CURRENT STATUS OF PELVIC LYMPH NODE DISSECTION IN PROSTATE CANCER: THE NEW YORK PLND NOMOGRAM

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Objective: Controversy persists concerning the role of pelvic lymph node dissection (PLND) in patients with clinically localized prostate cancer undergoing radical prostatectomy. The aim of this review is to critically evaluate the current status on PLND in prostate cancer.

Methods: A review of the literature was performed concerning radical prostatectomy and PLND with respect to oncological outcome, associated complications, nodal yield, indications and minimal number of nodes required.

Results: PLND is still the modality of choice for detecting lymph node metastasis in prostate cancer. Current imaging techniques are not accurate enough for detecting nodal metastases. Extended PLND has complications that increase with extent of dissection. Nodal yield at PLND is directly related to the lymph node invasion (LNI) rate and greater nodal yield is associated with superior staging accuracy. Based on MSKCC nomogram and in conjunction with prospective confirmation studies a novel nomogram (the New York nomogram) was designed.

Conclusion: Removing at least 10 lymph nodes is recommended to detect LNI. For patients with high and intermediate risk disease, extended PLND at least for external iliac, obturator and hypogastric lymph nodes should be performed during radical prostatectomy. However, for patients with low risk disease, PLND is not necessary and is not recommended, because the chance of metastasis is low.

Key Words: lymph node metastasis, localized prostate cancer, pelvic lymph node dissection, radical prostatectomy, frozen section

INTRODUCTION

Pelvic lymph node dissection (PLND) has been performed as a part of radical prostatectomy since more than 30 years ago. It represents accurate staging procedure for presence of lymph node invasion (LNI) in clinically localized prostate cancer.1 But the role of PLND in prostate cancer remains controversial. Although it is generally accepted that PLND provides important information regarding pathological tumor staging and prognosis, the extent of PLND (limited versus extended) and the candidates most suitable for this procedure are still a matter of debate. The prevalence of LNI ranges from 1.1% to 26% and is related to PLND extent.2-4 Indeed, extended PLNDs identify metastases that would not otherwise be detected by a limited PLND.5 No consensus has yet been reached about the extent of PLND or, more specifically, the number of lymph nodes that should be removed to achieve optimal cancer staging.2-4

Some authors based their decision on preoperative nomograms considering preoperative prostate-specific antigen (PSA) serum levels, clinical stage, number of positive biopsies, and Gleason score of prostate biopsies for risk calculations6-8 and others prefer performing PLND in all patients. Two nomograms based on the data of extended PLND have been published.9,10 In these nomograms the calculations have been based on PLNDs with a mean of < 10 lymph nodes removed.

METHODS

A review of the literature was performed concerning radical prostatectomy and PLND with respect to oncological outcome, associated complications, nodal
yield, indications and minimal number of nodes required.

Prostate gland lymphatic system and types of PLND

Prostate gland lymphatic system includes periprostatic subcapsular network and three groups of ducts: the ascending duct from the cranial gland running to the external iliac nodes, the lateral duct running to the hypogastric nodes, and the posterior duct running to the lateral and subaortic sacral nodes of the promontory.

There are multiple variations of PLND: limited PLND (lPLND) can be considered for the removal of the lymphatic tissue inferior to the bifurcation of the common iliac artery, bound inferiorly by the femoral canal, laterally by the pelvic sidewall, and medially and inferiorly by obturator nerve, collectively (external iliac nodes), standard PLND (sPLND) consists of a lPLND and all lymphatic tissue in the obturator fossa, deep and proximal to the obturator nerve (the obturator nodes) and extended PLND (ePLND) should include both of the above along with all fibrofatty tissue surrounding the hypogastric vessels posteriorly (the hypogastric nodes), Figure 1.11-15

In a study by Bader et al2 on metastatic cancer deposits from a cohort of 88 relatively high risk men with node positive disease after radical prostatectomy and extended pelvic lymphadenectomy, the most common site for metastasis (60%) was the obturator fossa, however, 58% had deposits in the internal iliac (hypogastric) and 36% in the external iliac nodal areas, while 19% had positive nodes in the hypogastric distribution alone. Allaf et al16 found a significant difference in lymph nodes yield between a standard PLND/extended PLND and limited PLND in open radical prostatectomy. Mattei et al17 have used a multimodality technique to precise mapping of the primary prostatic lymphatic metastases landing site. They have suggested that PLND for prostate cancer should include not only the external and obturator region as well as the portions medial and lateral to the internal iliac vessels, but also the common iliac lymph nodes at least up to the ureteric crossing, thus removing approximately 75% of all nodes potentially harboring metastasis.

Number of nodes

Heidenreich et al18 found that the number of dissected lymph nodes is directly associated with an increase in the detection of positive lymph nodes. Weingartner et al19 in a cadaveric study compared nodal counts in cadavers without prostate cancer subjected to sPLND with actual counts resected during radical prostatectomy and sPLND. They found that a mean of 20 dissected pelvic lymph nodes can be considered a representative sampling that enables exact staging of prostate cancer. Estimates of lymph node counts

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**Figure 1.** Pelvic lymph node dissection regions. External iliac vein lymph nodes group, obturator fossa lymph nodes and internal iliac (hypogastric) lymph nodes (1, 2 and 3 respectively).
necessary for optimal staging accuracy have ranged from 20 to 28\textsuperscript{19}.

In a study by Briganti et al\textsuperscript{20} 858 patients aged 45 to 85 years which predominantly had been treated with ePLND before radical retropubic prostatectomy participated. The pretreatment PSA level was 0.24 ng/mL to 49.9 ng/mL, lesions were stage T1c or T2 with a biopsy Gleason score of ≤ 6 or 7. 2 to 40 nodes were removed. They concluded that the LNI rate increased with the number of removed nodes, Figure 2, and removing of 10 nodes or less yields < 10% ability to detect LNI, however, 28 nodes yields 90% ability to detect LNI.\textsuperscript{20}

In a comparison between limited and extended laparoscopic PLNDs by Stone et al\textsuperscript{21} have been demonstrated a 2-fold increase in the number of removed lymph nodes (9 versus 18) and a 3-fold increase in the frequency of lymph node metastases (7% versus 23%).

Heidenreich et al have reported that a mean of 28 and 11 lymph nodes is removed by the extended and the limited technique, respectively; the number of positive lymph nodes increased from 12% to 26%.\textsuperscript{13,14} These data have been supported by Wawroschek et al\textsuperscript{22} and Briganti et al\textsuperscript{3,10} They reported positive lymph nodes in 32% and 20% of their patients, respectively. In another study by Schumacher et al\textsuperscript{23} have been demonstrated that the incidence of positive nodes in patients with clinically localized prostate cancer, a serum PSA < 10 ng/mL and a Gleason score ≥ 7 in the prostatectomy specimen was 25% after extended PLND. They evaluated 231 patients with a median serum PSA of 6.7 ng/mL and a median age of 62 years. They removed median of 20 (range 10-72) nodes. Positive nodes were found in 26 of 231 patients (11%), the majority of them (81%) had a Gleason score ≥ 7 in the surgical specimen. Of the patients with a Gleason score ≥ 7 in the prostatectomy specimen 25% had positive nodes, whereas only 3% with a Gleason score ≤ 6 were node positive.\textsuperscript{23} In summary on the basis of previous studies, it is recommended to remove at least 10 lymph nodes to detect LNI in prostate cancer.

**Patient selection for PLND**

Conventional computed tomography (CT) and magnetic resonance imaging (MRI) as imaging techniques are unreliable for the detection of small metastatic deposits (< 1 cm-1.5 cm) or for detecting pathologic enlargement or predicting pathologic lymph node status\textsuperscript{19} and therefore pelvic lymphadenectomy remains the gold standard for detecting LNI in prostate cancer.

Updated Partin tables,\textsuperscript{24} preoperative nomograms\textsuperscript{6,7} and Memorial Sloan-Kettering nomograms\textsuperscript{25} do not recommend performing PLND in patients with a preoperative PSA serum level < 10 ng/mL, a biopsy Gleason score < 7, and a clinical stage ≤ 2a because the incidence of positive lymph nodes is said to be approximately only 1%-5%,\textsuperscript{6-8} Figure 3. In a study by Schumacher et al\textsuperscript{23} the incidence of positive nodes in patients with clinically localized prostate cancer, a serum PSA < 10 ng/mL and a Gleason score ≥ 7 in the prostatectomy specimen was 25% after extended PLND. Crawford et al\textsuperscript{6} identified biopsy Gleason score ≤ 6, a preoperative PSA serum level ≤ 10.6 ng/mL, and stage cT1c as predictors for low risk lymph node metastases.

In a recent study by Yu et al\textsuperscript{26} the Partin tables have been validated. They examined the predictive ability of the tables in 11,185 men selected from the National Cancer Institute Surveillance, Epidemiology and End Results database from 2004 to 2005 who

![Figure 3. The New York PLND nomogram.](image-url)
underwent radical prostatectomy. Cagiannos et al developed a predictive nomogram that was based on sPLND and data from multiple institutions. Their nomogram had predictive accuracy of 0.78 based on 5510 patients and a 3.7% rate of LNI. Conrad et al published a diagnostic algorithm based on a variety of preoperative parameters of 600 patients undergoing radical prostatectomy. On the basis of number of biopsy cores in prostate cancer with Gleason score ≥ 7, three risk groups were identified. Risk for lymph node metastases was 45%, 19%, or 2% if 4-6, 1-3, or no biopsy was involved with Gleason score 8-10 prostate cancer respectively.

Allaf et al reported a significant diagnostic benefit of ePLND in a group of 2135 men with low risk prostate cancer compared with a group of 1835 men undergoing radical prostatectomy and limited PLND. Extended PLND removed more lymph nodes (11.6 versus 8.9, p < 0.0001) and detected more lymph node metastases (3.2% versus 1.1%, p < 0.0001) than limited PLND. Briganti et al have created a multivariable nomogram based on ePLND in patients with low risk and intermediate/high risk prostate cancer and have argued that the probability of correctly identifying those with LNI is, in part, dependent on the number of nodes sampled. The nomogram for low risk prostate cancer was developed in 781 patients and internally validated in 200 patients; multivariate analysis identified clinical stage, biopsy Gleason sum, and number of lymph nodes removed as significant predictors for occult lymphonodular metastases, and resulted in an accuracy of 78.6%.

In summary and on the basis of preoperative nomograms we recommend performing extended PLND in patients with high and intermediate risk disease, at least for external iliac, obturator and hypogastic lymph nodes, because the risk of positive lymph node in these patients is ≥ 2%. However, for patients with low risk disease, we recommend performing no PLND at all, because the chance of metastasis by most nomograms appears to range between 0% and 4% in these patients, Figure 3.

**Impact of PLND on survival**

The possibility of therapeutic benefit for pelvic lymphadenectomy has been suggested by some studies, but the results have been inconsistent.

Briganti et al demonstrated that patients with two or fewer positive lymph nodes on the final stage of disease had significantly better outcomes at 15 years compared with those with more than two positive lymph nodes. Palapattu et al found that 52% of men with a positive node density of less than 15%, a Gleason score ≤ 7, and negative seminal vesicle invasion remained free of biochemical failure (BCF) at 5 years. Allaf et al reported the therapeutic benefit of ePLND in patients with limited lymph node disease. Among men with lymph node metastases involving less than 15% of extracted nodes, the 5 year PSA progression-free survival was 43% versus 10% for the lPLND (p = 0.01). In another study, Daneshmand et al found that a positive node density of less than 20% improved disease progression rates and survival, Table 1.

<table>
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<tr>
<th>Study</th>
<th>No. of patients (yr)</th>
<th>Median follow up</th>
<th>CSS % 5 yr</th>
<th>CSS % 10 yr</th>
<th>BCR % 5 yr</th>
<th>BCR % 10 yr</th>
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**CSS = cancer-specific survival; BCR = biochemical recurrence rate**

*with adjuvant therapy*
Joslyn and Konety\textsuperscript{22} demonstrated that patients undergoing excision of at least four lymph nodes (node-positive and node-negative patients) or more than 10 nodes (only node-negative patients) had a lower risk of prostate cancer-specific death at 10 years than did those who did not undergo lymphadenectomy. They concluded that performing ePLND in patients undergoing radical prostatectomy could improve the accuracy of staging and reduce the risk of prostate cancer-specific death in the long term.

However, some studies suggest that the prevalence of node-positive disease may be routinely underestimated. Ross et al\textsuperscript{33} reported six of the 26 patients previously classified as N0 after radical prostatectomy and PLND to be positive for nodal involvement by superparamagnetic nanoparticle MRI. In another study Pagliarulo et al\textsuperscript{34} re-examined 3914 ‘negative’ nodes by immunohistochemistry in 274 pT3 patients. They found that 13.3\% of 180 patients who were originally defined as being N0 actually had lymph node metastasis. Survival rates in these patients were significantly poorer than patients who were truly lymph node negative.\textsuperscript{34}

With regard to biochemical recurrence rates of patients undergoing radical prostatectomy for low risk prostate cancer, some studies have suggested that lymph node dissection is apparently unnecessary.\textsuperscript{35,36}

Bhatta-dhar et al\textsuperscript{37} reviewed the records of 336 patients with favorable tumor characteristics (prostate-specific antigen 10 ng/mL or less, biopsy Gleason score 6 or less, and clinical stage T1 or T2) not receiving adjuvant or neoadjuvant therapy with (n = 140) and without (n = 196) PLND. They demonstrated that 6 year biochemical relapse-free rate for the PLND versus no-PLND group was 86\% and 88\%, respectively (p = 0.28) and concluded that omission of PLND in patients with favorable tumor characteristics does not adversely affect biochemical relapse rates. In a similar study Fergany et al\textsuperscript{38} compared biochemical relapse rates of 372 and 203 patients with low risk prostate cancer undergoing radical prostatectomy with and without PLND, respectively. The 4 year progression free survival rates were 91\% and 97\% following radical prostatectomy with or without PLND, respectively.

Impact of frozen section in PLND

Pelvic lymph nodes excised at the time of PLND are often assessed intraoperatively using frozen section (FS) analysis and presence of lymph node metastasis is associated with poor prognosis in prostate cancer. Radical prostatectomy may be aborted if a nodal metastasis is found on FS, under the assumption that patients with metastatic cancer do not benefit from radical surgery.\textsuperscript{37} The routine FS during PLND is common but not uniformly used, and has been questioned by several studies.\textsuperscript{38,39} In addition, the role of FS in identifying small lymph node metastases is in question.\textsuperscript{40}

In a large cohort, Song et al\textsuperscript{40} evaluated the accuracy of frozen section for detection of pelvic lymph node metastases in 349 men undergoing bilateral PLND. The number of lymph nodes sampled during surgery ranged from one (in 65\% of patients) to three or more (11\%). Twenty-eight cases of metastatic carcinoma were detected that 11 of which were identified during FS analysis, but FS failed to detect the other 17 cases. All of 17 false negatives, contained metastases smaller than 5 mm. The sensitivity of FS analysis was 36\%, with a false-negative rate of 64\% in their study. They concluded that frozen section is highly sensitive for detection of large metastases, but poorly sensitive for detection of metastases smaller than 5 mm. Song and coworkers recommended that a two-step approach applied to routine FS: an initial gross examination, followed by confirmatory frozen section analysis only for grossly suspicious pelvic lymph nodes.\textsuperscript{40}

In summary FS analysis is not accurate enough for detection of pelvic lymph node metastasis in prostate cancer.

Complications

Pelvic lymph node dissection is a challenging surgery technically and may be associated with intraoperative and postoperative complications to range from 25 to 50\%.\textsuperscript{14,41-43} Commonly described complications are the subsequent formation of lymphocele (the most common), obturator nerve injury, vascular injury, venous thrombo-embolism, pulmonary emboli, and increased operating room time.\textsuperscript{14,41}

Clark et al\textsuperscript{41} compared complication rates by randomly assigning patients to have an ePLND on one side of the pelvis and an IPLND on the other in 123 patients undergoing open radical prostatectomy. They reported a nonsignificant but likely clinically relevant difference, in which the side with the ePLND had more complications. In another study by Briganti et al\textsuperscript{40} the complication rates between 767 ePLND patients and 196 IPLND patients have been compared. They found that in patients subjected to ePLND, the overall rate of complications was 19.8\% versus 8.2\% in those treated with IPLND (p < 0.001). However, in individual analyses of specific complications, lymphocele formation (drain output in excess of 50 mL/day for more than 7 days after catheter removal) rate was significantly higher after ePLND (10.3\% versus 4.6\%; p = 0.01).

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Heidenreich et al\(^3\) reported 9% of his ePLND cohort (average: 28 nodes) had at least one complication, which did not differ from a comparison group (8.7%), in which more-limited PLND was performed. In their study operating room time was significantly longer in patients subjected to more-extensive PLND (179 min versus 125 min; \(p < 0.03\)). With regard to laparoscopic PLND, Stone et al\(^{21}\) demonstrated higher complication rate of laparoscopic ePLND compared with laparoscopic IPLND (35.9% versus 2%; \(p < 0.001\)).

**Sentinel lymph node dissection - an alternative to ePLND**

Despite the obvious advantage, ePLND has certain morbidity and is a time consuming procedure. To decrease the morbidity of ePLND the concept of radioisotope-guided sentinel lymph node (SLN) dissection in prostate cancer was introduced and Wawroscheck et al\(^{22}\) validated it. They reported that sensitivity of the SLN staging was comparable to that of ePLND with a significant reduction in the dissection extend. SLN dissection method is a combination of imaging, surgery and histology techniques. There is no lower threshold of size in this method and SLN dissection can detect micro metastases smaller than 2 mm. Jeschke et al\(^{23}\) performed laparoscopic SLN dissection in 140 patients with clinically localized prostate cancer, preceding radical prostatectomy. Mean PSA level was 8.26 ng/mL and clinical stage was T1C in 84.4% and T2 in 14.8% of the patients. They reported SLN metastases in 13.5% of patients and similar sensitivity as extended PLND with limitations in prostate cancer staging. In summary, SLN dissection has lower morbidity than ePLND with similar sensitivity, however, should be the subject of more studies.

**Conclusion**

There is controversy about the role of PLND for prostate cancer. Novel mapping and imaging techniques such as MR lymphography with superparamagnetic nanoparticles, suggest that even with an ePLND, up to one third of metastases will be missed. For all patients with high and intermediate risk disease, extended PLND at least for external iliac, obturator and hypogastric lymph nodes should be performed during radical prostatectomy, because the risk of positive lymph node in these patients is \(\geq 2\%\). However, for patients with low risk disease, we recommend performing no PLND at all, because the chance of metastasis by most nomograms appears to range between 0% and 4% in these patients, Figure 3. Also, in high risk patients the extent of PLND is controversial and should be the subject of more trials to determine long term therapeutic benefit.

**References**


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