# The Importance of Pelvic Lymph Node Dissection in Men With Clinically Localized Prostate Cancer

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Despite advances in noninvasive staging, pelvic lymph node dissection (PLND) remains the most accurate means of detecting lymph node metastases in men with clinically localized prostate cancer. Nomograms exist that can identify patients at low risk for lymphatic metastases according to preoperative information. In general, it seems reasonable to omit PLND in men with a biopsy Gleason sum of 6 or less and a prostate-specific antigen level of 10 ng/mL or less. Ultimately, however, this decision should be made according to physician and patient preference, considering the low contemporary morbidity associated with PLND. When PLND is performed, studies suggest that an extended dissection maximizes the detection rate of nodal involvement. Retrospective data indicate that an extended dissection might play a therapeutic role in a subset of patients with a limited lymph node burden. However, this might be an artifact of stage migration, and prospective studies are needed to evaluate this further. [Rev Urol. 2006;8(3):112-119]

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Key words: Prostate cancer • Lymphadenectomy • Clinical staging • Magnetic resonance imaging • Radioimmunoscintigraphy • Nomograms • Algorithms

> ■ he presence of lymph node metastasis in men diagnosed with clinically localized prostate cancer portends a poor prognosis. 1-3 Accurate identification of these men allows more precise prognostication and might have important implications regarding the initiation of adjuvant therapy. Although in unique situations imaging modalities might assist in the detection of lymph node metastases, in the vast majority of cases these tests are not yet reliable.<sup>4,5</sup> Early

enthusiasm for radioimmunoscintigraphy and molecular staging techniques has been tempered by their limited accuracy in clinical studies.<sup>6-8</sup> Pelvic lymph node dissection (PLND) remains the most accurate staging procedure for the detection of occult nodal involvement.9

The advent of prostate-specific antigen (PSA) screening has resulted in a steady decline in the incidence of pelvic lymph node metastasis, from

This articles aims to systematically review this controversial topic and clarify the current state of knowledge on the basis of the contemporary literature.

#### Goals of PLND

Historically, PLND was performed before radical prostatectomy, and lymph nodes were sent for frozen section analysis. In this context, the goal of PLND was to determine

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rates of 20% to 40% in the 1970s and 1980s to less than 6% today. 10,11 As a result of this stage shift, PLND is often omitted before various curative treatment approaches (radical retropubic prostatectomy, laparoscopic radical prostatectomy, perineal prostatectomy, radiation therapy, and cryotherapy) or is performed within a more restricted anatomic template. Nomograms and other algorithms have been developed to predict the likelihood of lymph node metastasis and identify patients suitable for PLND omission. 10,12,13

Given the individual variation in prostatic lymphatic drainage patterns and the fact that some investigators performing extended PLND have reported higher rates of lymph node metastases than those predicted by popular nomograms, some investigators favor performing extended PLND on the majority of patients with clinically localized prostate cancer. Recent studies have suggested that an extended PLND not only maximizes the detection of lymph node-positive disease but might also play a therapeutic role in a subset of patients. 14-16

Thus, the importance of PLND in men with clinically localized prostate cancer remains a matter of debate. whether one should proceed with radical surgery, the philosophy being that if metastatic disease was discovered, the patient was spared the morbidity of a prostatectomy. Interestingly, the false-negative rate of frozen section for micrometastatic disease can be as high as 30%.17 Today some surgeons will perform a laparoscopic lymphadenectomy before proceeding with definitive surgical treatment on patients with locally advanced disease or Gleason sum

be a therapeutic benefit associated with PLND. 14-16

# Clinical Staging

The goal of clinical staging is to use pretreatment parameters to predict the true extent of disease. This allows assessment of prognosis and facilitates educated decision making regarding treatment options. Ultimately, pathologic outcome is the most reliable means of predicting outcome of therapy in men with clinically localized prostate cancer.3

## Cross-Sectional Imaging

Cross-sectional imaging by computed tomography or magnetic resonance imaging (MRI) to evaluate lymph node involvement is not routinely recommended, owing to the low sensitivity (0-30%) of these modalities in imaging microscopic disease. 19,20 Specialized techniques, such as high-resolution MRI used in tandem with the intravenous administration of lymphotropic superparamagnetic nanoparticles, might allow the detection of small and otherwise undetectable lymph node disease. In a recent study involving 80 patients

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greater than 7 because it is those patients who are less likely to benefit from radical surgery in the setting of lymphatic spread.<sup>18</sup>

Another and more common reason to perform PLND is to present patients with the most accurate assessment of their disease burden, thus providing them with relevant treatment options and prognostic information. Some patients insist on undergoing PLND, regardless of their risk of metastasis, for peace of mind. Finally, some investigators contend that there might with clinical T1, T2, or T3 disease, MRI with lymphotropic superparananoparticles outpermagnetic formed conventional MRI and nomograms in the detection of lymph node-positive disease.21 Such techniques, however, require further clinical evaluation and validation before widespread use.

Radioimmunoscintigraphy and Molecular Staging Techniques Monoclonal antibody radioimmunoscintigraphy (ie, ProstaScint

| Table 1 Algorithms and Nomograms Predicting Lymph Node Metastases |      |                    |                     |  |   |                     |
|---|------|--------------------|---------------------|--|---|---------------------|
| Authors   | Year | No. of<br>Patients | Statistical<br>Tool | Definition of Low-Risk<br>Patient or Input Variables   | % Patients<br>Spared PLND                 | % False<br>Negative |
| Bluestein DL et al <sup>12</sup>                                  | 1994 | 1632               | LR                  | Gleason sum, PSA, cStage   | 61% of patients<br>with cStage<br>T1a-T2b | ≤ 3                 |
| Narayan P et al <sup>39</sup>                                     | 1994 | 932                | LR                  | $PSA \le 10 \text{ ng/mL}$ , Gleason sum $\le 6$   | 42  | 1                   |
| Bishoff JT et al <sup>40</sup>                                    | 1995 | 481                | LR                  | Gleason sum, PSA, cStage   | 20-63                                     | 2-10                |
| Parra RO et al <sup>41</sup>                                      | 1996 | 155                | None                | PSA < 10.0 ng/mL, Gleason sum < 7  | 47  | 0                   |
| Conrad S et al <sup>22</sup>                                      | 1998 | 344                | CART                | ≤ 3 cores with any Gleason 4 or 5<br>and no core with predominant<br>Gleason 4 or 5  | 80  | 2.2                 |
| Tewari A and<br>Narayan P <sup>42</sup>                           | 1998 | 1200               | ANN                 | Age, race, perineural invasion, Gleason sum, PSA, cStage, biopsy data (unilateral vs bilateral, no. of cores positive)         | 63  | ≤ 2                 |
| Crawford ED et al <sup>43</sup>                                   | 2000 | 4133               | ANN                 | Gleason sum $\leq$ 6, PSA $\leq$ 10.6 ng/mL, or cStage $\leq$ T2a  | 44  | 0.8                 |
| Batuello JT et al <sup>44</sup>                                   | 2001 | 6135               | ANN                 | Gleason sum, PSA, cStage   | 80  | ≤ 2                 |
| Naya Y and<br>Babaian RJ <sup>45</sup>                            | 2003 | 695                | CART                | All Gleason components < 4 or < 4 positive cores Gleason 4 or 5 and PSA < 15 ng/mL and no core with predominant Gleason 4 or 5 | 70  | 0.4                 |
| Cagiannos I et al <sup>13</sup>                                   | 2003 | 5510               | LR                  | Gleason sum, PSA, cStage   | 67*                                       | 1.5*                |

PLND, pelvic lymph node dissection; LR, logistic regression; PSA, prostate-specific antigen; cStage, clinical stage; CART, classification and regression tree; ANN, artificial neural network.

Scan; Cytogen Corporation, Princeton, NJ) has had limited accuracy in the detection of lymph node metastases because the antibody targets an intracellular epitope that is only exposed in dying or dead cells.<sup>6,7</sup> Although initially promising, molecular techniques using reverse transcription polymerase chain reaction (RT-PCR) have had varying sensitivities in detecting circulating cancer cells. In addition, a significant proportion of men with organ-confined disease in one study were found to have a positive PSA PCR assay.8 Thus, the significance of a positive assay remains unknown, and positive assays might lead to men being overstaged and denied curative treatment.

Combined Use of Treatment Parameters: Nomograms and Algorithms

Although numerous studies have integrated various clinical parameters to predict the pathologic stage of clinically localized prostate cancer, only a few have specifically focused on lymphatic metastases. These studies have resulted in nomograms, algorithms, and proprietary artificial neural networks that can predict the likelihood of lymph node metastases for a given set of input parameters. Most investigators have focused on Gleason sum, PSA, and clinical stage, but some have included details of the preoperative biopsy in their models. Table 1 summarizes a few pertinent

studies focusing on this topic. Most studies conclude that one can designate a significant percentage of patients (20%–80%) as "low risk" for lymph node metastases and avoid a PLND in those patients. All published models seem to be able to achieve this with an impressive false-negative rate (<10%). This is especially significant given the increasing use of treatment modalities that do not permit lymph node staging, such as brachytherapy and external beam radiation therapy.

Cagiannos and colleagues<sup>13</sup> recently constructed a nomogram to predict lymph node metastases, based on preoperative Gleason sum, PSA level, and clinical stage of 7014 patients from 7 institutions. Their

<sup>\*</sup>Numbers shown correspond to when model predicts a probability of 3% or less for nodal involvement.

conclusion was that it is appropriate to omit PLND when the nomogram predicts a probability of metastasis between 1.5% and 3.0% or less. For a 3.0% nomogram probability, 66.8% of patients would have been spared PLND, with a false-negative rate of 1.5%. Interestingly, the rate of lymph node metastases between participating institutions in this study ranged from 1.5% to 7.0%. Including institution as an additional variable in the nodal involvement) based on logistic regression analysis of Gleason sum, PSA level, and clinical stage. 10,24,25 This nomogram has been updated and validated in a number of multicenter studies, including a 1997 study with 4133 patients. 10 In this validation cohort, the Partin nomogram accurately predicted nodal metastases in 83% of patients. For patients with a Gleason sum of 6 or less and a PSA level of

10 ng/mL or less, the likelihood of Cagiannos and colleagues concluded that it is appropriate to omit PLND

when the nomogram predicts a probability of metastasis between 1.5% and

analysis changed the probability of lymph node metastasis generated by the nomogram, independent of Gleason sum, PSA level, and clinical stage. The extent of lymph node dissection at each institution is not provided and might account for this phenomenon.

3.0% or less.

Only a few nomograms predicting lymphatic spread have been validated. Bluestein and colleagues<sup>12</sup> randomized half of their patients into a training set and exposed the other half in a validation set. Conrad and coworkers<sup>22</sup> used classification and regression trees analysis and derived an algorithm (the Hamburg algorithm) based on Gleason sum and sextant biopsy information. This algorithm was internally validated, with consistent results on a cohort of 239 patients from the same institution. Haese and colleagues<sup>23</sup> verified the performance of the Hamburg algorithm in a cohort of 443 men treated for clinically localized prostate cancer at the Johns Hopkins Hospital.

The Partin tables represent a more comprehensive example of these algorithms because they reveal a percentage probability of having a final pathologic stage (including metastatic disease according to the Partin nomogram is 0 to 3%. For this reason, and consistent with most other nomogram predictions, some surgeons reserve PLND for men with a PSA level greater than 10 ng/mL and Gleason sum greater than 6.

# Complications and **Financial Implications**

The decline in lymph node-positive disease among PSA-screened men and the availability of algorithms that

expense includes pathologic consultation and operating room time (15-30 minutes). The significance of this additional financial burden can be appreciated by multiplying this premium by the number of radical retropubic prostatectomies performed annually (> 20,000 in the year 2000).

The complication rate associated with PLND ranges between 4% and 53%; however, these rates are derived from studies spanning several decades, including open and laparoscopic series, and involving different dissection templates. Table 2 summarizes select recent series reporting on the morbidity of PLND. Clark and colleagues<sup>28</sup> randomized 123 patients undergoing radical prostatectomy to an extended PLND on the right or left side, with the other side having a limited PLND. They reported a 10.6% overall complication rate, with 75% of these occurring on the extended side. Heidenreich and coworkers15 compared patients who underwent extended or limited PLND and found no difference in terms of complications between the 2 groups. The postoperative complication rate of both groups was approximately 9%. Kavoussi and colleagues29 assessed

It has been estimated that PLND adds approximately \$935 to \$3120 to the total cost of a radical retropubic prostatectomy.

can identify "low-risk" patients has led some urologists to abandon the routine use of PLND. The added operating room time (in the case of concomitant radical prostatectomy), the additional costs, and morbidity are all cited as additional reasons to omit PLND from the routine care of men with clinically localized disease.

It has been estimated that PLND adds approximately \$935 to \$3120 to the total cost of a radical retropubic prostatectomy.<sup>23,26,27</sup> The additional

the complications in 372 patients undergoing laparoscopic PLND at 8 medical centers. The overall complication rate was 15% (requiring open conversion in 13 cases) and included vascular injury in 11 patients, deep vein thrombosis in 5, obturator nerve injury in 2, and lymphocele/lymphedema in 5. This study represented the initial laparoscopic experience, and subsequent reports have documented improvement in the number and scope of these complications. It is generally

| Table 2                           |   |  |  |  |  |
|-----------------------------------|---|--|--|--|--|
| Select Recent Series Reporting on | the Morbidity of Pelvic Lymph Node Dissection |  |  |  |  |

|                                   |      |                    |                              |                              | Complication (%) |             |        |                   |                    |                              |       |
|-----------------------------------|------|--------------------|------------------------------|------------------------------|------------------|-------------|--------|-------------------|--------------------|------------------------------|-------|
| Authors                           | Year | No. of<br>Patients | Laparoscopic<br>(L)/Open (O) | Extended (E)/<br>Limited (L) | Lympho-<br>cele  | LE<br>Edema | DVT/PE | Pelvic<br>Abscess | Ureteral<br>Injury | Neurovas-<br>cular<br>Injury | Ileus |
| Kavoussi LR et al <sup>29</sup>   | 1993 | 372                | L                            | L                            | 1.3              | 0*          | 1.3    | 0.5               | 0.5                | 3.5                          | 1.3   |
| Campbell SC et al <sup>27</sup>   | 1995 | 245                | 0                            | L                            | 1.6              | _           | 1.6    | -                 | _                  | 0.8                          | _     |
| Raboy A et al <sup>46</sup>       | 1997 | 125                | L                            | L                            | 2.4              | _           | 0.8    | -                 | -                  | -                            | 0     |
| Stone NN et al <sup>33</sup>      | 1997 | 150                | L                            | L                            | -                | 0           | -      | 0                 | -                  | 0.7                          | _     |
| Stone NN et al <sup>33</sup>      | 1997 | 39                 | L                            | Е                            | -                | 10          | -      | 5.1               | -                  | 5.1                          | _     |
| Herrell SD et al <sup>47</sup>    | 1997 | 38                 | 0                            | L                            | 2.6              | 0           | 2.6    | 2.6               | 0                  | 0                            | 7.9   |
| Heidenreich A et al <sup>15</sup> | 2002 | 103                | 0                            | Е                            | 10.6             | _           | 6.3    | 0                 | 0.9                | 7.1                          | _     |
| Heidenreich A et al <sup>15</sup> | 2002 | 100                | 0                            | L                            | 9.0              | _           | 8.0    | 0                 | 0                  | 6.0                          | _     |
| Bader P et al <sup>16</sup>       | 2003 | 365                | 0                            | Е                            | 1.9              | _           | 2.7    | -                 | -                  | -                            | _     |
| Clark T et al <sup>28</sup>       | 2003 | 123                | 0                            | L/E <sup>†</sup>             | 3.3              | 4.1         | 1.6    | 0.8               | 0.8                | _                            | -     |
| Allaf ME et al <sup>14</sup>      | 2004 | 2135               | 0                            | Е                            | 0.1              | -           | _      | _                 | _                  | _                            | _     |

LE, lower extremity; DVT, deep vein thrombosis; PE, pulmonary embolus.

agreed, though, that the morbidity of PLND today is minimal.

#### **PLND Templates**

The extent of PLND has varied by era and individual surgeon. It is important to note the general boundaries of a typical limited and extended dissection. Extended PLND consists of excising the fibrofatty and lymphatic tissues in an area bordered superiorly by the bifurcation of the common iliac artery, inferiorly by the femoral canal, and laterally by the pelvic sidewall. Posteriorly, all tissues surrounding the obturator nerve, obturator vessels, and internal iliac artery are removed. Care is taken to preserve the tissues overlaying and surrounding the external iliac artery. These tissues contain the lymphatics that drain the lower extremities, and their disruption might result in lower extremity edema and lymphocele formation. A limited (or modified) PLND differs in

that the posterior extent of the dissection is the obturator fossa, and the internal iliac nodes are not removed. Closed suction drainage and meticulous ligation of lymphatic channels minimize the complications of PLND.

### The Case for Extended PLND

Lymphatic drainage of the prostate is variable and involves regions not sampled during "routine" PLND. Earlier surgical studies have confirmed that significant rates of nodal metastases (15%-30%) might be detected exclusively in areas outside of the boundaries of a limited dissection. 30,31 Recently, Bader and colleagues16 evaluated 365 patients with clinically localized prostate cancer who underwent extended pelvic lymphadenectomy at the time of radical prostatectomy. One fourth of these patients were found to have nodal involvement, of whom approximately 20% had metastases solely along the

internal iliac vessels. In the study by Heidenreich and coworkers, 15 42% of the patients undergoing extended lymph node dissection were found to have nodal involvement outside of the external iliac and obturator lymph nodes. Furthermore, recent lymphoscintigraphy studies have confirmed the individual variation in prostatic lymphatic drainage patterns.<sup>32</sup> In addition to retrieving more lymph nodes, an extended PLND seems to detect a greater proportion of patients with lymph node metastases when compared with a limited lymphadenectomy (Table 3). 14,15,33

Certain patients with node-positive disease who undergo radical prostatectomy have good long-term PSA-free survival. Han and colleagues<sup>34</sup> reported a 10% actuarial biochemical recurrence-free rate after radical prostatectomy at 10 years for patients found to have lymph node micrometastases. Several studies have

<sup>\*</sup>In this study, LE edema and lymphocele were reported as one category.

<sup>&</sup>lt;sup>†</sup>75% of complications occurred on side receiving extended pelvic lymph node dissection.

Table 3
Studies Demonstrating That Extended Pelvic Lymph Node Dissection
Detects a Greater Proportion of Patients With Lymph Node Metastases
When Compared With Limited Lymphadenectomy

| Author                            | Extent of Dissection | No. of Nodes<br>Retrieved | Total No. of Patients<br>(% with Positive Nodes) |
|-----------------------------------|----------------------|---------------------------|--|
| Stone NN et al <sup>33</sup>      | Extended             | 18                        | 39 (23)  |
|                                   | Limited              | 9                         | 150 (7)  |
| Heidenreich A et al <sup>15</sup> | Extended             | 28                        | 100 (26)   |
|                                   | Limited              | 11                        | 103 (12)   |
| Allaf ME et al <sup>14</sup>      | Extended             | 12                        | 2135 (3)   |
|                                   | Limited              | 9                         | 1865 (1)   |

documented an association between quantity of lymph nodes involved and survival. In 1987, Golimbu and coworkers35 retrospectively analyzed 42 patients with occult nodal disease who underwent pelvic lymphadenectomy and radical prostatectomy. In this series, patients with low tumor bulk and 1 positive lymph node had survival rates comparable to those of matched controls after a mean follow-up of 5 years. More recently, Bader and colleagues<sup>16</sup> reported delayed progression in patients with minimal lymph node involvement detected by extended lymphadenectomy and treated with radical prostatectomy. The investigators hypothesized that this might represent cure in some patients. In 2004, Allaf and coworkers<sup>14</sup> reported that among men with lymph node-positive disease involving less than 15% of extracted nodes, the 5-year PSA progression-free rate for extended lymph node dissection was 43%, compared with 10% for the more limited lymph node dissection (Figure 1).14 These investigators concluded that a significant benefit in biochemical recurrence-free survival might exist for certain subgroups undergoing the extended dissection, although this has not been proven.

An alternative explanation for the finding of a benefit to extended dissection is that it might be an artifact of stage migration (the Will Rogers phenomenon).<sup>36</sup> Other evidence to support the hypothesis that a lymph node dissection can contribute to biochemical cancer control comes from a case report in which a patient with a rising PSA level after a radical prostatectomy experienced a fall in PSA to

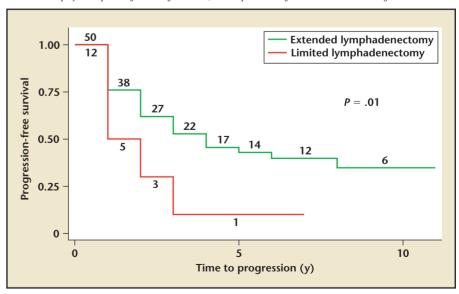
undetectable levels after excision of a positive lymph node at the time of a colonic resection.<sup>37</sup>

Some investigators believe that nomograms underestimate the true rates of lymph node metastases. They argue that algorithms are rarely based on an extended PLND and thus understage most patients.<sup>38</sup>

## **Conclusions**

Despite advances in noninvasive staging, PLND remains the most accurate means of detecting lymph node metastases in men with clinically localized prostate cancer. Nomograms exist that can identify patients at low risk for lymphatic metastases, on the basis of preoperative information. In general, it seems reasonable to omit PLND in men with a biopsy Gleason sum of 6 or less and a PSA level of 10 ng/mL or less. Ultimately, however, this decision should be made according to physician and patient preference, considering the low contemporary morbidity associated with PLND. When PLND is performed, studies suggest that an extended dissection

Figure 1. Kaplan-Meier survival analysis of men with clinically localized prostate cancer found to have <15% positive lymph nodes. The analysis is stratified by extent of lymph node dissection (extended lymphadenectomy n=50, limited lymphadenectomy n=12; log-rank P=.01). The number of patients at risk at the beginning of each time interval is displayed. Reprinted from Allaf ME et al, 14 with permission from the American Urological Association.



maximizes the detection rate of nodal involvement. Retrospective data indicate that an extended dissection might play a therapeutic role in a subset of patients with a limited lymph node burden. This, however, might be an artifact of stage migration, and prospective studies are needed to evaluate this further.

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#### **Main Points**

- Pelvic lymph node dissection (PLND) remains the most accurate staging procedure for the detection of occult nodal involvement in men diagnosed with clinically localized prostate cancer.
- Cross-sectional imaging by computed tomography or magnetic resonance imaging to evaluate lymph node involvement is not routinely recommended, owing to the low sensitivity of these modalities in imaging microscopic disease.
- Monoclonal antibody radioimmunoscintigraphy has had limited accuracy in the detection of lymph node metastases.
- Numerous studies have integrated various clinical parameters to predict the pathologic stage of clinically localized prostate cancer; most studies conclude that one can designate a significant percentage of patients (20%-80%) as "low risk" for lymph node metastases and avoid a PLND in those patients.
- The complication rate associated with PLND ranges between 4% and 53%; however, these rates are derived from studies spanning several decades, including open and laparoscopic series, and involving different dissection templates; today, it is generally agreed that the morbidity of PLND is minimal.
- In addition to retrieving more lymph nodes, an extended PLND seems to detect a greater proportion of patients with lymph node metastases when compared with a limited lymphadenectomy.

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