended ePLND. A total of 470 nodes were detected scintigraphically and 91 positive lymph nodes were found in 34 of the 74 patients during ePLND (46%). If the ePLND only went up to the common iliac chain, 32 of the 34 patients (94%) would have been correctly staged, but only 26 of the 34 patients (77%) would have had all their metastatic sites removed. Had the presacral lymph nodes been added to the ePLND, the number would have increased from 77% to 97% based on the lymphadenectomy template. Therefore, the role of a presacral PLND remains unclear but is not necessary unless a high likelihood of lymph node involvement is suspected.

Supporting the idea of using an extended field of resection, Heidenreich *et al.* emphasized the value of extended compared with standard PLND during RP. They found that ePLND is associated with a higher rate of LN metastases outside the fields of standard lymphadenectomy in cases of clinically localized prostate cancer.<sup>[16]</sup> In addition, a recent randomized prospective study of standard PLND vs ePLND (excluding presacral) looked at biochemical progression-free survival (BPFS) outcomes in 360 patients with clinically localized prostate cancer undergoing open RP.<sup>[42]</sup> The median nodal yield was 10 and 23, respectively, and the 5-year BPFS was not different in low-risk patients undergoing standard PLND or ePLND (90.1% and 91.3%, respectively,  $P = 0.807$ ); however, in intermediate-risk patients, a difference was seen (73.1% vs. 85.7%, respectively,  $P = 0.042$ ) that was even more dramatic in high-risk patients (51.1% vs. 71.4%, respectively,  $P = 0.036$ ).<sup>[42]</sup> Therefore, patients with intermediate- and high-risk disease should be undergoing ePLND.

### PATIENT SELECTION FOR PELVIC NODE DISSECTION

The decision to perform PLND during RP remains difficult because it is unclear which patients may benefit. Imaging techniques do not accurately identify lymph node metastasis and should not be relied upon to guide the decision for PLND. Several nomograms and tables have been developed

to predict the risk of lymph node invasion and determine which patients may benefit from PLND.<sup>[23,24,43-47]</sup> These tools can identify patients with a low risk of lymph node invasion and have contributed to a decrease in the utilization of routine PLND during RP.<sup>[48-50]</sup> However, it is important to note that many of these studies are based on standard PLND and may therefore significantly underestimate the true prevalence of lymph node invasion.<sup>[23,24]</sup>

Most nomograms predict pathologic stage using pre-operative clinical stage, biopsy Gleason score and pre-operative PSA.<sup>[43-47]</sup> The Partin tables were updated in 2007 to more accurately reflect the general stage shift toward less-advanced cancers.<sup>[51]</sup> This update demonstrated an accuracy of 89% in predicting pathologic stage in a large population of over 5000 patients in which 1% had positive lymph nodes. A more recent external validation of the Partin tables in 2010 examined the predictive ability of the tables in over 11,000 men selected from the National Cancer Institute Surveillance, Epidemiology and End Results database from 2004 to 2005 who underwent RP.<sup>[52]</sup> This study found that the area under the curve was 0.77 in predicting lymph node invasion in this expanded multicenter population. Haese and colleagues applied the Hamburg nomogram for predicting lymph node invasion to a similar dataset from John Hopkins and were able to externally validate their predictive model.<sup>[53]</sup> The Memorial Sloan-Kettering nomogram targets lymph node invasion that was based on standard PLND and data from multiple institutions.<sup>[44]</sup> This nomogram depicts a predictive accuracy of 78% based on over 5000 patients with a 3.7% rate of lymph node invasion.

An update to the Partin tables nomogram was released in 2012.<sup>[54]</sup> This updated the current nomogram for a contemporary cohort of patients. This study found no change in the distribution of the previous Partin nomogram, and the risk of lymph node-positive disease was significantly higher for Gleason 9–10 than 8. In addition, men with Gleason 6 disease or 3 + 4 disease have <2% risk of harboring lymph node-positive disease and may have lymphadenectomy omitted at RP.

Briganti and colleagues have created one of the few nomograms based on an ePLND and have argued that the probability of correctly identifying those with lymph node invasion is dependent on the number of nodes retrieved.<sup>[27]</sup> They were able to internally validate their conclusions as they reported an accuracy of 76% for 602 patients when using an ePLND.<sup>[23]</sup> To further validate that the Briganti nomogram is superior due to the use of an ePLND, Walz *et al.* compared this nomogram with the Cagiannos nomogram and the updated 2007 Partin tables, which both utilize a standard PLND.<sup>[55]</sup> In this study of 173 patients, a median of 15 nodes were removed. Twelve patients (6.9%) had lymph node invasion. The Briganti nomogram achieved a receiver operating characteristic curve of 0.88. When

using the Cagiannos nomogram and 2007 Partin tables, the receiver operating characteristic curve was 0.83 and 0.84, respectively. This demonstrated that the use of an ePLND can provide improved accuracy predictions as a standard PLND underestimates the true risk of lymph node invasion.

Using these nomograms and other available data, the American Urological Association (AUA), National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) have created guidelines for who should undergo PLND.<sup>[14]</sup> Lymph node-positive disease is detected in 5–6%, 20–25% and 30–40% of patient undergoing RP and ePLND with regard to low-, intermediate- and high-risk prostate cancer.<sup>[16]</sup> Therefore, the EAU guidelines recommend an ePLND during RP in patients with intermediate- and high-risk disease.<sup>[14]</sup> The NCCN has also made similar recommendations.<sup>[13]</sup>

### ROBOTIC LYMPH NODE DISSECTION

The surgical management of prostate cancer is a mainstay of therapy for men with localized disease.<sup>[56]</sup> Robot-assisted RP (RARP) has become more popular than traditional open RP due to improved post-operative recovery, diminished blood loss and improved quality-of-life outcomes with minimally invasive RP.<sup>[57]</sup> Despite the comparable safety profile and overall feasibility of RARP compared with open RP, disparities in lymph node counts have been reported with PLND occurring more frequently with open RP.<sup>[58,59]</sup> When performed properly, RARP with PLND can achieve a lymph node yield similar to that achieved in open PLND without increasing the risk of complications.<sup>[27,49,60]</sup> Robotic ePLND can safely achieve lymph node yields of 16–24 nodes.<sup>[33,61]</sup> Several studies have supported the technical feasibility of robotic PLND, especially ePLND, and there is no reason to believe that this approach is inferior to the open technique.<sup>[62-65]</sup>

### COMPLICATIONS OF PELVIC LYMPH NODE DISSECTION

Complications can arise from PLND, with an occurrence rate of 5–50%. The most common complication is lymphocele formation, which is found on post-operative imaging, with most being clinically insignificant but with some requiring treatment.<sup>[11,35,36,66]</sup> Other more rare complications include vascular injury, thrombus, bleeding, nerve damage and ureteral injury. The general notion is that the more extended a dissection is, the higher is the potential for complications; however, this is not necessarily true.

Briganti *et al.* compared ePLND with limited PLND dissection and found a higher rate of complications with ePLND (19.8% vs. 8.2%), and the rate of lymphocele formation rates was higher in ePLND (10.3% and 4.6%, respectively,  $P = 0.01$ ).<sup>[66]</sup> Clark *et al.* randomly assigned 123 patients

to have extended PLND on one side and a limited PLND on the other side during RP and found a three-fold higher rate of complications on the side undergoing ePLND.<sup>[35]</sup> Heidenreich *et al.* reported on 203 patients comparing standard PLND (100) with ePLND (103), with similar rates of lymphoceles (9% vs. 10.6%, respectively).<sup>[36]</sup> The choice of using ePLND over standard PLND can also lead to an increased operative room (OR) time and possibly increased length of hospital stay. It has been suggested that a potential complication for ePLND is a reduction in sexual function; however, this has not been proven and not considered a real risk of ePLND.<sup>[67]</sup>

Robotic PLND has been well described and is very feasible and safe. Yuh *et al.* reported no increased rate of minor or major complications for ePLND versus limited PLND (22.8% minor and 4.5% major vs. 22.8% minor and 6.9% major, respectively). Additionally, there was no difference in the rate of lymphoceles among limited PLND and ePLND (2.5% and 2.9%).<sup>[68]</sup> They did demonstrate a slightly longer operative time and possibly a longer hospital stay; however, the differences were minimal. Another study also comparing robotic ePLND with standard PLND did not find a difference in the overall complications (16.7% and 18.2%,  $P = 0.41$ ).<sup>[69]</sup>

### CONCLUSIONS

RARP has demonstrated efficacy for the treatment of patients with prostate cancer. The question is whether to perform a lymph node dissection and using what template? This is more clear now than in the past for patients with intermediate- and high-risk disease. These patients should undergo extended PLND with meticulous dissection and thorough removal of lymphatic tissues with the following limits of dissection: Proximally, the common iliac vessels distal to the crossing of the ureter, the external iliac vessels laterally to the genitofemoral nerve and distally to the node of cloquet, the internal iliac vessels medially and the obturator fossa. Inclusion of the presacral and subaortic packet remains unclear, but may be beneficial in patients with greater concern for lymph node involvement realizing that there may be slightly greater complications. This template can be achieved safely and effectively with a robotic approach.

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