Role of Pelvic Lymphadenectomy in the Treatment of Bladder Cancer: A Mini Review

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Although radical cystectomy with pelvic lymph node dissection (PLND) is the standard treatment for muscle-invasive bladder cancer, the optimal extent of PLND and the minimum number of nodes that should be examined for pathology remain unclear. However, evidence is growing that extended PLND has additional diagnostic and therapeutic benefits relative to standard PLND. In particular, a more meticulous and extended PLND may improve the disease-free survival of node-negative patients because it removes undetected micrometastases. Indeed, some patients with positive nodes can be cured by surgery alone, even those with gross adenopathy. Increasing lines of evidence also suggest that the extent of the primary bladder tumor, the number of lymph nodes that are removed, and the lymph node tumor burden are important prognostic variables in patients undergoing cystectomy. Therefore, extended PLND may not only provide improved prognostic information, it may also have a clinically significant therapeutic benefit for both lymph node-positive and node-negative patients undergoing radical cystectomy. Although the absolute limits of PLND remain to be determined, evidence supports the notion that a more extended PLND should include the common iliac vessels and presacral lymph nodes at cystectomy. Such PLND should only be performed in patients who are appropriate surgical candidates. Prospective, randomized trials are needed to properly establish the extent of PLND that is required to generate these benefits.

Key Words: Cystectomy; Lymph node excision; Urinary bladder neoplasms

INTRODUCTION

High-grade muscle-invasive bladder cancer is regarded as a potentially lethal disease that has a high propensity for spreading. If left untreated, 85% of these patients will die from the disease within 2 years of diagnosis [1]. Radical cystectomy with bilateral pelvic lymph node dissection (PLND) is the standard treatment for high-grade invasive bladder cancer. In 1982, Skinner recognized for the first time that PLND could be curative for those bladder cancer patients who have only a few small positive lymph nodes [2]. He concluded that a meticulous PLND that extends to the common iliac vessels and the distal aorta and vena cava does not increase the morbidity or mortality associated with cystectomy and can make a difference in terms of survival. However, despite the accumulating evidence suggesting that a more extensive PLND is an important component in the surgical management of bladder cancer, how extensive PLND should be and what role it plays in reducing bladder cancer mortality remain unclear.

LYMPHATIC DRAINAGE OF THE BLADDER

The primary drainage of the bladder starts from the external and internal iliac and obturator sites, secondary drainage is from the common iliac sites, and tertiary drainage to the presacral nodes is from the trigone and posterior bladder wall [3].

Standard PLND is currently defined by the following boundaries: the common iliac bifurcation (cephalad extent), the genito-femoral nerve (lateral), the circumflex caudal iliac vein and lymph node of Cloquet (distal), and...
the hypogastric vessels (posterior), including the obturator fossa. The whole primary lymphatic drainage system of the bladder is contained within these boundaries. Extended PLND should include the nodes contained within the following boundaries: the aortic bifurcation and common iliac vessels (proximal/cephalad); the genito-femoral nerve (lateral); the circumflex (distal) and caudal iliac vein and lymph node of Cloquet; the hypogastric vessels (posterior), including the obturator fossa; and the presacral lymph nodes anterior to the sacral promontory. These boundaries potentially guarantee the complete removal of the primary, secondary, and tertiary lymph node drainage systems of the bladder, which will aid the accuracy of staging.

The group from Mansoura suggested that the endopelvic (obturator and internal iliac) lymph nodes could serve as lymphatic drainage sentinels; they also speculated that if histology of frozen sections of endopelvic nodes revealed that the nodes were negative, there was no justification for extending the PLND superiorly [4,5]. This possibility should be confirmed by larger studies.

### INCIDENCE OF NODE INVOLVEMENT FOLLOWING RADICAL CYSTECTOMY

The reported incidence of regional lymph node involvement following radical cystectomy for bladder cancer is between 13% and 30% (Table 1) [3,4,6-34]. This incidence correlates positively with the stage of the primary tumor: the higher the stage, the greater the incidence of node involvement [10,12]. The rate of lymph node metastasis increases from 5% in non-muscle-invasive bladder cancer to 18% in superficial muscle-invasive cancer, 27% in deep-muscle-invasive cancer, and 45% in extravesical cancer (pT3-4) [13]. In addition, Herr reported that the number of patients with positive nodes increases with the number of lymph nodes that are removed [35]. Table 1 summarizes the incidence of node metastases in patients treated by radical cystectomy.

### ASSOCIATION BETWEEN LYMPH NODE DISSECTION AND THE NUMBER OF RETRIEVED NODES

The absolute boundaries of the PLND may be the most im-

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**Table 1.** Incidence of node metastases detected after radical cystectomy

| References          | Year | No. of patients | No. of node metastases | Node metastases (%) |
|---------------------|------|-----------------|------------------------|---------------------|
| Ghoneim et al [6]   | 1997 | 1,026           | 188                    | 19.5                |
| Poulsen et al [7]   | 1998 | 191             | 50                     | 26.2                |
| Vieweg et al [8]    | 1999 | 652             | 193                    | 28.1                |
| Bassi et al [9]     | 1999 | 369             | 78                     | 21.1                |
| Leissner et al [10] | 2000 | 447             | 136                    | 30.4                |
| Herr and Donat [11] | 2001 | 763             | 193                    | 25.3                |
| Mills et al [12]    | 2001 | 452             | 83                     | 18.4                |
| Stein et al [13]    | 2001 | 1,054           | 246                    | 23.3                |
| Gschwend et al [14] | 2002 | 686             | 193                    | 28.1                |
| Gaitonde et al [15] | 2002 | 105             | 17                     | 16.2                |
| Madersbacher et al [16]| 2003 | 507             | 121                    | 23.9                |
| Vazina et al [3]    | 2004 | 176             | 43                     | 24.4                |
| Leissner et al [4]  | 2004 | 290             | 81                     | 27.9                |
| Abdel-Latif et al [17]| 2004 | 418             | 110                    | 26.3                |
| Nishiyama et al [18]| 2004 | 1,113           | 162                    | 14.6                |
| Fleischmann et al [19]| 2005 | 507             | 124                    | 24.5                |
| Hautmann et al [20] | 2006 | 788             | 142                    | 18.0                |
| Shariat et al [21]  | 2006 | 833             | 198                    | 23.8                |
| Homma et al [22]    | 2006 | 146             | 25                     | 17.1                |
| Koppie et al [23]   | 2006 | 1,110           | 243                    | 21.9                |
| Stein et al [24]    | 2007 | 1,621           | 383                    | 23.6                |
| Steven and Poulsen [25]| 2007 | 336             | 64                     | 19.0                |
| Dhar et al [26]     | 2008 | 336             | 43                     | 12.8                |
| Ghoneim et al [27]  | 2008 | 991             | 233                    | 23.6                |
| Wiesner et al [28]  | 2009 | 152             | 46                     | 30.2                |
| Osawa et al [29]    | 2009 | 435             | 83                     | 19.1                |
| Jensen et al [30]   | 2009 | 170             | 43                     | 25.3                |
| Bruins et al [31]   | 2009 | 1,600           | 369                    | 23.1                |
| Stephenson et al [32]| 2010 | 763             | 178                    | 23.3                |
| Seiler et al [33]   | 2010 | 840             | 162                    | 19.3                |
| Dangle et al [34]   | 2010 | 120             | 36                     | 30.0                |
portant factor determining the number of lymph nodes that can be removed during cystectomy. The extent of PLND and the number of retrieved nodes are summarized in Table 2 [3-5,7,10,12,17,22-26,28-30,34-43]. In two large cystectomy series that involved extended PLND, the mean number of lymph nodes removed was 30 to 43 [4,37]. Poulsen et al reported that extending the boundaries of the PLND increased the mean number of retrieved lymph nodes from 14 in a standard PLND to 25 when the dissection was extended to the bifurcation of the aorta [7].

The number of lymph nodes that are assessed for pathology also depends on several other factors, including the pathologist’s diligence in searching for and preparing the lymph nodes for histopathological evaluation and how the specimen is actually submitted for pathological evaluation. Simply converting from an en bloc technique to the submission of six separate lymph node packets increases the mean number of retrieved lymph nodes by more than three-fold [44]. In addition, individual variation between patients in terms of lymph node numbers may also affect the number of nodes that are retrieved.

**LYMPH NODE STATUS AND PROGNOSIS**

Lymph node status is known to be an important prognostic variable in bladder cancer. Patients with nodal metastases are at high risk of cancer recurrence and death from the disease. Therefore, adjuvant treatment with chemotherapy could benefit this patient population. However, although accurate determination of lymph node status is vital in determining patient prognosis, it is unclear to what extent it should influence decision-making regarding adjuvant therapy.

1. **Number of removed lymph nodes**

A Danish group was the first to assess how the extent of PLND influenced survival [7]. For this purpose, 194 consecutive patients treated by radical cystectomy were analyzed retrospectively. The authors reported that the 5-year recurrence-free survival rate was 62% for the extended PLND group and 56% for the limited PLND group; this difference did not achieve statistical significance. However, a subgroup analysis of 117 patients with ≤pT3a primary tumors showed that extended and limited PLND were associated with survival rates of 85% and 64%, respectively; this difference was significant.

Leissner et al reviewed their experience with 447 radical cystectomy cases [10]. The planned field of dissection was up to the aortic bifurcation and the mean number of removed nodes was 14.7. They found that the number of retrieved nodes correlated with cancer-specific survival and that a significant survival advantage was noted when ≥16

### Table 2. Extent of pelvic lymph node dissection and the number of retrieved nodes

| References          | Year | No. of patients | Extent                  | No. of nodes |
|---------------------|------|-----------------|-------------------------|--------------|
| Poulsen et al [7]   | 1998 | 72              | Aortic bifurcation      | 25.0         |
|                     |      |                 | Common iliac bifurcation | 14.0         |
| Leissner et al [10] | 2000 | 302             | Common iliac bifurcation | 14.6         |
| Mills et al [12]    | 2001 | 452             | Common iliac bifurcation | 20.0         |
| Herr [35]           | 2003 | 162             | Distal common iliac     | 13.3         |
| Stein et al [37]    | 2003 | 244             | 2 cm above aortic bifurcation | 30.0         |
| Vazina et al [3]    | 2004 | 176             | Aortic bifurcation      | 26.0         |
| Leissner et al [4]  | 2004 | 290             | Above aortic bifurcation | 43.1         |
| Abdel-Enein et al [5]| 2004| 200             | Distal aortic           | 50.6         |
| Abdel-Latif et al [17]| 2004| 110             | Distal common iliac     | 17.9         |
| Herr et al [38]     | 2004 | 268             | Variable                | 10.0         |
| Herr et al [39]     | 2004 | 1,091           | Variable                | 12.5         |
| Fleischmann et al [40] | 2005| 101             | Common iliac bifurcation | 23.0         |
| Honma et al [22]    | 2006 | 146             | Common iliac bifurcation | 13.9         |
| Koppie et al [23]   | 2006 | 1,042           | Variable                | 9.0          |
| Kassouf et al [41]  | 2006 | 108             | Aortic bifurcation      | 12.0         |
| Stein et al [24]    | 2007 | 1,621           | Inferior mesenteric     | 34.0         |
| Steven and Poulsen [25]| 2007| 336             | 1-2 cm above aortic bifurcation | 27.0         |
| Dhar et al [26]     | 2008 | 322             | Aortic bifurcation      | 22.0         |
|                     |      | 336             | Common iliac bifurcation | 12.0         |
| Kassouf et al [42]  | 2008 | 248             | Aortic bifurcation      | 12.0         |
| Wright et al [43]   | 2008 | 1,260           | Not available           | 9.0          |
| Wiesner et al [28]  | 2009 | 152             | Below inferior epigastic | 43.5         |
| Osawa et al [29]    | 2009 | 60              | Common iliac bifurcation | 12.0         |
| Jensen et al [30]   | 2009 | 170             | Below inferior epigastic | 25.4         |
| Jeong et al [36]    | 2009 | 130             | Variable                | 18.3         |
| Dangle et al [34]   | 2010 | 120             | Aortic bifurcation      | 36.9         |
nodes were removed: if more than 16 lymph nodes were re-
moved, the 5-year recurrence-free survival increased from
63% to 85% in organ-confined tumors, from 40% to 55% in
pT3 tumors, and from 25% to 53% in patients with up to
five lymph node metastases.

Further support for a thorough PLND at cystectomy is
demonstrated by the fact that even N0 patients demon-
strate improved survival if more nodes are removed, pre-
sumably because this eliminates micrometastatic disease
[35]. Moreover, when Herr et al analyzed 667 patients un-
dergoing radical cystectomy, they found that the survival
of both node-negative and node-positive patients was im-
proved and the local recurrence rate was reduced when
more lymph nodes were removed [45].

These data underscore the importance of a more ex-
tended PLND regardless of the presence of node meta-
stases. However, the reasons for the observations de-
scribed above are less clear. Some clinicians suggest that
extended PLND has a potential therapeutic effect that is
due to the surgical clearance of micrometastases. Equally
if not more plausible explanations are that the retrieval of
more lymph nodes improves the accuracy of staging, the
guidance of downstream adjuvant therapies, and the dif-
ferential selection based on health status; however, these
possibilities have been relatively discounted.

These findings indicate that the higher lymph node
counts obtained by an extended PLND are associated with
improved survival. This observation, together with the fact
that up to 25% of the patients who undergo radical cys-
tectomy have nodal metastases and 30% of patients with
node-positive disease can be cured by surgery, suggests
that thorough PLND is needed to completely remove the
disease burden [13]. However, at present, there is still no
widely held consensus regarding the limits or absolute
boundaries of PLND or the minimum number of lymph no-
des that should be removed.

2. Tumor burden
Several studies have demonstrated that greater numbers
of cancer-containing nodes are associated with worse sur-
vival outcomes, which suggests that a higher number of
positive nodes is indicative of a greater tumor burden.

When Smith and Whitmore analyzed 134 patients who
were found after radical cystectomy to have lymph node
metastases, they discovered that survival correlated di-
rectly with the number of metastatic lymph nodes [46].
This study was followed by several studies examining the
prognostic impact of the tumor burden as defined by the
number of positive nodes. This included the study by Herr
and colleagues [45], who showed that the survival of pa-
ients with positive nodes who underwent radical cys-
tectomy was significantly better if ≤ 4 positive nodes were
present than if there were > 4 positive nodes (37% vs. 13%).
In addition, they went on to show that when > 11 nodes
were resected, patients showed better survival and less re-
currence [45]. Similar observations were made by other
groups. For example, Steven and Poulsen [25] found that
overall survival was improved if ≤ 5 or fewer positive nodes
were detected (50% vs. 13%). Mills et al also showed this
[12], whereas Stein et al found that patients with ≤ 8 meta-
static nodes had significantly better 10-year recurrence-
free survival rates than did those with > 8 metastatic nodes
(40% vs. 10%) [37]. Moreover, when the Mansoura group
stratified positive nodes (1 vs. 2-5 vs. > 5), this variable was
statistically significant in both the univariate and the mul-
tivariate analyses [17]. This was also the case for a pop-
ulation-based study that used the SEER database (1 vs. 2
vs. 3 vs. > 3 positive nodes) [43].

However, in the study by Kassouf et al, although the
number of involved nodes was significantly associated with
recurrence-free survival in the univariate analysis, this
variable lost statistical significance in the multivariate
analysis [41].

3. The concept of lymph node density
In 2003, Herr introduced the concept of ratio-based lymph
node staging for bladder cancer, in which the ratio is the
number of positive nodes divided by the total number of re-
trieved nodes [35]. This lymph node density concept was
an attempt to standardize lymph node staging, which had
been complicated by variability in the extent of PLND, the
meticulousness with which the pathologist identified and
reported nodal counts, and the innate anatomy of in-
dividual patients. By standardizing lymph node staging in
this manner, patients could be stratified according to
node-positivity and adjuvant therapies, and clinical trials
could be applied more uniformly. Although various lymph
node density cutoff values have been reported in the liter-
ature, the most commonly used lymph node cutoff is 20%.
Almost all studies performed on this issue have confirmed
the independent prognostic significance of lymph node
density upon multivariate analysis [17,22,25,28,29,31,35-
37,40-43,47]. These data are summarized in Table 3.

Because the tumor-node-metastasis (TNM) classification
does not account for the surgeon’s ability to remove the af-
fected nodal tissue, it may underestimate the extent of re-
gional nodal involvement. Herr et al reported that in a mul-
tivariate analysis, lymph node density stratified patients
according to disease-specific survival better than did either
the conventional staging system or the absolute number of
positive lymph nodes [45]. Similarly, Kassouf et al found
that, of the variables tested, only a lymph node density
greater than 20% was significantly predictive of a de-
creased disease-specific survival [42]. In contrast, Fleisch-
mann et al reported that when multivariate analysis was
performed by use of primary tumor stage, the number of
positive lymph nodes, lymph node density, and extra-
capsular nodal extension, only extracapsular nodal ex-
tension retained statistical significance [40].

Several studies have compared the absolute number of
positive nodes with lymph node density in terms of their
ability to predict disease-specific survival. Stein et al re-
ported that on multivariate analysis, the number of lymph
nodes involved (> 8 vs. ≤ 8) performed better than did lymph

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TABLE 3. Survival rates according to lymph node density

| References          | Year | No. of patients | Cut-off (%) | 5-year RFS | 5-year DSS | 5-year OS |
|---------------------|------|-----------------|-------------|------------|------------|-----------|
| Her [35]            | 2003 | 162             | < 20        | -          | 64.0%      | -         |
|                     |      |                 | > 20        | -          | 8.0%       | -         |
| Stein et al [37]    | 2003 | 244             | < 20        | 44.0%      | -          | 43.0%     |
|                     |      |                 | > 20        | 17.0%      | -          | 8.0%      |
| Konety et al [47]   | 2003 | 361             | 1-25        | -          | HR 1.00    | -         |
|                     |      |                 | 26-50       | -          | HR 0.89    | -         |
|                     |      |                 | 51-75       | -          | HR 1.55    | -         |
|                     |      |                 | 76-100      | -          | HR 1.72    | -         |
| Abdel-Latif et al [17]| 2004| 110             | < 10        | 56.2%      | -          | -         |
|                     |      |                 | 10-20       | 41.0%      | -          | 40.0%     |
|                     |      |                 | > 20        | 15.0%      | -          | 15.0%     |
| Fleischmann et al [40]| 2005| 101             | < 20        | 41.0%      | -          | -         |
|                     |      |                 | > 20        | 15.0%      | -          | -         |
| Honma et al [22]    | 2006 | 25              | < 20        | -          | 58.0%      | -         |
|                     |      |                 | > 20        | -          | 15.0%      | -         |
| Kassouf et al [41]  | 2006 | 108             | < 25        | 38.1%      | -          | 37.3%     |
|                     |      |                 | > 25        | 10.6%      | -          | 18.7%     |
| Steven and Poulsen [25]| 2007| 64              | < 20        | 47.0%      | -          | -         |
|                     |      |                 | > 20        | 25.0%      | -          | -         |
| Kassouf et al [42]  | 2008 | 248             | < 20        | -          | 54.6%      | -         |
|                     |      |                 | > 20        | -          | 15.3%      | -         |
| Wright et al [43]   | 2008 | 1,260           | < 12.5      | -          | HR 1.00    | HR 1.00   |
|                     |      |                 | 12.6-25     | -          | HR 1.24    | HR 1.31   |
|                     |      |                 | 25.1-50     | -          | HR 1.62    | HR 1.54   |
|                     |      |                 | > 50        | -          | HR 2.47    | HR 2.40   |
| Wiesner et al [28]  | 2009 | 46              | < 11        | -          | 38.0%      | -         |
|                     |      |                 | > 11        | -          | 7.0%       | -         |
| Osawa et al [29]    | 2009 | 60              | < 25        | -          | -          | 39.6%     |
|                     |      |                 | > 25        | -          | -          | 10.3%     |
| Bruins et al [31]   | 2009 | 181             | < 4         | 52.0%      | -          | 46.0%     |
|                     |      |                 | > 4         | 29.0%      | -          | 28.0%     |
| Jeong et al [36]    | 2009 | 130             | < 18        | -          | HR 1.00    | -         |
|                     |      |                 | > 18        | -          | HR 2.77    | -         |

RFS: recurrence-free survival, DSS: disease-specific survival, OS: overall survival, HR: hazard ratio

node density (> 20 vs. ≤ 20%) in predicting recurrence-free survival, though both factors remained statistically significant [37]. Similarly, Abdel-Latif et al demonstrated that whereas both the number of positive nodes (1 vs. 2-5 vs. > 5) and the lymph node density (≤ 10 vs. 10-20 vs. > 20%) were statistically significant in univariate analyses, only the number of positive nodes remained significant in multivariate modeling [17]. In contrast, Kassouf et al reported that whereas lymph node density (> 25 vs. ≤ 25%) remained significantly associated with overall and recurrence-free survival in a multivariate model, the number of positive nodes lost statistical significance in univariate analyses, only the number of positive nodes remained significant in multivariate modeling [17]. Thus, lymph node density may be an attractive alternative to lymph node staging. However, because all lymph node density studies performed to date are retrospective, it remains unclear whether lymph node density improves prognostication relative to the standard nodal staging system or the absolute number of positive nodes.

4. New parameters
The current TNM system is based on the number of positive lymph nodes and the size of the largest positive lymph node. Recently, a new concept in bladder oncology, namely, the aggregate size of all lymph node metastases, was investigated. Stephenson et al reported that, after adjusting for pathologic T stage, lymphovascular invasion, lymph node density, comorbidity, and extranodal extension, the aggregate lymph node metastasis diameter was a significant predictor of recurrence-free survival and overall survival [32]. However, important limitations of this study were that few patients underwent an extended PLND and the analysis was retrospective.
MORBIDITY ASSOCIATED WITH PELVIC LYMPH NODE DISSECTION

A retrospective analysis did not detect a difference between limited and extended PLND groups in terms of mortality; moreover, the lymphocele formation rate was similar for these two groups (1.5% and 1.6%, respectively) [7]. Similarly, another study showed that lymphoceles and lymphoedema occurred in 2% and 1% of patients who had <16 and ≥16 lymph nodes removed, respectively [10]. Moreover, perioperative deaths or early complications that related directly to the PLND were not observed in 1,054 patients who all underwent an extended PLND [13]. These findings were confirmed recently by a study that questioned whether an extended PLND would increase morbidity in patients who underwent radical cystectomy [48]. Although the extended PLND increased the operative duration by 63 min, the limited and extended PLND groups did not differ significantly in terms of perioperative mortality, early complications, or the need for blood transfusions. Similarly, when a multicentre study prospectively evaluated the role of an extended PLND in 290 patients undergoing cystectomy for bladder cancer, none of the participating centers reported any significant adverse effects that were related to the extended PLND [4]. These findings suggest that despite prolonging the operation, an extended PLND does not increase the complication rate either during or after surgery. Indeed, it appears that the morbidity associated with an extended PLND is low and comparable to that associated with a more limited PLND.

It should be noted that although the administration of neoadjuvant radiation or chemotherapy before cystectomy does not increase the morbidity and mortality associated with cystectomy, patients who have received these treatments should be judged carefully with regard to also undergoing extended PLND [49]. This is because patients who have had higher doses of radiation therapy (>60 Gy) are at greater risk of vascular and associated injuries when undergoing a cystectomy [50].

CONCLUSIONS

A recent SEER analysis of 3,603 cystectomies that were performed between 1992 and 2003 revealed that PLND did not seem to be performed routinely during this period; moreover, when it was performed, the number of nodes retrieved was suboptimal [51]. However, a more recent SEER analysis showed that there has been an improvement over time in terms of the performance of PLND and the node counts obtained during radical cystectomy [52].

Lymph node assessment is an important component of bladder cancer staging because nodal status correlates strongly with prognosis. PLND also contributes to the cure of some patients with nodal metastases. Lymph node density may become a more useful prognostic variable in patients with high-risk node-positive disease.

Although the optimal extent of PLND remains to be defined and cannot be determined on the basis of the retrospective studies that have been published to date, current observations suggest that an extended PLND not only provides prognostic information, it also has a clinically significant therapeutic benefit for patients with invasive bladder cancer. However, whether extended PLND improves overall survival or whether that benefit applies only to particular subgroups should be addressed by randomized clinical trials. Such future studies will help to identify the optimal staging template and to clarify the therapeutic benefits of PLND.

Conflicts of Interest

The authors have nothing to disclose.

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