Anatomic Extent of Pelvic Lymph Node Dissection: Impact on Long-term Cancer-specific Outcomes in Men With Positive Lymph Nodes at Time of Radical Prostatectomy

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OBJECTIVE To evaluate the impact of an extended pelvic lymph node (LN) dissection (EPLND) on the oncologic outcomes of men with LN-positive prostate cancer.

METHODS Patients were identified who underwent an open radical prostatectomy by one of two surgeons at the Johns Hopkins Hospital between 1992 and 2003. The first surgeon routinely performed a limited pelvic LN dissection (LPLND), whereas the second performed an EPLND. Men with positive LNs from each cohort were compared for differences in oncologic outcomes.

RESULTS Positive LNs were found in 94 men (2.2%), 21 (22.3%) with an LPLND and 73 (77.7%) with an EPLND. On average, LPLND and EPLND yielded 11.4 and 14.6 nodes, respectively ($P = .022$). The two groups were similar in terms of the number of positive LNs (1.4 vs 1.8, $P = .223$) and the proportion of patients with <15% positive nodes (57.1% vs 69.9%, $P = .300$). At a median follow-up of 10.5 years, patients who underwent an EPLND had superior oncologic outcomes compared with the LPLND group: 5-year biochemical recurrence-free survival of 30.1% vs 7.1% ($P = .018$), 10-year metastasis-free survival of 62.2% vs 22.2% ($P = .035$), and 10-year cancer-specific survival of 83.6% vs 52.6% ($P = .199$). This analysis demonstrated an augmented improvement in biochemical recurrence-free survival in men with <15% positive nodes.

CONCLUSION In addition to affording valuable staging information, an EPLND may confer a therapeutic benefit to patients found to have positive LNs at the time of radical prostatectomy. UROLOGY 82: 653–659, 2013. © 2013 Elsevier Inc.

Pelvic lymph node (LN) dissection (PLND) at the time of radical prostatectomy (RP) is currently the most reliable method for detecting LN metastases in men with prostate cancer. In the current prostate-specific antigen (PSA) era, 1%-3% of patients will have positive LNs at the time of surgery.[1,2] Among these men, 50% will have a recurrence within 10 years of RP, making LN status a significant predictor of disease progression.[3-5] Although it is well established that the extent of PLND correlates with improved staging accuracy,[6-9] the therapeutic benefit of an extended template PLND (EPLND) remains a topic of considerable debate.[10-13]

We previously reported that an EPLND is associated with improved biochemical recurrence-free survival (BFS) in men with positive LNs found at the time of RP.[14] This finding is consistent with data from other centers that have demonstrated an association with increasing nodal yield and improved oncologic outcomes.[15-17] EPLND is hypothesized to confer a therapeutic benefit by minimizing the burden of histologically undetectable metastatic disease.[18] In this report, we update the results of our earlier analysis by comparing the long-term oncologic outcomes of 2 experienced high-volume surgeons whose surgical technique differed only by the extent of PLND.

MATERIALS AND METHODS

Study Population

As an extension of our earlier report,[14] we retrospectively queried the Johns Hopkins RP Database for patients with ≥1 positive LNs who underwent an open RP between the years 1992 and 2003 by 2 surgeons at our institution. One surgeon

Financial Disclosure: *The authors declare that they have no relevant financial interests.*
Funding Support: *This work was funded from grants from the Patrick C. Walsh Prostate Cancer Research Fund to T.J.B. and M.E.A.*

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Submitted: January 6, 2013, accepted (with revisions): March 12, 2013

0090-4295/13/$36.00
http://dx.doi.org/10.1016/j.urology.2013.03.086

Table 1. Comparison of patient characteristics between lymphadenectomy groups

Variable	Limited (n = 21)	Extended (n = 73)	*P* Value
Age, y	58 (46-70)	57 (38-71)	.507
PSA, ng/mL	15.1 (3.9-79.1)	16.5 (2.5-66.0)	.221
Clinical stage			.226
cT1c-cT2a	15 (71.4)	37 (50.7)	
cT2b	5 (23.8)	23 (31.5)	
cT2c-cT3	1 (4.8)	13 (17.8)	
Gleason sum			
Biopsy			.454
2-6	8 (38.1)	33 (45.2)	
7	12 (57.1)	31 (42.5)	
8-10	1 (4.8)	9 (12.3)	
Pathologic			.901
2-6	0 (0.0)	3 (4.1)	
7	14 (66.7)	50 (68.5)	
8-10	7 (33.3)	20 (27.4)	
Pathologic features			
Extraprostatic extension	20 (95.2)	69 (94.5)	>.99
Seminal vesicle invasion	11 (52.4)	34 (46.6)	.805
Positive surgical margin	7 (33.3)	19 (26.0)	.582
Lymph nodes, No.			
Total	11.4 (4-20)	14.6 (6-31)	.022
Positive	1.4 (1-5)	1.8 (1-10)	.223
PPN <15%, No.	12 (57.1)	51 (69.9)	.300
Salvage treatment*			
Hormonal	9 (69.2)	41 (69.5)	>.99
Radiation	1 (7.7)	5 (8.5)	>.99
Chemotherapy	2 (15.4)	5 (8.5)	.602

PPN, percent positive nodes; PSA, prostate-specific antigen.
Continuous data are shown as the mean (range) and categoric data as number (%).
* Denominator is equal to number of patients who progressed: $n = 13$ for limited pelvic lymph node dissection and $n = 59$ for extended pelvic lymph node dissection.

(P.C.W.) routinely performed an EPLND (superior: bifurcation of common iliac artery; inferior: femoral canal to pelvic sidewall; posterior: obturator and internal iliac vessels), whereas the second (H.B.C.) performed a limited PLND (LPLND; differed by posterior extent termination at the obturator nerve). During the study period, the first surgeon performed 2279 such procedures compared with 1986 performed by the second surgeon. Patients who received neoadjuvant or immediate adjuvant therapy were excluded from the study. The resulting cohort was dichotomized by treating surgeon (ie, extent of PLND) and compared for differences in baseline characteristics and the primary outcomes of BFS, metastasis-free survival (MFS), and cancer-specific survival (CSS).

Surgical Technique and Pathologic Evaluation

The surgical technique used by the 2 surgeons[14] and the method of RP specimen evaluation[19] have previously been described. Of note, in both techniques LNs were submitted to pathology en bloc, without special handling of discrete LN packets. All identified nodes were counted and analyzed for histologic evidence of metastases. Specimens were not specifically rereviewed for the purposes of this report.

Statistical Analysis

Groups were compared using the Fisher exact test for categoric data and the Mann-Whitney *U* test for continuous variables. Differences in the time-dependent oncologic outcomes were analyzed using the log-rank test and Cox proportional hazards modeling. Because our earlier work found the largest improvement in BFS was in patients with <15% positive LN,[14] subanalyses of BFS, MFS, and CSS were performed focusing on this group.

BFS was defined as a postoperative PSA <0.2 ng/dL[20] and MFS as the absence of new lesions on cross-sectional imaging or bone scan. CSS data were ascertained via communication with the family or from the National Death Index (http://www.cdc.gov/nchs/ndi.htm). Statistical analyses were performed in SPSS 19.0 software (IBM Corp., Armonk, NY), and a *P* value of <.05 was considered statistically significant.

RESULTS

During the study period, 4265 men underwent an RP with PLND (1,986 LPLND and 2,279 EPLND). Positive LNs were found in 94 (2.2%) of these patients, 21 (22.3%) of whom underwent an LPLND, and 73 (77.7%) an EPLND. After dichotomizing by extent of PLND, we observed no difference between groups in terms of age at the time of surgery, preoperative PSA, clinical stage, or biopsy or pathologic Gleason sum (Table 1). Further, no differences were found in the frequency of extraprostatic extension, seminal vesicle invasion, or positive surgical margins. Compared with the LPLND group, men who underwent an EPLND had a greater mean nodal yield (11.4 vs 14.6, $P = .022$); however, the 2 surgical approaches yielded a similar mean number of positive LNs (1.4 vs 1.8, $P = .209$). There were no differences

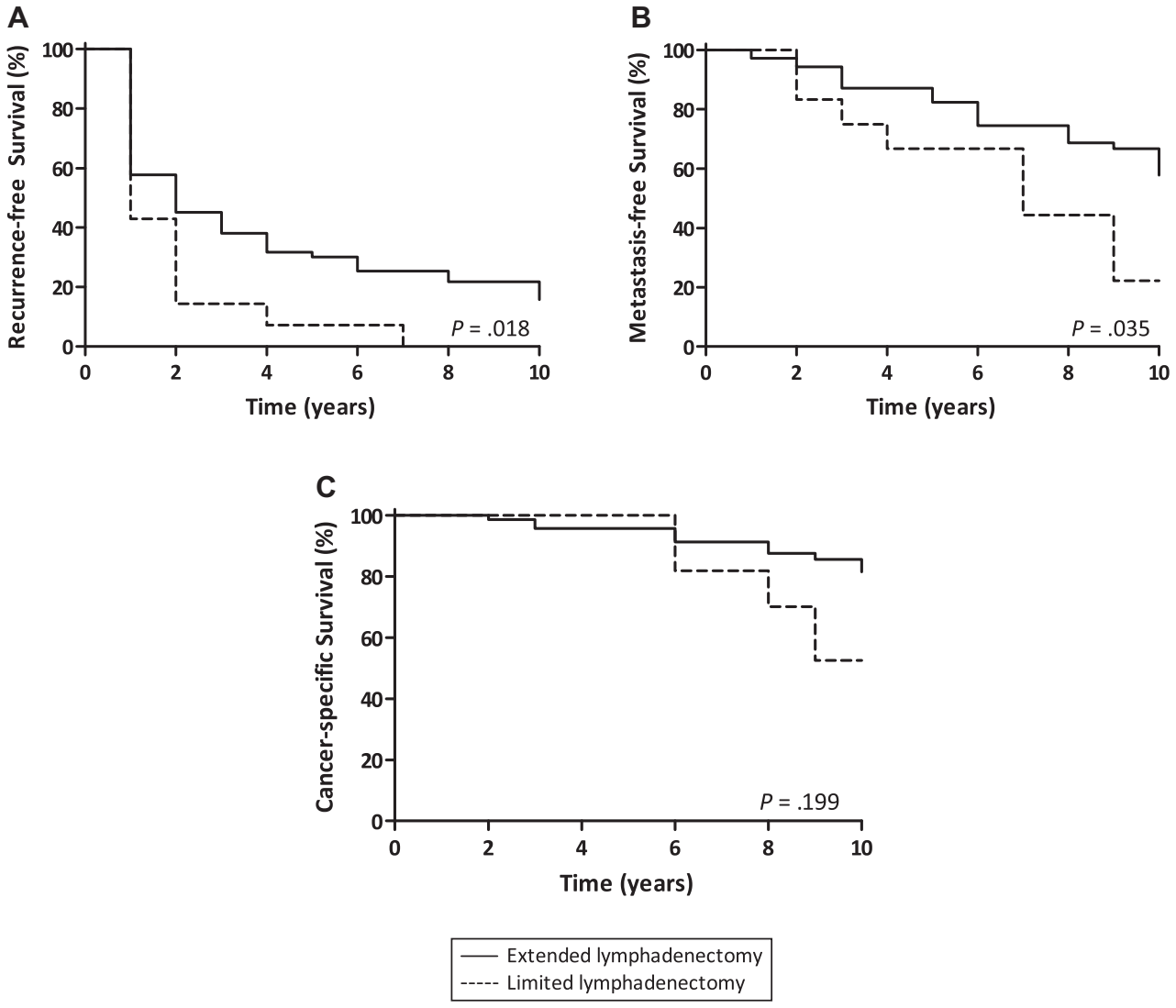

Figure 1. Kaplan-Meier curves of **(A)** recurrence-free, **(B)** metastasis-free, and **(C)** cancer-specific survival comparing limited with extended pelvic lymphadenectomy.

between groups in the frequency of salvage treatment used for disease progression (Table 1).

Patients were monitored for a median of 10.5 years, with no difference in the length of follow-up between groups (8.0 years for LPLND vs 12.0 years for EPLND, $P = .113$). Figure 1 depicts the Kaplan-Meier curves for the oncologic outcomes of BFS, MFS, and CSS. Patients in the EPLND group consistently had superior oncologic outcomes compared with the LPLND group: 5-year BFS of 30.1% vs 7.1% ($P = .018$), 10-year MFS of 62.2% vs 22.2% ($P = .035$), and 10-year CSS of 83.6% vs 52.6% ($P = .199$). Subsequent analysis with Cox proportional hazard modeling (Table 2) confirmed that men who underwent an EPLND had a trend toward improved BFS (hazard ratio [HR], 0.569; 95% confidence interval [CI], 0.313-1.034; $P = .064$) and also had significant improvements in MFS (HR, 0.421; 95% CI, 0.180-0.983; $P = .045$). No difference, however, was observed between

Table 2. Cox proportional hazards analyses for oncologic outcomes related to extent of pelvic lymph dissection*

Outcome	HR (95% CI)	*P* Value
Biochemical recurrence		
EPLND vs LPLND	0.569 (0.313-1.034)	.064
EPLND vs LPLND (<15% +LNs)	0.350 (0.150-0.819)	.016
Metastatic recurrence		
EPLND vs LPLND	0.421 (0.180-0.983)	.045
EPLND vs LPLND (<15% +LNs)	0.391 (0.110-1.384)	.145
Prostate cancer specific mortality		
EPLND vs LPLND	0.495 (0.163-1.504)	.215
EPLND vs LPLND (<15% +LNs)	0.990 (0.124-7.916)	.993

CI, confidence interval; EPLND, extended pelvic lymph node dissection; HR, hazard ratio; LN, lymph node; LPLND, limited pelvic lymph node dissection.

* Subanalyses include only those patients with <15% positive lymph nodes.

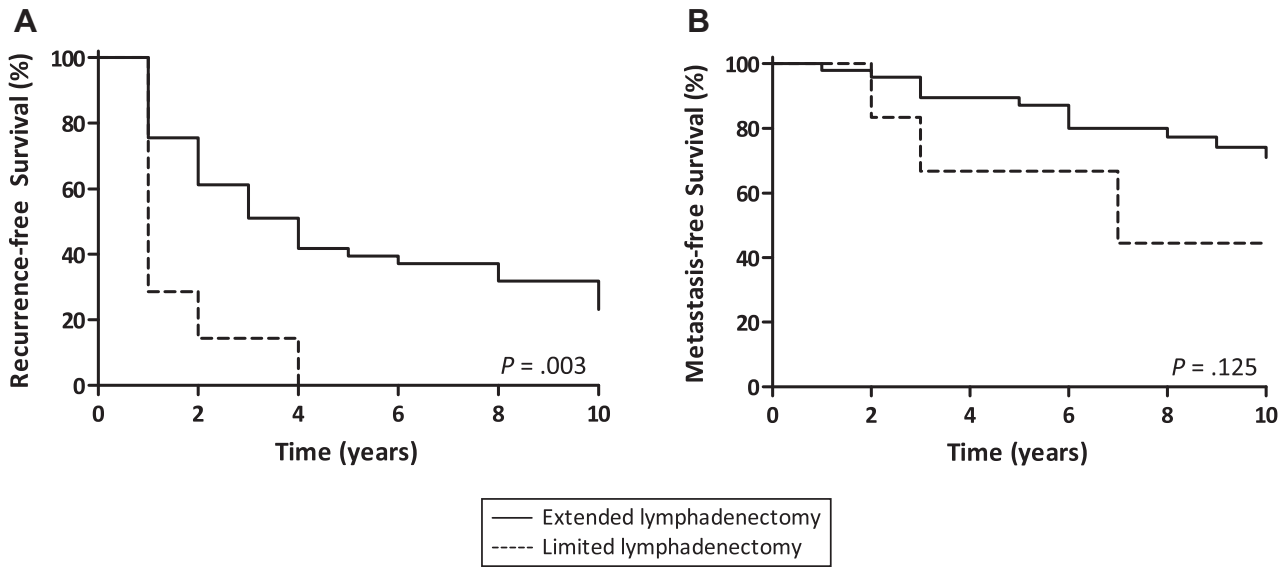

Figure 2. Kaplan-Meier curves of **(A)** recurrence-free and **(B)** metastasis-free survival comparing limited with extended pelvic lymphadenectomy among men with <15% positive lymph nodes.

groups for the outcome of CSS (HR, 0.495; 95% CI, 0.163-1.504; $P = .215$).

Among the 94 patients with positive LNs, 63 (67.0%) had <15% positive nodes, with a similar proportion in each group ($P = .300$, Table 1). Patients in this subgroup who underwent an EPLND had a 5-year BFS rate of 39.4%, whereas all such patients who underwent an LPLND recurred by 4 years ($P = .003$, Fig. 2). When Cox proportional hazards analysis was restricted to this group of men with <15% positive LNs (Table 2), EPLND was associated with an augmented improvement in BFS (HR, 0.350; 95% CI, 0.150-0.819; $P = .016$).

DISCUSSION

In a 2004 analysis from our institution, Allaf et al[14] reported that EPLND at the time of RP was associated with a trend toward improved BFS ($P = .07$). A subgroup analysis found that this improvement was greatest for those patients with <15% positive LNs ($P = .01$). Consistent with these results, Schiavina et al[15] recently reported that men with intermediate- to high-risk prostate cancer with ≥10 retrieved LNs (ie, a more extensive PLND) were at a decreased risk of biochemical recurrence. This effect was most pronounced in the group with ≤2 positive nodes. Similarly, Joslyn and Konety reported that patients in the Surveillance Epidemiology and End Results (SEER) database who had at least 4 excised LNs had improved CSS compared with those who did not undergo PLND.[16] Interestingly, among men with negative LNs, a nodal yield of >10 was required for a therapeutic benefit. Lastly, Masterson et al[17] found that in men with negative LNs, an increased number of resected nodes correlated with improved recurrence-free survival. However, despite the data from these studies, considerable controversy remains within the urologic community regarding the role of EPLND, because not all authors have found a benefit in favor of this practice.[21,22]

EPLND is felt to confer a therapeutic benefit by minimizing the burden of histologically undetectable metastases.[18] Among men classified as having N0 disease on a standard pathologic evaluation, 15%-20% may actually harbor occult micrometastases.[23,24] Pagliarulo et al[23] reported that 13.3% of men were upstaged after immunohistologic analysis of LNs for PSA. When compared with the true N0 population, these patients were at an increased risk of biochemical failure and death. In a similar study, Farrari et al[24] found that 17% of men with histologically defined N0 disease had PSA messenger ribonucleic acid (mRNA) levels >100-fold higher than healthy controls. Compared with other men with N0 disease, this group was at an increased risk of biochemical recurrence. These data suggest that a significant proportion of men felt to have N0 disease may actually harbor occult micrometastases and therefore stand to benefit from an EPLND.

The results of the present study confirm the earlier observations of Allaf et al[14] by demonstrating that EPLND is associated with a trend toward improved BFS (HR, 0.569; 95% CI, 0.313-1.034; $P = .064$). Also consistent with this report, the observed trend was most pronounced in the patients with <15% positive LNs (HR, 0.350; 95% CI, 0.150-0.819; $P = .016$). Combined, these data suggest that EPLND confers a therapeutic benefit and that this effect may be largest in the subset of men with a relatively small burden of positive LNs. With longer follow-up, we newly report that EPLND is associated with significant improvements in MFS (HR, 0.421; 95% CI, 0.180-0.983; $P = .045$; Fig. 1). Of note, we did

not observe a significant difference in MFS in the patients with <15% LNs. This is likely due to our small sample size; however, given the trend seen in Figure 2B, we suspect this will ultimately prove significant with longer follow-up.

Although the results of our study argue in favor of an EPLND, one must consider the risk of complications related to this practice. To date, a handful of studies have shown a higher rate of complications with an extended template dissection.[25-28] For example, Briganti et al[27] reported that EPLND was associated with an overall complication rate of 19.8% compared with 8.2% with LPLND (P <.001). This trend was mostly driven by the increase in the rate of lymphoceles in the EPLND group (10.3% vs 4.6%, P <.001). Musch et al[28] similarly found that EPLND is an independent risk factor for lymphocele formation and the need for reintervention. In contrast to these data, Heidernreich et al[6] found a similar complication rate between approaches. Possible reasons for this discrepancy include differences in surgical technique and in the definition of a clinically significant complication, namely, that of a lymphocele. With updated information, we found that in our own series, only 3 patients in the EPLND group (total RPs performed was 2279) developed a lymphocele of true clinical relevance that required intervention.[14] Therefore, although it is prudent to balance the potential for complications with EPLND, we argue that the complication rate is relatively low, and therefore, an EPLND should be performed whenever possible.

The present study is not without limitations. Most notably is our retrospective single-center design that compared the experiences of only 2 surgeons. This undoubtedly introduced some degree of selection and information bias. Further, as with any study in which the intervention is also used to classify patients, our analysis was prone to misclassification bias; that is, the so-called Will Rogers phenomenon by which a number of patients who underwent an LPLND were misclassified as having node-negative disease. Clearly, a prospective design would limit these factors; however, no randomized trial to date has been designed to evaluate the extent of PLND.

Additional limitations of our study include the nonstandardized method of en bloc specimen submission for pathologic analysis and the relatively short follow-up for detecting differences in CSS. The method of en bloc specimen submission likely reduced the accuracy of LN analysis, as previously Bochner et al[29] have demonstrated that en bloc submission is associated with lower LN counts compared with submission of discrete LN packets.

Lastly, the median length of follow-up of only 10.5 years was likely too short to detect differences in CSS, because data from our own institution have previously established that death from prostate cancer typically occurs 10-20 years after the detection of biochemical recurrence.[30] With additional follow-up, we believe that we will be able to detect a difference in this outcome given our findings for BFS and MFS.

CONCLUSIONS

The results of the current study demonstrate that EPLND is associated with greater nodal yields and may result in improved oncologic outcomes in men with LN-positive prostate cancer. The oncologic benefit of an EPLND appears to be greatest in men with <15% positive LNs. Although a prospective trial is required to confirm our results, at the present time, we recommend considering an EPLND at the time of RP.

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EDITORIAL COMMENT

The National Comprehensive Cancer Network (NCCN) guideline recommends an extended pelvic lymph node dissection (EPLND) whenever PLND is performed for prostate cancer. In this study, 2 of the world's most experienced prostate cancer surgeons present compelling data confirming the oncologic benefit of EPLND. Their findings are consistent with the preponderance of currently available evidence. However, all of the currently available data on EPLND are retrospective. Furthermore, although the importance of EPLND is well accepted in intermediate- and high-risk patients, its role in low-risk patients is less clear.

It would be interesting to know more about the patients with low-risk disease in this series. Specifically: How often were positive nodes detected in this group? How were oncologic outcomes affected? It would also be important to know how continence or erectile function was affected. These functional outcomes and their effect on quality of life are particularly important in the low-risk patients in whom the risk of death from prostate cancer is quite low.

The overall morbidity of EPLND remains somewhat unclear. Some have found higher rates of lymphoceles and ileus and increased length of stay. However, the current series and others have found minimal effects on perioperative complications.[1] A recent analysis from Cornell suggests that EPLND compromises potency when more than 20 nodes are removed.[2] Anatomically, this may be explained by compromising the parasympathetic nerves, which lie deep in the pelvis near the branches of the hypogastric artery. More information is needed on the morbidity of EPLND in prostate cancer patients, particularly its effect on potency.

A randomized controlled trial would be useful to further evaluate the risks and benefits of EPLND in low-risk prostate cancer patients. It has been suggested that having a control arm in which men were only offered limited PLND would not be ethical.[3] However, the rate of nodal involvement in low-risk patients is so low that the NCCN guideline recommends no imaging of the pelvic nodes. Furthermore, when low-risk patients are treated with radiotherapy, it is standard practice not to perform PLND. Therefore, an arm with no PLND would be ethical because the pelvic nodes would be managed in a manner similar to current standard therapy.

A Southwest Oncology Group (SWOG) trial is currently underway randomizing men with bladder cancer to standard or EPLND. In bladder cancer, the available evidence is even more compelling that there is an oncologic benefit to EPLND, yet this trial has received investigational review board approval. Clinicaltrials.gov lists 2 trials outside the United States randomizing men with prostate cancer to standard or EPLND.

It would be feasible to randomize men with low-risk prostate cancer to EPLND, limited PLND, or no PLND. Considerable time would be required to detect the small difference anticipated in oncologic outcomes such as cancer-specific survival and overall survival. However, the perioperative outcomes and functional outcomes, such as potency, should be evident in the near-term.

The current dictum that PLND must always be an extended template for prostate cancer seems too simplistic. There is a continuum of risk in this disease. Intuitively, we should try to personalize our treatment according to the patient's risk rather than an all-or-nothing approach. A randomized controlled trial would help us better understand how to do this.

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http://dx.doi.org/10.1016/j.urology.2013.03.088
UROLOGY 82: 658–659, 2013. © 2013 Elsevier Inc.

REPLY

We agree with the author that the decision to perform an extended template pelvic lymph node dissection (EPLND) in men with low-risk prostate cancer should be balanced against the risk of complications, the most common of which is lymphocele formation. In our experience, however, the risk of this complication is acceptably low when the use of subcutaneous prophylactic heparin is omitted in the perioperative period. This practice is premised on a large body of data, including a recent study from Memorial Sloan-Kettering Cancer Center, which found that after controlling for the number of removed nodes, the use of heparin was associated with a 6.7-fold (95% confidence interval, 1.5-30.1; $P = .01$) independent risk of developing a symptomatic lymphocele.[1] In our practice, prophylactic heparin is omitted for most patients, and this has resulted in a symptomatic lymphocele rate of <1% for men undergoing an EPLND. Considering these data along with the recent work of Epstein at al,[2] which found that approximately one-fourth of men with Gleason <7 prostate cancer will be upstaged at the time of radical prostatectomy to intermediate- or high-risk disease, we now advocate for EPLND for most men with low-risk tumors. However, this is ultimately surgeon-dependent at the Johns Hopkins Hospital.

Notably, the author also questions how continence and erectile function were affected by the extent of the lymph node dissection. To this point, they reference an article by Sagalovich et al,[3] which found that patients who had at least 20 lymph nodes removed at the time of robot-assisted radical prostatectomy had a higher rate of erectile dysfunction (but not incontinence) at 26 weeks postoperatively. A number of factors influence postprostatectomy erectile dysfunction, including but not limited to nerve sparing, age, systemic comorbidities, the surgeon's experience, and use of androgen-deprivation therapy.[4] The results of that study are thought-provoking, but their data come from a retrospective single-surgeon series and have yet to be borne out by other studies. Certainly, these are not common complications that have received much attention in the existing lymphadenectomy literature.[5]

Like the author, we too believe that additional level I evidence is required for us to more fully weigh the relative risks and benefits of an EPLND. As the author points out, Southwest Oncology Group (SWOG) S1011, which aims to evaluate standard vs EPLND performed during radical cystectomy, is currently underway. Although the oncologic data will not be applicable to prostate cancer, certainly, there will be a lot to learn about the risk of complications in relation to the extent of PLND.

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http://dx.doi.org/10.1016/j.urology.2013.03.089
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