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Anatomical 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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Abstract

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

Methods—Between 1992 and 2003, two surgeons at one hospital performed 1,986 and 2,279 open radical prostatectomies. The first surgeon routinely performed a limited pelvic lymph node dissection (LPLND) while the second performed an EPLND. Men with positive lymph nodes (LNs) from each cohort were compared for differences in oncologic outcomes.

Results—In total, 94 (2.2%) men were found to have positive LNs, 21 (22.3%) from a LPLND and 73 (77.7%) an EPLND. On average, LPLND and EPLND yielded 11.4 and 14.6 nodes, respectively ($p = 0.022$). Between groups, there was no difference in the number of positive LNs (1.4 vs. 1.8, $p = 0.223$) or the proportion of patients with $<15\%$ positive nodes (57.1% vs. 69.9%, $p = 0.300$). At median follow-up of 10.5 years, EPLND patients had superior oncologic outcomes compared to the LPLND group: 5-year biochemical recurrence-free survival of 30.1% vs. 7.1% ($p = 0.018$); 10-year metastasis-free survival of 62.2% vs. 22.2% ($p = 0.035$); and 10-year cancer-specific survival of 83.6% vs. 52.6% ($p = 0.199$). This analysis demonstrated an augmented improvement in biochemical recurrence-free survival in men with $<15\%$ positive nodes.

Conclusions—In addition to affording valuable staging information, an EPLND may confer a therapeutic benefit to patients found to have positive lymph nodes at the time of radical prostatectomy.

Keywords

lymphadenectomy; pelvic lymph node dissection; prostate cancer; radical prostatectomy

Introduction

Pelvic lymph node dissection (PLND) at the time of radical prostatectomy (RP) is currently the most reliable method for detecting lymph node (LN) metastases in men with prostate

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cancer. In the current PSA era, 1–3% of patients will be found to have positive LNs at the time of surgery.^{1, 2} Among these men, 50% will recur 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}.

Previously, we have 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 which have demonstrated an association with increasing nodal yield and improved oncologic outcomes.^{15–17} It is hypothesized that EPLND confers a therapeutic benefit by minimizing the burden of histologically undetectable metastatic disease.¹⁸ Herein, we update the results of our earlier analysis by comparing the long-term oncologic outcomes of two experienced high-volume surgeons whose surgical technique differed only by the extent of PLND.

Material and Methods

Study Population

As an extension of our earlier report¹⁴, we retrospectively queried the Johns Hopkins RP Database for patients with ≥ 1 positive LN who underwent an open RP between the years 1992 and 2003 by two surgeons at our institution. One surgeon (P.C.W.) routinely performed an EPLND (superior: bifurcation of common iliac artery; inferior: femoral canal to pelvic side wall; posterior: obturator and internal iliac vessels) while 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 2,279 such procedures compared to 1,986 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 (i.e. extent of PLND) and compared for differences in baseline characteristics as well as the primary outcomes of BFS, metastasis-free survival (MFS) and cancer-specific survival (CSS).

Surgical Technique and Pathologic Evaluation

The surgical technique employed by the two surgeons¹⁴ as well as the method of RP specimen evaluation¹⁹ has previously been described. Of note, for both techniques LNs were submitted to pathology *en bloc* without special handling of discrete LN packets. All identified nodes were counted and analyzed for histological evidence of metastases. Specimens were not specifically re-reviewed for the purposes of this report.

Statistical Analysis

Groups were compared using the Fisher's exact test for categorical 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. Based on our earlier work which found the largest improvement in BFS in patients with <15% positive LN¹⁴, subanalyses of BFS, MFS and CSS were performed focusing on this group.

BFS was defined as a postoperative PSA < 0.2 ng/dL²⁰ and MFS as the absence of new lesions on cross-sectional imaging or bone scan. CSS data was ascertained via communication with family or from the National Death Index (<http://www.cdc.gov/nchs/ndi.htm>). Statistical analyses were performed in SPSS 19.0 (IBM Corp., Armonk, NY) and a *p*-value of < 0.05 considered statistically significant.

Results

In total, 4,265 men underwent an RP with PLND during the study period (1,986 LPLND and 2,279 EPLND). Of these patients, 94 (2.2%) were found to have positive LNs, 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, pre-operative PSA, clinical stage, biopsy or pathological Gleason sum (Table 1). Further, there were no differences in the frequency extraprostatic extension, seminal vesicle invasion, or positive surgical margins. Compared to the LPLND group, men who underwent an EPLND had a greater mean nodal yield (11.4 vs. 14.6, $p = 0.022$), however, the two surgical approaches yielded a similar mean number of positive LNs (1.4 vs. 1.8, $p = 0.209$). Between groups, there were no differences in the frequency of salvage treatment utilized for disease progression (Table 1).

Patients were followed for a median of 10.5 years, with no difference in the length of follow-up between groups (8.0 years for LPLND versus 12.0 years for EPLND, $p = 0.113$). Figure 1 depicts the Kaplan-Meier curves for the oncologic outcomes of BFS, MFS and CSS. Patients who underwent an EPLND consistently had superior oncologic outcomes compared to the LPLND group: 5-year BFS of 30.1% vs. 7.1% ($p = 0.018$); 10-year MFS of 62.2% vs. 22.2% ($p = 0.035$); and 10-year CSS 83.6% vs. 52.6% ($p = 0.199$). Subsequent analysis with Cox proportional hazard modeling (Table 2) confirmed that men who underwent an EPLND had a trend towards improved BFS (HR 0.569 [95% CI 0.313–1.034], $p = 0.064$) as well as significant improvements in MFS (HR 0.421 95% CI 0.180–0.983], $p = 0.045$). No difference, however, was observed between groups for the outcome of CSS (HR 0.495 [95% CI 0.163–1.504], $p = 0.215$).

Among the 94 patients with positive LNs, 63 (67.0%) had <15% positive nodes, with a similar proportion in each group (Table 1, $p = 0.300$). 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 (Figure 2, $p = 0.003$). 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], $p = 0.016$).

Discussion

In a 2004 analysis from our institution, Allaf *et al.* reported that EPLND at the time of RP was associated with a trend towards improved BFS ($p = 0.07$).¹⁴ In subgroup analysis, it was found that this improvement was greatest for those patients with <15% positive LNs ($p = 0.01$). Consistent with these results, Schiavina *et al.* recently reported that men with intermediate to high risk prostate cancer with 10 retrieved LNs (i.e. a more extensive PLND) were at a decreased risk of biochemical recurrence ($p = 0.023$).¹⁵ This effect was most pronounced in the group of patients with 2 positive nodes ($p = 0.014$). 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 to those who did not undergo an PLND.¹⁶ Interestingly, among men with negative LNs, a nodal yield of >10 was required for a therapeutic benefit. Lastly, Masterson *et al.* found that in men with negative LNs an increased number of resected nodes correlated with improved recurrence-free survival.¹⁷ However, despite the above-mentioned data, there remains considerable controversy within the urologic community regarding the role of EPLND as 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 standard pathological evaluation, 15–20% may actually harbor occult micrometastases.^{23, 24} In one report, Pagliarulo and coworkers found that 13.3% of men were upstaged after immunohistologic analysis of LNs for PSA.²³ When compared to the true N0 population, these patients were at an increased risk of biochemical failure and death. In a similar study, Ferrari *et al.* found that 17% of men with histologically defined N0 disease had PSA mRNA levels >100-fold higher than normal controls.²⁴ Compared to 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.* by demonstrating that EPLND is associated with a trend towards improved BFS (HR 0.569 [95% CI 0.313–1.034], $p = 0.064$).¹⁴ Also consistent with this report, the observed trend was most pronounced in the group of patients with <15% positive LNs (HR 0.350 [95% CI 0.150–0.819], $p = 0.016$). Combined, these data suggest that an 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 (Figure 1; HR 0.421, [95% CI 0.180–0.983], $p = 0.045$). Of note, we did not observe a significant difference in MFS in the group of 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.

While 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 and coworkers reported that EPLND was associated with an overall complication rate of 19.8%, as compared to 8.2% with LPLND ($p < 0.001$).²⁷ This trend was mostly driven by the increase in the rate of lymphoceles in the EPLND group (10.3% vs. 4.6%, $p < 0.001$). Similarly, Musch *et al.* found that EPLND is independent risk factor for lymphocele formation and the need for re-intervention.²⁸ In contrast to these data, Heidenreich and coworkers found a similar complication rate between approaches.⁶ Possible reasons for this discrepancy include differences in surgical technique as well as 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 RP performed was 2,279) developed a lymphocele of true clinical relevance which required intervention.¹⁴ Therefore, while 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.

While the presented data argues in favor of an EPLND, it is important to acknowledge the limitations of our analysis. Most notably is our retrospective single-center design which compared the experiences of only two surgeons. This undoubtedly introduced some degree of selection and information bias. Further, like any study in which the intervention is also used to classify patients, our analysis was prone to misclassification bias, i.e. 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, to date no randomized trial has been designed to evaluate the extent of PLND.

Additional limitations of our study include the non-standardized method of *en bloc* specimen submission for pathological analysis as well as the relatively short follow-up for detecting differences in CSS. With regard to the method of *en bloc* specimen submission, this likely reduced the accuracy of LN analysis, as previously Bochner and coworkers have demonstrated that en bloc submission is associated with lower LN counts when compared to submission of discrete LN packets.²⁹ Lastly, with regard to the median length of follow-up of only 10.5 years, this was likely too short to detect differences in CSS, as data from our own institution has previously established that death from prostate cancer typically occurs 10–20 years after the detection of biochemical recurrence.³⁰ With additional follow-up, we suspect that we will be able to detect difference in this outcome given our findings for BFS and MFS.

Conclusions

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

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

Table 1

Comparison of patient characteristics between type of lymphadenectomy technique

Variable	Limited (n=21)		Extended (n=73)		p-value
	value/n	(range/percent)	value/n	(range/percent)	
Mean Age (years)	58	(46–70)	57	(38–71)	0.507
Mean PSA (ng/mL)	15.1	(3.9–79.1)	16.5	(2.5–66.0)	0.221
Clinical Stage					0.226
cT1c to cT2a	15	(71.4%)	37	(50.7%)	
cT2b	5	(23.8%)	23	(31.5%)	
cT2c to cT3	1	(4.8%)	13	(17.8%)	
Biopsy Gleason Sum					0.454
2 to 6	8	(38.1%)	33	(45.2%)	
7	12	(57.1%)	31	(42.5%)	
8 to 10	1	(4.8%)	9	(12.3%)	
Pathological Gleason Sum					0.901
2 to 6	0	(0.0%)	3	(4.1%)	
7	14	(66.7%)	50	(68.5%)	
8 to 10	7	(33.3%)	20	(27.4%)	
Pathological Features					
Extraprostatic Extension	20	(95.2%)	69	(94.5%)	1.000
Seminal Vesicle Invasion	11	(52.4%)	34	(46.6%)	0.805
Positive Surgical Margin	7	(33.3%)	19	(26.0%)	0.582
Total LN, mean	11.4	(4–20)	14.6	(6–31)	0.022
Positive LN, mean	1.4	(1–5)	1.8	(1–10)	0.223
PPN <15%	12	(57.1%)	51	(69.9%)	0.300
Salvage Treatment [†]					
Hormonal	9	(69.2%)	41	(69.5%)	1.000
Radiation	1	(7.7%)	5	(8.5%)	1.000

Variable	Limited (n=21)		Extended (n=73)		p-value
	value/n	(range/percent)	value/n	(range/percent)	
Chemotherapy	2	(15.4%)	5	(8.5%)	0.602

[†]Denominator is equal to number of patients who progressed. n = 13 for LPLND and n = 59 for EPLND.
PPN = percent positive nodes; PSA = prostate specific antigen; LN = lymph node

Table 2

Cox proportional hazards analyses for oncologic outcomes related to extent of pelvic lymph dissection. Subanalyses include only those patients with <15% positive lymph nodes.

Outcome	Hazard Ratio (95% CI)	<i>p</i> -value
Biochemical Recurrence		
EPLND vs. LPLND	0.569 (0.313–1.034)	0.064
EPLND vs. LPLND (<15% +LNs)	0.350 (0.150–0.819)	0.016
Metastatic Recurrence		
EPLND vs. LPLND	0.421 (0.180–0.983)	0.045
EPLND vs. LPLND (<15% +LNs)	0.391 (0.110–1.384)	0.145
Prostate Cancer Specific Mortality		
EPLND vs. LPLND	0.495 (0.163–1.504)	0.215
EPLND vs. LPLND (<15% +LNs)	0.990 (0.124–7.916)	0.993

CI = confidence interval; EPLND = extended pelvic lymph node dissection; LPLND = limited pelvic lymph node dissection; LN = lymph node