Review Article

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

Ja Hyeon Ku

Department of Urology, Seoul National University Hospital, Seoul, Korea

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

Corresponding Author:
Ja Hyeon Ku
Department of Urology, Seoul National University Hospital, 28, Yeongeon-dong, Jongno-gu, Seoul 110-744, Korea
TEL: +82-2-2072-0361
FAX: +82-2-742-4665
E-mail: kuuro70@snu.ac.kr

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-

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	682	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
Honma 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 median 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
		45	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
Abol-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 removed, 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 demonstrate improved survival if more nodes are removed, presumably because this eliminates micrometastatic disease [35]. Moreover, when Herr et al analyzed 667 patients undergoing radical cystectomy, they found that the survival of both node-negative and node-positive patients was improved and the local recurrence rate was reduced when more lymph nodes were removed [45].

These data underscore the importance of a more extended PLND regardless of the presence of node metastases. However, the reasons for the observations described 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 differential 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 cystectomy 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 nodes that should be removed.

2. Tumor burden

Several studies have demonstrated that greater numbers of cancer-containing nodes are associated with worse survival 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 directly 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 patients with positive nodes who underwent radical cystectomy 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 recurrence [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 metastatic 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 multivariate analyses [17]. This was also the case for a population-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 retrieved 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 individual 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 literature, 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 affected nodal tissue, it may underestimate the extent of regional nodal involvement. Herr et al reported that in a multivariate 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 decreased disease-specific survival [42]. In contrast, Fleischmann 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 extracapsular nodal extension, only extracapsular nodal extension 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 reported that on multivariate analysis, the number of lymph nodes involved (>8 vs. ≤8) performed better than did lymph

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	38.9%	-	-
			>20	16.4%	-	-
Fleischmann et al [40]	2005	101	<20	41.0%	-	40.0%
			>20	15.0%	-	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. $\leq20\%$) 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 [41]. With regard to population-based studies, Konety et al reported that whereas the number of positive nodes did not correlate significantly with survival, the lymph node density showed some predictive ability, especially at a cutoff of 50% [47]. However, Wright et al found that the number of positive nodes (1 vs. 2 vs. 3 vs. >3) and lymph node density (divided into quartiles) both correlated significantly with disease-specific and overall survival [43].

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.

REFERENCES

1. Prout GR, Marshall VF. The prognosis with untreated bladder tumors. Cancer 1956;9:551-8.
2. Skinner DG. Management of invasive bladder cancer: a meticulous pelvic node dissection can make a difference. J Urol 1982;128:34-6.
3. Vazina A, Dugi D, Shariat SF, Evans J, Link R, Lerner SP. Stage specific lymph node metastasis mapping in radical cystectomy specimens. J Urol 2004;171:1830-4.
4. Leissner J, Ghoneim MA, Abol-Enein H, Thüroff JW, Franzaring L, Fisch M, et al. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. J Urol 2004;171:139-44.
5. Abol-Enein H, El-Baz M, Abd El-Hameed MA, Abdel-Latif M, Ghoneim MA. Lymph node involvement in patients with bladder cancer treated with radical cystectomy: a patho-anatomical study--a single center experience. J Urol 2004;172:1818-21.
6. Ghoneim MA, El-Mekresh MM, el-Baz MA, el-Attar IA, Ashamallah A. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. J Urol 1997;158:393-9.
7. Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. J Urol 1998;160:2015-9.
8. Vieweg K, Gschwend JE, Herr HW, Fair WR. Pelvic lymph node dissection can be curative in patients with node positive bladder cancer. J Urol 1999;161:449-54.
9. Bassi P, Ferrante GD, Piazza N, Spinadin R, Carando R, Pappagallo G, et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. J Urol 1999;161:1494-7.
10. Leissner J, Hohenfellner R, Thüroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU Int 2000;85:817-23.
11. Herr HW, Donat SM. Outcome of patients with grossly node positive bladder cancer after pelvic lymph node dissection and radical cystectomy. J Urol 2001;165:62-4.
12. Mills RD, Turner WH, Fleischmann A, Markwalder R, Thalmann GN, Studer UE. Pelvic lymph node metastases from bladder cancer: outcome in 83 patients after radical cystectomy and pelvic lymphadenectomy. J Urol 2001;166:19-23.
13. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001;19:666-

75.

14. Gschwend JE, Dahm P, Fair WR. Disease specific survival as endpoint of outcome for bladder cancer patients following radical cystectomy. Eur Urol 2002;41:440-8.

15. Gaitonde K, Goyal A, Nagaonkar S, Patil N, Singh DR, Srinivas V. Retrospective review and long-term follow-up of radical cystectomy in a developing country. BJU Int 2002;89(Suppl 1):57-61.

16. Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, et al. Radical cystectomy for bladder cancer today--a homogeneous series without neoadjuvant therapy. J Clin Oncol 2003;21:690-6.

17. Abdel-Latif M, Abol-Enein H, El-Baz M, Ghoneim MA. Nodal involvement in bladder cancer cases treated with radical cystectomy: incidence and prognosis. J Urol 2004;172:85-9.

18. Nishiyama H, Habuchi T, Watanabe J, Teramukai S, Tada H, Ono Y, et al. Clinical outcome of a large-scale multi-institutional retrospective study for locally advanced bladder cancer: a survey including 1131 patients treated during 1990-2000 in Japan. Eur Urol 2004;45:176-81.

19. Fleischmann A, Thalmann GN, Markwalder R, Studer UE. Prognostic implications of extracapsular extension of pelvic lymph node metastases in urothelial carcinoma of the bladder. Am J Surg Pathol 2005;29:89-95.

20. Hautmann RE, Gschwend JE, de Petriconi RC, Kron M, Volkmer BG. Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. J Urol 2006; 176:486-92.

21. Shariat SF, Karakiewicz PI, Palapattu GS, Lotan Y, Rogers CG, Amiel GE, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. J Urol 2006;176:2414-22.

22. Honma I, Masumori N, Sato E, Maeda T, Hirobe M, Kitamura H, et al. Removal of more lymph nodes may provide better outcome, as well as more accurate pathologic findings, in patients with bladder cancer--analysis of role of pelvic lymph node dissection. Urology 2006;68:543-8.

23. Koppie TM, Vickers AJ, Vora K, Dalbagni G, Bochner BH. Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? Cancer 2006;107:2368-74.

24. Stein JP, Penson DF, Cai J, Miranda G, Skinner EC, Dunn MA, et al. Radical cystectomy with extended lymphadenectomy: evaluating separate package versus en bloc submission for node positive bladder cancer. J Urol 2007;177:876-81.

25. Steven K, Poulsen AL. Radical cystectomy and extended pelvic lymphadenectomy: survival of patients with lymph node metastasis above the bifurcation of the common iliac vessels treated with surgery only. J Urol 2007;178:1218-23.

26. Dhar NB, Klein EA, Reuther AM, Thalmann GN, Madersbacher S, Studer UE. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. J Urol 2008;179:873-8.

27. Ghoneim MA, Abdel-Latif M, el-Mekresh M, Abol-Enein H, Mosbah A, Ashamallah A, et al. Radical cystectomy for carcinoma of the bladder: 2,720 consecutive cases 5 years later. J Urol 2008; 180:121-7.

28. Wiesner C, Salzer A, Thomas C, Gellermann-Schultes C, Gillitzer R, Hampel C, et al. Cancer-specific survival after radical cystectomy and standardized extended lymphadenectomy for node-positive bladder cancer: prediction by lymph node positivity and density. BJU Int 2009;104:331-5.

29. Osawa T, Abe T, Shinohara N, Harabayashi T, Sazawa A, Kubota K, et al. Role of lymph node density in predicting survival of pa-

tients with lymph node metastases after radical cystectomy: a multi-institutional study. Int J Urol 2009;16:274-8.

30. Jensen JB, Ulhoi BP, Jensen KM. Lymph node mapping in patients with bladder cancer undergoing radical cystectomy and lymph node dissection to the level of the inferior mesenteric artery. BJU Int 2009;Epub ahead of print

31. Bruins HM, Huang GJ, Cai J, Skinner DG, Stein JP, Penson DF. Clinical outcomes and recurrence predictors of lymph node positive urothelial cancer after cystectomy. J Urol 2009;182:2182-7.

32. Stephenson AJ, Gong MC, Campbell SC, Fergany AF, Hansel DE. Aggregate lymph node metastasis diameter and survival after radical cystectomy for invasive bladder cancer. Urology 2010;75: 382-6.

33. Seiler R, von Gunten M, Thalmann GN, Fleischmann A. Pelvic lymph nodes: distribution and nodal tumour burden of urothelial bladder cancer. J Clin Pathol 2010;63:504-7.

34. Dangle PP, Gong MC, Bahnson RR, Pohar KS. How do commonly performed lymphadenectomy templates influence bladder cancer nodal stage? J Urol 2010;183:499-503.

35. Herr HW. Superiority of ratio based lymph node staging for bladder cancer. J Urol 2003;169:943-5.

36. Jeong IG, Park J, Song K, Ro JY, Song C, Hong JH, et al. Comparison of 2002 TNM nodal status with lymph node density in node-positive patients after radical cystectomy for bladder cancer: analysis by the number of lymph nodes removed. Urol Oncol 2009;Epub ahead of print

37. Stein JP, Cai J, Groshen S, Skinner DG. Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. J Urol 2003;170:35-41.

38. Herr HW, Faulkner JR, Grossman HB, Natale RB, deVere White R, Sarosdy MF, et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol 2004;22: 2781-9.

39. Herr H, Lee C, Chang S, Lerner S. Bladder Cancer Collaborative Group. Standardization of radical cystectomy and pelvic lymph node dissection for bladder cancer: a collaborative group report. J Urol 2004;171:1823-8.

40. Fleischmann A, Thalmann GN, Markwalder R, Studer UE. Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. J Clin Oncol 2005;23:2358-65.

41. Kassouf W, Leibovici D, Munsell MF, Dinney CP, Grossman HB, Kamat AM. Evaluation of the relevance of lymph node density in a contemporary series of patients undergoing radical cystectomy. J Urol 2006;176:53-7.

42. Kassouf W, Agarwal PK, Herr HW, Munsell MF, Spiess PE, Brown GA, et al. Lymph node density is superior to TNM nodal status in predicting disease-specific survival after radical cystectomy for bladder cancer: analysis of pooled data from MDACC and MSKCC. J Clin Oncol 2008;26:121-6.

43. Wright JL, Lin DW, Porter MP. The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. Cancer 2008; 112:2401-8.

44. Bochner BH, Cho D, Herr HW, Donat M, Kattan MW, Dalbagni G. Prospectively packaged lymph node dissections with radical cystectomy: evaluation of node count variability and node mapping. J Urol 2004;172:1286-90.

45. Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. J Urol

2002;167:1295-8.

46. Smith JA, Whitmore Jr WF. Regional lymph node metastasis from bladder cancer. J Urol 1981;126:591-3.

47. Konety BR, Joslyn SA, O'Donnell MA. Extent of pelvic lymphade-nectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemi-ology and End Results Program data base. J Urol 2003;169:946-50.

48. Brossner C, Pycha A, Toth A, Mian C, Kuber W. Does extended lymphadenectomy increase the morbidity of radical cystectomy? BJU Int 2004;93:64-6.

49. Stein JP, Quek ML, Skinner DG. Lymphadenectomy for invasive bladder cancer. II. technical aspects and prognostic factors. BJU Int 2006;97:232-7.

50. Crawford ED, Skinner DG. Salvage cystectomy after irradiation failure. J Urol 1980;123:32-4.

51. Hollenbeck BK, Ye Z, Wong SL, Montie JE, Birkmeyer JD. Hospital lymph node counts and survival after radical cystec-tomy. Cancer 2008;112:806-12.

52. Hellenthal NJ, Ramírez ML, Evans CP, deVere White RW, Koppie TM. Trends in pelvic lymphadenectomy at the time of radi-cal cystectomy: 1988 to 2004. J Urol 2009;181:2490-5.