Lymphadenectomy for invasive bladder cancer. II. technical aspects and prognostic factors

JOHN P. STEIN, MARCUS L. QUEK and DONALD G. SKINNER

From the Department of Urology, University of Southern California Keck School of Medicine, USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Accepted for publication 19 August 2005

KEYWORDS

bladder cancer, cystectomy, lymphadenectomy, lymph-node metastases, prognosis

INTRODUCTION

The role of a lymphadenectomy in genitourinary tumours has gained recent attention. There is little debate about the benefits of a lymph-node dissection (LND) in testicular tumours and penile cancer. Evidence also supports the concept of LND in patients undergoing radical prostatectomy for prostate cancer [1] and radical nephrectomy for RCC [2]. The role of LND also appears to be an important component in patients with high-grade, invasive bladder cancer undergoing cystectomy. The rationale is based on the natural history of the disease. Invasive bladder tumours tend to progressively invade from their superficial origin in the mucosa, to the lamina propria, and sequentially into the muscularis propria, perivesical fat and contiguous pelvic organs, with an increasing incidence of lymph node involvement at each site.

An extended regional lymphadenectomy can provide not only prognostic information, but also a clinically significant therapeutic benefit for patients with invasive bladder cancer. Despite the accumulating evidence that a more extensive LND is an important component in the surgical management of bladder TCC, there is controversy about the limits of an appropriate lymphadenectomy. In this review we discuss the technical issues related to the LND and its pathological analysis. We also review data on the prognostic information that can be gained through an extended lymphadenectomy.

SURGICAL BOUNDARIES OF THE LYMPHADENECTOMY

An 'extended' lymphadenectomy must include all lymph nodes in the boundaries of: the aortic bifurcation and common iliac vessels (proximally); the genitofemoral nerve (laterally); the circumflex iliac vein and lymph node of Cloquet (distally); the hypogastric vessels (posteriorly), including the obturator fossa, pre-sciatic nodes bilaterally, and the presacral lymph nodes anterior to the sacral promontory. An extended dissection may also extend superiorly to the level of the inferior mesenteric artery. A so-called 'standard' lymphadenectomy is more limited, with the cephalad extent generally beginning at the level of the common iliac bifurcation. The lateral and distal limits are similar to the extended dissection. In general, the proximal dissection extending along the common iliacs and great vessels includes all nodal tissue anterior and lateral, while the nodal dissection along the external iliacs is completely circumferential.

FACTORS INFLUENCING THE NUMBER OF LYMPH NODES EVALUATED OR RETRIEVED

The lymphadenectomy in patients undergoing radical cystectomy is an important diagnostic tool that provides staging and possibly also therapeutic benefits. The number of lymph nodes assessed pathologically depends upon several factors including: (i) the boundaries of the LND (extended verses standard or even more limited); (ii) the pathologist's diligence in searching and preparing the lymph nodes for histopathological evaluation; and (iii) how the specimen is actually submitted for pathological evaluation. Furthermore, variation within patients in lymph node numbers may also affect the number of nodes retrieved. These factors collectively contribute to determining the actual number of lymph nodes retrieved, and the exact incidence and extent of lymph-node tumour involvement.

Diligent pathological evaluation is essential for identifying the total number of nodes removed and the amount of nodal metastases. In general, most lymph nodes are identified visually and by palpation, with no need for clearing techniques or solvents. With this technique, in a large group of 244 patients with lymph node-positive disease, undergoing an *en bloc* radical cystectomy and extended lymphadenectomy, a median of 30 lymph nodes were removed and evaluated [3]. It was recently suggested that to facilitate nodal evaluation, separate nodal packets should be submitted intra-operatively by the surgeon [4]. Simply converting from an *en bloc* technique to submission of six separate lymph-node packets (while maintaining the limits of dissection) the mean number of lymph nodes removed increased by more than three times [5]. We have adopted a similar approach at our institution, with submission of 12 individual lymph-node packets. This modification has significantly increased the median number of lymph nodes removed/evaluated from 30 to 56 (unpublished data).

The absolute limits of the LND may be the most important factor and have the greatest impact upon the number of lymph nodes removed during cystectomy. In two large cystectomy series, in which there was an extended lymphadenectomy, the median number of lymph nodes removed was 30–43 [3,6]. Extending the boundaries of the LND, Poulsen *et al.* [7] reported an increase in the mean number of lymph nodes removed from 14 in a standard dissection, to 25 when the dissection was carried up to the bifurcation of the aorta. Bochner *et al.* [4] confirmed these findings, reporting significantly more nodes removed with an extended dissection than a more standard dissection, at 36.5 vs 8.5, respectively. Furthermore, the concept of a more extended lymphadenectomy increasing

© 2006 BJU INTERNATIONAL | 97, 232–237 | doi:10.1111/j.1464-410X.2006.05901.x

the lymph node yield was also confirmed with a laparoscopic approach [8]. The median number of lymph nodes removed in an extended laparoscopic lymphadenectomy was 22, compared to only three with a limited dissection.

It is clear that the influence of the surgeon and pathologist are both important factors in determining the lymph-node count and involvement of tumour. Although the exact number of nodes that should be removed at the time of cystectomy is unknown, it appears that extending the limits of the dissection and submitting the lymph nodes in packets increases the number of lymph nodes retrieved and evaluated. Fat-clearing, immunohistochemical and molecular techniques may increase the nodal counts, but these specialized methods are more expensive, time-consuming, and may not necessarily provide any additional prognostic information, particularly if an extended lymphadenectomy is performed. Indeed, a recent report evaluated various factors that contribute to the variability in the number of reported lymph nodes removed at cystectomy; only the extent of the LND was found to significantly influence the nodal yield [5].

WHAT IS THE REQUIRED NUMBER OF LYMPH NODES THAT MUST BE REMOVED? THE IMPACT OF THE SURGICAL PROCEDURE

There is a growing body of evidence in bladder cancer and in other malignancies requiring surgical excision, to suggest that a minimum number of lymph nodes should be removed and evaluated. In colorectal cancer, a meticulous dissection with a total mesorectal excision led to a 20–25% reduction in the risk of pelvic recurrence, and a similar substantial improvement in survival [9–12]. A complete LND with removal of a minimum number of lymph nodes has also been documented in breast [13] and gastric cancers [14].

The dedication and technical commitment of the surgeon to an appropriate cystectomy with an adequate lymphadenectomy is also important to the success and clinical outcomes in patients with high-grade bladder cancer. The importance of surgical technique is well illustrated in the role this played in a recently reported randomized multi-institutional cooperative group trial [15].

In this prospective study, 270 patients underwent cystectomy, with half of the patients receiving neoadjuvant chemotherapy. In a separate analysis of this trial, various surgical factors were subsequently analysed [16]. In these 270 patients, 24 had no LND, 98 had a limited dissection of the obturator lymph nodes only, and 146 patients had a so-called standard (not extended) pelvic LND. The 5-year survival rates for these groups were 33%, 46% and 60%, respectively. The median number of lymph nodes removed for the entire cohort was 10. As expected, the survival rate for patients with <10 lymph nodes removed was significantly lower than patients with >10 lymph nodes removed, at 44% vs 61%, respectively. In a multivariate analysis, the extent of the LND, number of lymph nodes removed, and the number of patients operated by the individual surgeon were the most significant factors influencing survival in patients undergoing cystectomy for bladder cancer. We emphasize that, although this well publicized study was not intended to analyse the surgical approach and/or technical differences in the treatment of bladder cancer, it was the surgical factors, not the neoadjuvant chemotherapy, that were most critical as predictors in the outcomes of these patients [16].

Many factors can influence the surgical approach and extent of the lymphadenectomy in patients with bladder cancer. Patient age, associated comorbidities and the extent of disease may all play a role in the decision process. In addition, the comfort and experience of the surgeon is also important. It was suggested in prostate cancer that experienced urological oncologists performing radical prostatectomy, in high-volume centres, tend to achieve better outcomes than surgeons who perform fewer cases in low-volume institutions [17]. This may also apply to radical cystectomy. Interestingly, in a recent analysis of the Surveillance, Epidemiology and End-Results (SEER) programme cancer registry, only 40% of patients who underwent cystectomy for bladder cancer had a LND, and in half of all eligible patients the urologist elected not to perform a cystectomy at all [18]. It is apparent that the surgical management of bladder cancer in this country varies tremendously and, despite a growing body of evidence to suggest that an aggressive surgical approach with an appropriate lymphadenectomy may benefit patients, this is not always done.

Guidelines for the surgical management of patients with TCC undergoing cystectomy have recently been proposed by the Bladder Cancer Collaborative Group [19]. In all, 16 experienced surgeons from four academic institutions contributed 1091 cystectomy patients over a 3-year period. The authors concluded that at least 10 cystectomies per year are required to maintain proficiency. At least 10–14 lymph nodes should be retrieved, with a margin-positive rate of <10% of all cases (<15% for bulky tumours and <20% for salvage cases). Notably, the authors also found that a complete/standard lymphadenectomy correlated with fewer positive margins and increased node counts in patients with positive- and negative-nodal disease [19]. This too argues for a more extensive lymphadenectomy in patients undergoing radical cystectomy for bladder cancer.

THE MORBIDITY AND MORTALITY OF LYMPHADENECTOMY

Understanding that a LND is important in the management of patients undergoing radical cystectomy for bladder cancer, coupled with the fact that a more extensive lymphadenectomy may provide more accurate pathological staging and survival benefits, one must carefully evaluate the risks associated with an extended LND. This is an important issue, particularly in patients with bladder cancer, who tend to be elderly with associated comorbidities.

In a series of 1054 patients [20], uniformly undergoing an extended lymphadenectomy, the reported perioperative mortality was 3%, with an early complication rate of 28%. There were no perioperative deaths or early complications related directly to the LND. Furthermore, in the subgroup analysis of patients with lymph node-positive disease, the operative mortality was 1%, with an early complication rate of 27% [3]. There were no differences when comparing this pathological group to those patients with organ-confined and extravesical tumours, with no lymph-node tumour metastases. Although the administration of neoadjuvant radiation and/or chemotherapy before cystectomy had no impact upon the morbidity and mortality of the cystectomy, prudent judgement must be used in selecting patients. Patients having higher doses or radiation therapy (>60 Gy) are at higher risk of vascular and associated

injuries at the time of cystectomy, and may not be appropriate candidates for an extended lymphadenectomy [21].

These findings were recently confirmed in a study that questioned whether an extended lymphadenectomy would increase morbidity in patients undergoing radical cystectomy [22]. In all, 46 patients undergoing an extended lymphadenectomy (cephalad dissection at the level of the inferior mesenteric artery) were compared to 46 undergoing a more 'standard' dissection, with the cephalad extent at the region of the common iliac artery bifurcation. Patients were well matched for associated comorbidities and American Society of Anesthesiologist (ASA) grade. Overall, 30% of patients were found to have lymph-node metastases. Although the extended lymphadenectomy increased the operative duration by 63 min, there was no significant difference in perioperative mortality, early complications, or the need for blood transfusions between the groups. The authors concluded that despite prolonging the operation, an extended lymphadenectomy does not apparently result in an increased complication rate during or after (within 30 days) surgery [22].

In a retrospective analysis, the outcomes of an extended LND (cephalad limits at the level of the aortic bifurcation) were compared to a more limited pelvic LND bounded proximally by the bifurcation of the common iliac vessels [7]. The lateral, distal and posterior dissections were similar. As expected, the median number of lymph nodes removed was significantly higher in the extended than in the limited group. There was no difference in the mortality, and a lymphocele formed in two (1.6%) patients in the extended and in one (1.5%) in the limited group [7]. The findings were similar in patients undergoing cystectomy and an extended LND. In 447 patients there were lymphoceles and lymphoedema in 2% of patients with <16 lymph nodes removed and in 1% with ≥16 lymph nodes removed [23]. Collectively, these studies suggest the morbidity associated with an extended lymphadenectomy is low and comparable to a more limited LND.

A recent multicentre study prospectively evaluated the role of an extended lymphadenectomy in 290 patients undergoing cystectomy for bladder cancer [6]. Although an extended LND required 60 min longer than a more limited lymphadenectomy, immediately after surgery none of the participating centres reported any significant adverse effects related to the extended lymphadenectomy. In some cases there was greater postoperative lymphatic drainage; however, all drains in that report were safely removed 3–10 days after the operation [6].

Even in experienced hands the exact time taken for an extended lymphadenectomy can be 30–60 min longer than a more limited dissection. The surgeon should be committed to a complete and meticulous lymphadenectomy. Experience in LND along large vessels is helpful. The surgeon should feel comfortable with the basic premises of vascular surgery, and have a sound understanding of the regional anatomy. If done properly an extended LND supports the remaining portion of the operation, which can then be done safely, with proper vascular control, and reduces the potential for significant blood loss. Furthermore, this surgical approach also apparently helps to reduce the incidence of positive surgical margins [19], which should not exceed 3% even for locally advanced tumours with lymph node involvement [24].

PROGNOSTIC FACTORS IN PATIENTS WITH LYMPH-NODE METASTASES AFTER RADICAL CYSTECTOMY

To provide risk stratification and to better direct the need for adjuvant treatments, various prognostic factors have been identified in patients with lymph-node metastases after radical cystectomy. Such patients are at greater risk of tumour recurrence and progression than other pathological subgroups (organ-confined and extravesical, lymph node-negative tumours) [7,20,25]. Traditional risk factors stratifying patients with lymph-node metastases include the extent of the primary bladder tumour (p stage), and the total number of lymph nodes involved with tumour (tumour burden). There is also evidence to suggest that the survival in these patients involves the extent of the lymphadenectomy that is reflected by the number of lymph nodes removed. Lastly, the concept of lymph-node density also provides significant prognostic information in patients with lymph node-positive disease after radical cystectomy. Despite the high-risk nature of node-positive bladder cancer, nearly a third of patients will have long-term survival after radical cystectomy [3,20]. Therefore, evaluating certain risk factors in patients with node-positive disease will provide risk stratification and should help to better direct the need for adjuvant therapy based upon established indices.

NUMBER OF LYMPH NODES INVOLVED (TUMOUR BURDEN)

The number of positive lymph nodes, or number of lymph nodes involved with tumour (tumour burden) is recognized as an important prognostic factor in patients with bladder cancer after radical cystectomy [3,20,23,26–35]. As expected, survival and recurrence are inversely related to an increasing tumour burden. Smith and Whitmore [36] initially reported on 134 patients with lymph-node metastases after radical cystectomy and found that survival directly correlated with the number of lymph nodes involved. Lerner *et al.* [29] reported on 132 patients with nodal metastases and found that patients with five or fewer positive lymph nodes had a significantly better recurrence-free and overall survival than those with six or more lymph nodes involved with tumour.

Herr *et al.* [35] examined a cohort of 322 patients undergoing radical cystectomy and found that survival was significantly better for the 64 (20%) patients with node-positive disease if they had four or fewer positive lymph nodes than those with more than four (37% vs 13%, respectively). Furthermore, in this node-positive group of patients, if more than 11 lymph nodes were removed (total) there was better survival and local pelvic control of the tumour. These data underscore the importance of a more extended lymphadenectomy in patients with node-positive bladder cancer. Interestingly, in that study of 258 lymph node-negative patients, survival was also directly proportional to the number of lymph nodes removed. The authors appropriately comment that the more lymph nodes identified may reflect a more complete radical cystectomy and lymphadenectomy in both lymph node-positive and -negative patients. These findings were subsequently supported in a larger group of 148 node-positive patients by the same author [37].

Several other studies also support the correlation between the number of lymph-node metastases and survival in patients after

radical cystectomy. In the largest reported series of 244 lymph node-positive patients, with a long-term follow-up (median 10 years), the number of lymph nodes involved with tumour was a significant and independent prognostic factor for survival in patients after cystectomy [3]. Patients with eight or fewer positive lymph nodes had significantly higher survival rates than those with more than eight positive lymph nodes. The 5- and 10-year recurrence-free survival for patients with eight or fewer positive lymph nodes was 41% and 40%, respectively, compared to a 10% recurrence-free survival at 10 years when more than eight lymph nodes were involved with tumour [3].

EXTENT OF THE PRIMARY BLADDER TUMOUR (PATHOLOGICAL STAGE)

The prognosis of patients with node-positive disease after radical cystectomy is strongly associated with the pathological stage of the primary bladder tumour (p stage) [3,20,26,29,30,34,38]. Vieweg *et al.* [30] showed that survival was significantly related to the stage of the primary tumour in 193 patients with node-positive disease after cystectomy. In that series, patients with organ-confined (P0-P3a) node-positive disease had a 58% probability of surviving 5 years, compared to only a 22% 5-year survival in patients with extravesical, lymph node-positive disease. The University of Southern California (USC) group reported that the recurrence-free and overall survival in 244 patients with lymph node-positive disease was significantly related to the pathological subgroup (organ-confined vs extravesical) of the primary bladder tumour [3]. Patients with organ-confined, lymph node-positive tumours had a 5- and 10-year recurrence-free survival of 46% and 44%, respectively. These survival rates were significantly better than the 30% 5- and 10-year rates for patients with extravesical, lymph node-positive disease. Furthermore, in a multivariate analysis the extent of the primary bladder tumour remained a significant and independent prognostic factor in patients with lymph node-positive tumours [30]. Similar findings were reported by the Mansoura group, in which the primary bladder tumour stage significantly influenced both incidence and survival in patients with node-positive disease after radical cystectomy [26].

NUMBER OF LYMPH NODES REMOVED (EXTENT OF LYMPHADENECTOMY)

The number of lymph nodes removed at the time of cystectomy appears to relate to the extent or completeness of the LND. As noted, Poulsen *et al.* [7] showed that extending the limits of the LND from the bifurcation of the common iliac vessels up to the level of the aortic bifurcation increased the median number of lymph nodes removed from 14 to 25. Although the absolute limits or extent of the LND have not been precisely defined, there is increasing data to suggest that a minimum number of lymph nodes should be removed and pathologically evaluated during radical cystectomy [3,18,19,23,31,33,35,37]. This concept of the total number of lymph nodes removed has been shown to be of prognostic significance in other genitourinary malignancies, e.g. RCC [2] and prostate cancer [1].

The extent of the lymphadenectomy (number of lymph nodes removed) appears to have prognostic significance in both lymph node-positive and -negative patients with bladder cancer after radical cystectomy. Herr *et al.* [35] reported on 667 patients undergoing radical cystectomy, comprising 489 (77%) node-negative and 148 (23%) node-positive patients. Survival for both node-negative and -positive patients was improved, with a reduced local recurrence rate, when more lymph nodes were removed. Leissner *et al.* [23] evaluated 447 patients who had radical cystectomy and found a significantly better survival if more lymph nodes were removed. This was true for those with no lymph-node metastases and for those with five or fewer positive lymph nodes. In that study, if more than 16 lymph nodes were removed the 5-year recurrence-free survival increased from 63% to 85% in organ-confined tumours, from 40% to 55% in pT3 tumours, and from 25% to 53% in patients with at most five lymph-node metastases. Furthermore, if at least 20 lymph nodes were removed ≈80% of lymph node-positive patients would be identified, suggesting that this would be a reasonable number of lymph nodes to be removed and evaluated at cystectomy [23].

Similarly, Poulsen *et al.* [7] showed that extending the limits of the pelvic LND was of benefit in the subset of patients with organ-confined, lymph node-negative bladder tumours. The 5-year recurrence-free survival with organ-confined, node-negative tumours was 85% with an extended LND compared to 64% with similar pathology undergoing a more limited LND. Furthermore, an extended LND reduced the pelvic and distant metastases rate in these patients [7]. Additional confirmation came from an analysis of >20 000 patients with bladder cancer (1923 undergoing cystectomy) included in the SEER cancer registry [18]. In this large cohort it was determined that the risk of death was significantly higher in patients with fewer than four lymph nodes removed at cystectomy, independent of stage and lymph node-positive disease. In that study, the most important survival factor in patients undergoing cystectomy, effectively controlling for age, tumour stage, histology, chemotherapy and radiation therapy, was the removal of 10–14 lymph nodes at the time of surgery [18].

It was proposed that an extended LND (in both node-positive and -negative patients) may relate to the removal of undetected lymph-node micrometastases, and thus may improve survival in patients undergoing cystectomy. Despite these data suggesting that more lymph nodes removed at the time of cystectomy for all patients is beneficial and that an extended LND will remove more nodes, there is currently no uniform consensus on the limits or absolute boundary of the LND, or the minimum number of lymph nodes that should be removed.

LYMPH-NODE DENSITY (NUMBER OF LYMPH NODES INVOLVED/NUMBER OF LYMPH NODES REMOVED)

Both the extent of the lymphadenectomy and lymph-node tumour burden are known to be significant risk factors in patients undergoing radical cystectomy. To account for the number of lymph nodes removed (extent of the LND) and the total number of lymph nodes involved (tumour burden), the concept of lymph-node density for patients with node-positive bladder cancer has been suggested [3]. Lymph-node density is defined as the number of lymph nodes involved with tumour divided by the total number of lymph nodes removed. If the tumour burden and the extent of the lymphadenectomy are important variables in patients with node-positive bladder cancer, it is logical that lymph-node density should also be prognostic. In the USC group of 244 lymph node-positive patients, lymph-node density was a significant and independent prognostic

factor. Patients with a lymph-node density of ≤20% had a 43% 10-year recurrence-free survival, compared to only a 17% survival at 10 years when the lymph-node density was >20%.

Herr [31] reported results on this concept of lymph-node density, described as 'ratio-based' lymph node staging. In 162 patients with lymph node-positive disease, this ratio system better defined the surgical outcomes in these patients. The 5-year survival in patients with node-positive disease and a lymph-node density of <20% was 64%, significantly higher than the 8% 5-year survival for the same pathological group of patients with a lymph-node density of >20%. Similarly, the proportion of positive lymph nodes to excised lymph nodes (lymph-node density) for metastatic bladder cancer correlated with the risk of death from bladder cancer in the SEER registry of patients undergoing radical cystectomy [18].

The concept of lymph-node density collectively accounts for the lymph-node burden and the extent of the LND, both of which clearly have prognostic significance. Lymph-node density better stratifies lymph node-positive patients into various risk groups that may be useful in future staging systems. Future adjuvant therapies and clinical trials should consider applying this concept, as it may help to reduce the surgical bias and extent of the lymphadenectomy, both of which are currently not standardized.

EXTRACAPSULAR EXTENSION OF NODAL METASTASES

The importance of extracapsular nodal extension in patients undergoing cystectomy for bladder cancer was first published by Mills *et al.* [28], who showed a statistically significant survival advantage for patients with no lymph-node capsule perforation than in those without. Indeed, they found that in their series of node-positive patients, only capsule perforation was independently significant, with a greater than doubling of the risk of dying from the disease if the capsule was perforated. The same group reported similar results in a larger cohort of patients and suggested that capsule perforation should be reported routinely and should be included in future staging systems [39].

CONCLUSIONS

Radical cystectomy with bilateral pelvic iliac lymphadenectomy is a standard treatment for high-grade, invasive bladder cancer, arguably providing the best survival outcomes and the lowest local recurrence rates. An extended LND may provide a survival advantage in both node-positive and -negative tumours without significantly increasing the morbidity or mortality of the surgery. The extent of the primary bladder tumour (p stage), number of lymph nodes removed, the lymph-node tumour burden, and extracapsular nodal penetration are all important prognostic variables in patients undergoing cystectomy with pathological evidence of lymph-node metastases. Lymph-node density may become an even more useful prognostic variable in these high-risk, node-positive patients with bladder cancer. This concept simultaneously incorporates both the lymph-node tumour burden (number of lymph nodes involved) and the number of lymph nodes removed (extent of the lymphadenectomy), which may improve stratification of node-positive patients after radical cystectomy. This notion may also be useful in future staging systems. The use of adjuvant therapies and clinical trials should consider applying these concepts as it may help to reduce bias and provide a certain standard or quality of surgery which should be incorporated into the cystectomy and extent of the lymphadenectomy, which are currently not standardized.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Barth PJ, Gerharz EW, Ramaswamy A, Riedmiller H.** The influence of lymph node counts on the detection of pelvic lymph node metastasis in prostate cancer. *Pathol Res Pract* 1999; **195**: 633–6

2 **Terrone C, Guercio S, De Luca S *et al.*** The number of lymph nodes examined and staging accuracy in renal cell carcinoma. *BJU Int* 2003; **91**: 37–40

3 **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

4 **Bochner BH, Herr HW, Reuter VE.** Impact of separate versus en bloc pelvic lymph node dissection on the number of lymph nodes retrieved in cystectomy specimens. *J Urol* 2001; **166**: 2295–6

5 **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

6 **Leissner J, Ghoneim MA, Abol-Enein H *et al.*** Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. *J Urol* 2004; **171**: 139–44

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 **Finelli A, Gill IS, Desai MM, Moinzadeh A, Magi-Galluzzi C, Kaouk JH.** Laparoscopic extended pelvic lymphadenectomy for bladder cancer: technique and initial outcomes. *J Urol* 2004; **172**: 1809–12

9 **MacFarlane JK, Ryall RD, Heald RJ.** Mesorectal excision for rectal cancer. *Lancet* 1993; **341**: 457–60

10 **Arbman G, Nilsson E, Hallbook O, Sjodahl R.** Local recurrence following total mesorectal excision for rectal cancer. *Br J Surg* 1996; **83**: 375–9

11 **Caplin S, Cerottini JP, Bosman FT, Constanda MT, Givel JC.** For patients with Dukes' B (TNM Stage II) colorectal carcinoma, examination of six or fewer lymph nodes is related to poor prognosis. *Cancer* 1998; **83**: 666–72

12 **Tepper JE, O'Connell MJ, Niedzwiecki D *et al.*** Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol* 2001; **19**: 157–63

13 **Mathiesen O, Carl J, Bonderup O, Panduro J.** Axillary sampling and the risk of erroneous staging of breast cancer. An analysis of 960 consecutive patients. *Acta Oncol* 1990; **29**: 721–5

14 **Siewert JR, Bottcher K, Stein HJ, Roder JD.** Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. *Ann Surg* 1998; **228**: 449–61

15 **Grossman HB, Natale RB, Tangen CM *et al.*** Neoadjuvant chemotherapy plus cystectomy compared with cystectomy

alone for locally advanced bladder cancer. *N Engl J Med* 2003; **349**: 859–66
16 **Herr HW.** Surgical factors in bladder cancer: more (nodes) + more (pathology) = less (mortality). *BJU Int* 2003; **92**: 187–8
17 **Eastham JA, Kattan MW, Riedel E *et al.*** Variations among individual surgeons in the rate of positive surgical margins in radical prostatectomy specimens. *J Urol* 2003; **170**: 2292–5
18 **Konety BR, Joslyn SA, O'Donnell MA.** Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. *J Urol* 2003; **169**: 946–50
19 **Herr H, Lee C, Chang S, Lerner S.** Standardization of radical cystectomy and pelvic lymph node dissection for bladder cancer: a collaborative group report. *J Urol* 2004; **171**: 1823–8
20 **Stein JP, Lieskovsky G, Cote R *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
21 **Crawford ED, Skinner DG.** Salvage cystectomy after irradiation failure. *J Urol* 1980; **123**: 32–4
22 **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
23 **Leissner J, Hohenfellner R, Thuroff 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
24 **Quek ML, Stein JP, Clark PE *et al.*** Microscopic and gross extravesical extension in pathological staging of bladder cancer. *J Urol* 2004; **171**: 640–5
25 **Vieweg J, Gschwend JE, Herr HW, Fair WR.** The impact of primary stage on survival in patients with lymph node positive bladder cancer. *J Urol* 1999; **161**: 72–6
26 **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
27 **Leadbetter WF, Cooper JF.** Regional gland dissection for carcinoma of the bladder; a technique for one-stage cystectomy, gland dissection, and bilateral uretero-enterostomy. *J Urol* 1950; **63**: 242–60
28 **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
29 **Lerner SP, Skinner DG, Lieskovsky G *et al.*** The rationale for en bloc pelvic lymph node dissection for bladder cancer patients with nodal metastases: long-term results. *J Urol* 1993; **149**: 758–65
30 **Vieweg J, 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
31 **Herr HW.** Superiority of ratio based lymph node staging for bladder cancer. *J Urol* 2003; **169**: 943–5
32 **Frank I, Cheville JC, Blute ML *et al.*** Transitional cell carcinoma of the urinary bladder with regional lymph node involvement treated by cystectomy: clinicopathologic features associated with outcome. *Cancer* 2003; **97**: 2425–31
33 **Knap MM, Lundbeck F, Overgaard J.** The role of pelvic lymph node dissection as a predictive and prognostic factor in bladder cancer. *Eur J Cancer* 2003; **39**: 604–13
34 **Vieweg J, Whitmore WF Jr, Herr HW *et al.*** The role of pelvic lymphadenectomy and radical cystectomy for lymph node positive bladder cancer. The Memorial Sloan-Kettering Cancer Center experience. *Cancer* 1994; **73**: 3020–8
35 **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
36 **Smith JA Jr, Whitmore WF** Jr. Regional lymph node metastasis from bladder cancer. *J Urol* 1981; **126**: 591–3
37 **Herr HW.** Extent of surgery and pathology evaluation has an impact on bladder cancer outcomes after radical cystectomy. *Urology* 2003; **61**: 105–8
38 **Wishnow KI, Johnson DE, Ro JY, Swanson DA, Babaian RJ, von Eschenbach AC.** Incidence, extent and location of unsuspected pelvic lymph node metastasis in patients undergoing radical cystectomy for bladder cancer. *J Urol* 1987; **137**: 408–10
39 **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

Correspondence: John P. Stein, University of Southern California, Norris Comprehensive Cancer Center, MS #74, Department of Urology, 1441 Eastlake Ave., Suite 7416, Los Angeles, CA 90089, USA.
e-mail: stein@hsc.usc.edu

Abbreviations: **LND**, lymph node dissection; **SEER**, Surveillance, Epidemiology and End-Results; **USC**, University of Southern California.