

REVIEW

Pelvic lymphadenectomy in prostate cancer

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This review analyzes the anatomy of the prostate gland's lymphatic drainage, the optimal anatomic extend of pelvic lymph node dissection (PLND) and which dissection may be superior, who should undergo a PLND during prostatectomy, and its potential therapeutic benefits and complications. The prostate gland's lymphatic drainage can be variable, but frequently metastatic disease is found in the internal iliac chain. We conclude that the extended PLND yields the most lymph nodes and therefore may be superior. Some have demonstrated an unproven survival benefit after performing an extended PLND, possibly from removal of occult disease or from more accurate staging.

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The role of pelvic lymph node dissection (PLND) during radical prostatectomy has generated considerable debate. The central role of a PLND is to determine the locoregional extent of cancer, and to help evaluate the need for adjuvant therapy and the risk of progression and recurrence. Some believe that PLND is therapeutic and promotes a cancer-specific survival benefit.^{1–4}

This review aims to critically analyze: (1) the anatomy of the prostate gland's lymphatic drainage, (2) the anatomic boundaries of PLND and which dissection may be superior, (3) who should undergo a PLND during prostatectomy, (4) the potential therapeutic benefits of performing PLND and (5) the complications of PLND.

PLND anatomically defined

Anatomic studies have been performed to define the periprostatic subcapsular lymphatic network that drains the prostate.^{5,6} The network is composed of the ascending, lateral and posterior groups. The ascending ducts drain into the external iliac lymph nodes, the lateral ducts into the hypogastric node chain, and the posterior ducts draining from the caudal prostate to the subaortic lymph nodes of the sacral promontory.^{5,6}

Weingartner *et al.*⁷ performed extensive PLND on cadavers. A mean lymph node (LN) yield of 20 was found and the authors suggested that this number serve as a guideline for sufficient PLND. Interestingly, they analyzed prostate cancer patients' LNs and found that

they were relatively enlarged, whether they contained cancer or not, compared to non-cancer cadavers.

Three approaches to the PLND have been described: limited, standard and extended.^{8,9} (Table 1, Figure 1)

The exact nomenclature and surgical boundaries of PLND vary between institutions and lack standardization. International consensus on anatomic boundaries and use of descriptive terminology is needed.⁹ Standardization would promote uniformity of practice and improve the comparison of future studies on PLND in prostate cancer.

What is the optimal anatomic extend of PLND?

Considerable debate exists over the appropriate boundaries of PLND during radical retropubic prostatectomy (RRP). Proponents of the extended PLND argue that it significantly increases yield of both total LNs and LN metastases. Heidenreich *et al.*^{10,11} compared a group undergoing extended ($n=103$) vs standard ($n=100$) PLND. In total 42% of all LN metastases were detected outside the regions of the standard PLND and involved the internal iliac and presacral regions. Nodal yield was significantly higher (28 LNs vs 11 LNs), as was detection of metastases (27 vs 12% of LN tissue) for extended PLND and standard, respectively. Others have demonstrated a similar significant increase in LNs and metastasis yield after extended PLND compared to standard or limited PLND.^{2,12} Bader *et al.*¹³ provided further evidence that an extended PLND is needed to provide adequate clinical staging and potential therapeutic benefit. Men with clinically organ-confined prostate cancer underwent RRP and extended PLND, and had their LNs prospectively evaluated for number and location of LN metastases. Of 365 patients, 88 (24%)

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Table 1 Types of PLND for prostate cancer

Types of PLND	Lymph nodes
Limited	Obturator fossa lymph nodes
Standard	Obturator fossa and external iliac artery lymph nodes
Extended	Obturator fossa, external, internal and common iliac lymph nodes

Abbreviation: PLND, pelvic lymph node dissection.

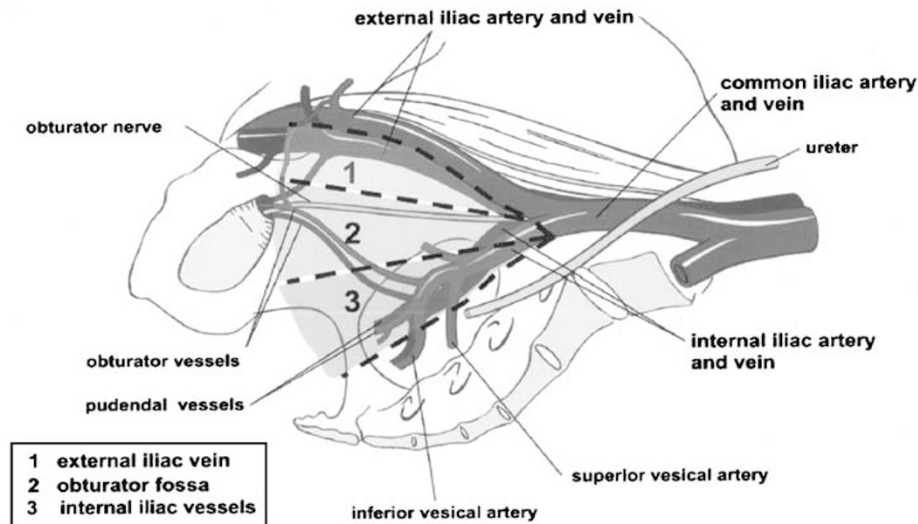


Figure 1 Boundaries of extended lymph node dissection. Reprinted from Burkhard FC, Studer UE. The role of lymphadenectomy in prostate cancer. *Urol Oncol* 2004; 22: 198–202 (with permission from Elsevier).

had positive LNs. Internal iliac LNs were positive for metastasis and the solitary site in 58 and 19%, respectively. In their series, a PLND that spared the internal iliac bed would have left 58% of patients with positive LNs with residual disease and 19% would have been incorrectly staged as LN negative for cancer. Similar findings were reported by Briganti *et al.*^{14,15} and Wawroschek *et al.*^{16,17}

The total number of LNs removed during PLND is vital to ensure the accuracy of the staging procedure. As mentioned earlier, in cadaver studies, a mean LN yield of 20 was found to be sufficient. It has been demonstrated that the number of LNs dissected is directly associated with an increased yield of metastatic LNs.^{2,10–12}

In contrast, some argue that an extended PLND only causes increased morbidity and cost. Clark *et al.*¹⁸ performed a prospective randomized study of 123 patients undergoing RRP with either limited (external iliac and obturator fossa nodes) or extended (common iliac, internal iliac, external iliac, obturator fossa and presacral nodes) PLND. The randomization protocol assigned the extended dissection only unilaterally; on the opposite side, a limited dissection was performed. They concluded that extended PLND did not yield a substantially higher rate of positive nodes than the limited dissection. Complications such as lymphocele or lower extremity edema occurred more commonly in the extended PLND. The study has been criticized because the numbers of subjects were too low for an equivalence study; a unilateral focus of metastatic cancer would have been missed if it occurred on the side of the limited dissection; the majority of the patients had low metastatic risk; and the pathology review methods were not

fully described. Berglund *et al.*¹⁹ found no difference in 5-year failure-free survival in patients who underwent limited lymphadenectomy compared to those who did not have the procedure. In addition, a higher rate of complications was associated with extended lymphadenectomy.

Who should undergo PLND?

The primary function of PLND is to determine the local extent of cancer, the risk of progression or recurrence and the need for adjuvant therapy. In addition, a therapeutic and cancer-specific survival benefit may occur after PLND.^{1–4} With the rise of the prostate-specific antigen (PSA) era, a downward stage migration resulting from the earlier detection of prostate cancer has led to a decreased incidence of positive LNs.^{20–22} To determine who should undergo a PLND, the benefits must be weighed against the associated comorbidities and applied to those who are at risk of metastatic disease.

A number of nomograms have been developed to help identify patients at risk for prostate cancer LN metastasis such as the Partin tables and the Kattan nomogram.^{22–26} Based on these nomograms, patients who are considered low risk (preoperative PSA <10 ng/ml, a biopsy Gleason score (GS) <7, clinical stage <cT2b) often do not undergo PLND during RRP because the likelihood of positive LNs is less than 3%.^{23,25,27}

Although these tools provide guidance during clinical decision making, the methods behind generating them have several drawbacks. (1) They rely on historical

PLND studies with poorly defined dissection borders and in most cases are based on a limited PLND. (2) A documented trend toward higher Gleason grade assignments in contemporary patients may cause nomograms to underestimate metastatic risk.^{22–26,28} (3) Final RRP pathology is frequently downgraded or upgraded when compared to preoperative biopsy specimen.²⁹ Briganti *et al.*^{14,15} recently published a nomogram predicting the probability of lymph node invasion among patients undergoing RRP and an extended PLND. This nomogram is awaiting inter-institutional review and validation.

A number of groups have demonstrated that the likelihood of finding positive lymph nodes in patients with low-risk prostate cancer (preoperative PSA <10 ng/ml, a biopsy Gleason score <7, clinical stage <cT2b) is low. Narayan *et al.*³⁰ performed retrospective analysis on 932 patients to determine in which patients a PLND could be avoided. They concluded that a PLND was unnecessary in patients with Gleason scores less than or equal to 6 and preoperative PSA less than or equal to 10 ng/ml. Bluestein *et al.*³¹ came to a similar conclusion noting that the risk of positive LNs is between 1 and 2% in low-risk patients. Kawakami *et al.*³² analyzed a community-based cohort of RRP and PLND patients from 1992 to 2004. The rate of patients undergoing PLND decreased from 94 to 80%. Overall positive lymph nodes were identified in 0.87, 2.0 and 7.1% of men in the low-, intermediate- and high-risk groups, respectively. The overall LN yield was quite low at 5.7 lymph nodes (median 5.0), revealing some PLND may be inadequate.

In addition to stratifying risk of positive LNs based on PSA and Gleason grade, others have looked at number of cores containing Gleason score greater than or equal to 7 as a variable to determine when to biopsy.^{33–36}

Some argue that the above studies underestimate metastatic LN risk for a given PSA and Gleason grade because they are based on PLND that did not include the internal iliac fossa.¹¹ These groups' PLND typically yielded 6–9 LNs and therefore may have understaged the patients for a given PSA and Gleason score. Schumacher and colleagues³⁷ analyzed patients with a PSA less than 10 ng/ml who underwent RRP and PLND, and found positive lymph nodes in 11% of the men. In patients with GS less than or equal to 6, only 3% had positive LNs while 25% of men with pathologic GS 7 or higher had positive nodes.

Interestingly, investigators have found that biopsy specimens understage and undergrade the tumor 30–40% of the time.^{38,39} Grossfeld *et al.* examined a longitudinal registry of patients with prostate cancer who underwent RRP and found undergrading of primary and secondary Gleason patterns occurred in 13 and 29% of patients, respectively, whereas understaging occurred in 24%.³⁸ Another group found upgrading in 40–46% of patients.³⁹

In summary, earlier nomograms are based on the limited or standard PLND and may underestimate risk. An extended PLND should be performed in all patients with intermediate and high-risk disease. In patients with PSA less than 10 ng/ml and GS less than or equal to 6, PLND can be avoided. However, given the high rate of understaging and grading of biopsy specimens, these patients may be at a higher risk for metastatic disease than previously thought.

Are there therapeutic benefits to performing PLND?

Controversy exists over the therapeutic benefits of PLND and whether it improves disease-specific and overall survival. The landscape of prostate cancer treatment continues to change as the PSA era promotes a stage migration to lower risk disease. Multiple reports support the contention that in patients with low-volume LN metastasis, PLND may have a therapeutic impact. Han *et al.*⁴⁰ reported a 10% actuarial biochemical recurrence-free rate 10 years after radical prostatectomy for patients found to have lymph node micrometastases. Catalona *et al.*⁴¹ demonstrated a therapeutic benefit in a small group of men ($n = 12$) with positive LNs who received no adjuvant therapy. The disease-free rate at 5 and 7 years was 75 and 58%, respectively. Similarly, in another small series,⁴² patients with low tumor bulk and one positive LN had survival rates comparable to those matched controls at 5-year follow-up. Recently, Bader *et al.*¹ demonstrated the probability of PSA relapse, symptomatic progression and tumor-related death increased with each additional positive LN removed. They performed a careful extended PLND and RRP on 367 men with clinically organ-confined prostate cancer; 92 (25%) had positive LNs. After 45 months (median), 39% with only one positive LN remained without signs of progression, while 10 and 14% of patients with two or more positive LNs remained disease free.

In a retrospective study⁴³ in the pre-PSA era, 156 patients underwent staging PLND for organ-confined prostate cancer but were found to have positive LNs. The group was divided into those receiving an RRP ($n = 114$) and those who did not ($n = 42$). The median cancer-specific survival was 11.2 and 5.8 years ($P = 0.005$), and in patients with one or two positive lymph nodes the median cancer-specific survival was 10.2 and 5.9 years for RRP and non-RRP groups, respectively. Their data suggest that patients with limited LN positive disease selected for RRP have a survival advantage over those denied such therapy and that this advantage is independent of adjuvant therapy.

Others have found no survival advantage to PLND. In 2000, Salomon *et al.*⁴⁴ found no overall survival and recurrence-free survival benefits from performing a PLND during perineal prostatectomy. They divided patients to get PLND ($n = 43$) or no PLND ($n = 25$). Each had a PSA less than 10 ng/ml and GS less than 7. The actuarial 5-year recurrence-free survival rate was not significantly different at 78 and 80%, respectively, between the non-PLND and the PLND group. The study did have some limitations: (1) small study enrollment, (2) the PLND template was not defined and (3) patients had low metastatic risk, thus making the true therapeutic benefit difficult to judge.

Similarly, another group³⁹ who examined the therapeutic value of PLND retrospectively examined 336 men who underwent RRP. At the discretion of the surgeon, 140 patients underwent PLND. This group was matched for GS less than 7, PSA less than 10 ng/ml, and clinical T1 or T2 disease with patients who were spared the PLND. A PLND that did not include the internal iliac chain was performed and produced a 0.7% metastasis rate. The 6-year biochemical relapse-free rate for the PLND vs non-PLND group was 86 and 88%, respectively

($P=0.28$). On multivariate analysis, PLND was not an independent predictor of outcome ($P=0.33$). The study is limited by its lack of randomization, the overall low risk of the cohort, and the fact that PLND did not include internal iliac nodes.

In summary, controversy exists over the long-term therapeutic impact of PLND. Some studies support the notion that an extended PLND in patients with low-volume LN metastasis improves outcomes.

What are the complications of PLND?

The overall complication rate of PLND is low. Complication rates as high as 10–20% were reported in older series.⁴⁵ Some support a more limited PLND because they believe that there is less morbidity and lower costs.^{18,46} In contrast, Heidenreich et al.^{10,11} demonstrated that the overall incidence of intraoperative and perioperative complications were similar for limited and extended PLND. Blood loss (650 vs 590 cc), rectal injury (1.1 vs 1%) and obturator injury (2.2 vs 1%) were not significantly different for extended vs limited PLND, respectively. Similarly, perioperative complications such as deep vein thrombosis (4.7 vs 6%), emboli (1.2 vs 2%), and lymphoceles (10.6 vs 9%) were not significantly different for extended vs limited PLND, respectively. The following practice recommendations to limit morbidity associated with PLND^{11,47} have been made: lymphatics lateral to the external iliac artery should be preserved, lymphatics should be carefully dissected and individually clipped, a postoperative drain should be placed and left until the output is less than 50 cc per 24 h, and low-molecular-weight heparin should be administered subcutaneously at the time of surgery. It does not appear that PLND affects erectile function after RRP, although most groups do not report potency data.^{48,49}

In summary, complications of PLND include intraoperative events such as vessel and nerve injury and postoperative events such as lymphocele formation. In modern series, the incidence of such complications appears relatively low. Although the morbidity of PLND does not appear to change significantly based on dissection extent, the extended PLND carries slightly higher morbidity.

The central roles of a PLND are to determine the locoregional extent of disease, to help evaluate risk of progression and recurrence and to determine the need for adjuvant therapy. The prostate gland's lymphatic drainage can be variable, but frequently metastatic disease is found in the internal iliac chain. The extended PLND yields the most LNs and therefore may be superior. Some have demonstrated a survival benefit after performing an extended PLND, possibly from removal of occult disease or from more accurate staging; however, such a benefit has not been proven.

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