Biochemical recurrence after robot-assisted extended pelvic lymphadenectomy for prostate cancer

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Introduction: *Extended lymph node dissection (ELND) compared to limited lymph node dissection (LLND) at time of prostatectomy improves staging and lymph node (LN) yield. The effect on biochemical recurrence (BCR) and survival is less well understood. We sought to evaluate the benefit of robotic ELND and LLND with respect to BCR.*

Materials and methods: *Between 2008-2012, 584 consecutive men with intermediate or high risk clinically localized adenocarcinoma of the prostate underwent robotic assisted radical prostatectomy (RARP) with concomitant LLND (n = 326) or ELND (n = 258). Survival estimates were made using the Kaplan-Meier method. Log-rank statistic was used for comparison of curves. BCR predictors were determined with multivariable Cox regression analysis. Chi-square and Wilcoxon rank-sum tests were used to compare discrete and continuous variables, respectively, across the two groups.*

Results: *Median follow up for ELND and LLND patients was 46 and 54 months, respectively. ELND yielded more LNs (20 versus 6, $p < 0.0001$) and had higher node positivity (15.1% versus 3.4%, $p < 0.0001$). BCR free survival (BCRFS) at 3 and 5 years for ELND and LLND was 85% and 75% ($p = 0.01$), and 76% and 67% ($p = 0.10$), respectively. In subgroup analysis, ELND was associated with higher 5 year BCRFS in node-negative patients (84% versus 68%, $p = 0.0005$) and in intermediate risk patients (93% versus 80%, $p = 0.0002$). In multivariable analysis, ELND was a significant predictor of BCRFS in node-negative (HR = 0.50, $p = 0.003$) and intermediate risk patients (HR = 0.54, $p = 0.03$).*

Conclusions: *ELND improves LN yield and detection of positive nodes. BCR analysis suggests a reduced risk of PSA failure for robotic ELND in intermediate risk and node-negative patients.*

Key Words: prostate cancer, extended lymph node dissection, biochemical recurrence

Introduction

The presence of lymph node (LN) metastasis in men with prostate cancer has been associated with reduced biochemical recurrence (BCR) free survival (BCRFS) and overall survival (OS).[1] As staging radiography with computed tomography (CT) or magnetic resonance imaging (MRI) remains limited in assessing LN status, the most reliable method for detecting LN metastases is pelvic lymph node dissection (PLND) at the time of radical prostatectomy (RP).[2] As compared to a limited lymph node dissection (LLND), an extended lymph node dissection (ELND) more thoroughly excises lymphatic tissue that may contain prostate cancer metastases.[3] The use of meticulous ELND to identify patients with LN invasion is not only important for staging but also for planning optimal adjuvant therapy after surgery.[4,5] Although international guidelines recommend that an ELND be performed whenever a LN dissection is indicated,[3,6] an unsettling decline in the use and extent of PLND in the contemporary era has been reported.[7] Possible reasons for inconsistent

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utilization are potentially higher risk of perioperative complications associated with the procedure, and lack of prospective, randomized evidence supporting the role of ELND in cancer control.[8]

Several centers have reported an association with increasing LN yield and improved oncologic outcomes.[9-12] The therapeutic benefit of performing an ELND is hypothesized to represent a reduced burden of histologically detectable or undetectable metastatic disease.[13] The purpose of the present study was to compare our experience with intermediate or high risk prostate cancer patients undergoing robot-assisted radical prostatectomy (RARP) and either LLND or ELND with a focus on BCR.

Materials and methods

Between 2008 and 2012, 584 consecutive men, Figure 1, with intermediate or high risk clinically localized prostate cancer underwent RARP along with bilateral LLND (n = 326) or ELND (n = 258) performed by two experienced surgeons. LLND was performed in all patients between 2008-2010, followed by ELND being performed in all patients between 2010-2012. Patients were consented and prospectively enrolled in our institutional review board approved study. Patient demographics, pre and postoperative clinical characteristics, and pathological outcomes were collected prospectively.

Patients were included based on D'Amico risk criteria, specifically those with a prostate-specific antigen [PSA] > 10 ng/mL, Gleason score ≥ 7, or clinical stage ≥ T2b. Patients undergoing prostatectomy as secondary or salvage therapy or those who received neoadjuvant hormonal therapy were excluded. Patients with clinical nodal enlargement or distant metastases (cN1 or M1) were also excluded. Staging bone scans as well as CT or T3 MRI of the abdomen and pelvis were performed according to National Comprehensive Cancer Network (NCCN) guidelines.

Surgical technique

PLND was performed through a six-port transperitoneal approach using the four-arm da Vinci (Intuitive Surgical, Sunnyvale, CA, USA) robotic surgical system.

The anatomical region of dissection for LLND included the obturator fossa and the area overlying the external iliac vein. Our ELND technique includes as boundaries the ureteric crossing of the common iliac artery proximally, the lateral border of the external iliac artery laterally, the node of Cloquet distally, as well as the obturator fossa.[14] The ureters were identified bilaterally and guided the identification of the common iliac bifurcation. The nodal tissue around the bifurcation was dissected free. When possible, the proximal extents of dissection were controlled with Weck clips and divided. The external iliac artery was skeletonized from its origin down to the circumflex iliac vessels with dissection limited to the lateral edge of the artery. The obliterated umbilical artery was reflected away from the iliac vessels, and the lymphatic tissue medially was sent with the internal iliac specimen. Lymphofatty tissue surrounding the internal iliacs and branches was similarly removed. Nodal tissue around the internal iliac often coalesced with the obturator packet. The node of Cloquet distally and surrounding tissue was dissected and sent separately; the obturator packet was removed last.

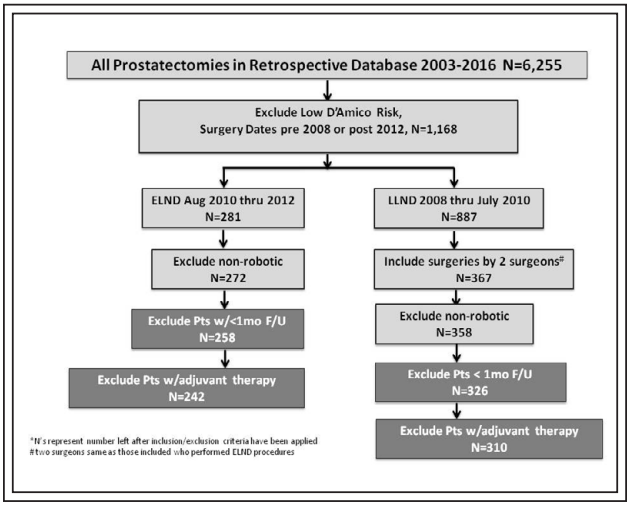

Figure 1. Inclusion criteria.

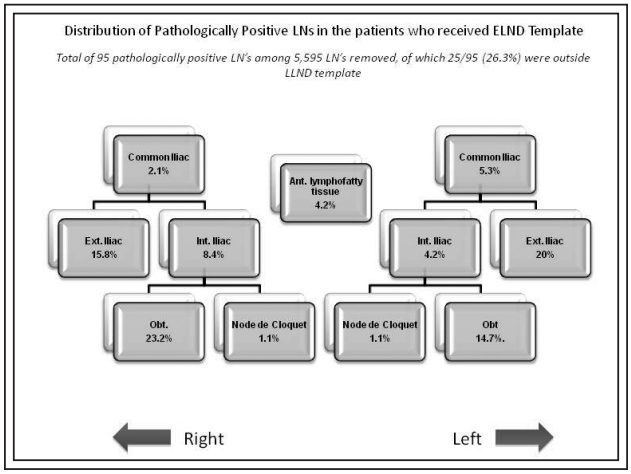

Figure 2. Distribution of positive lymph nodes in ELND patients.

Cautery was used for most of the dissection, although clips were used more judiciously in ELND to prevent lymphatic leakage.

Additionally, the anterior lymphofatty tissue has been included in our template, as these LNs may have malignant features.[15] LNs were sent in two packets (right and left) in LLND and 11 packets, Figure 2, in ELND.

Follow up

Patients were routinely followed with PSA measurements according to NCCN guidelines. BCR was defined as PSA ≥ 0.2 ng/mL with confirmatory PSA. Patients with multiple adverse features such as positive surgical margin, extracapsular extension, or seminal vesicle invasion were offered adjuvant treatment, defined as any use of radiation therapy or systemic therapy after prostatectomy. Node positive patients that had an appropriate PSA response after RARP and LN dissection were not routinely offered adjuvant therapy. Patients receiving any adjuvant or salvage therapy (radiation therapy or systemic hormone therapy) were excluded from BCR and multivariable analyses, Figure 1.

Statistical analysis

Chi-square and Wilcoxon rank-sum tests were used to compare discrete and continuous variables, respectively, across the two groups. Survival estimates were made using the Kaplan-Meier method, and the log-rank statistic was used for overall curve comparison. Point-wise survival estimates, confidence intervals and corresponding p-values were reported at 12 month intervals, using K-M survival estimates and survival standard errors for calculations. Threshold of 0.01 was used to determine statistical significance to control for comparisons made at multiple time points, using a Bonferroni correction.

Univariable and multivariable Cox regression analysis was used to identify predictors of BCR. Clinical patient characteristics and pathologic outcomes, along with ELND versus LLND, were all examined, and the stepwise selection method was used to finalize a multivariable model. Data analysis was performed using a standard statistical package (SAS).

Results

Both LLND and ELND cohorts, Table 1, were similar with respect to age, ethnicity, body mass index, PSA, and Charlson Comorbidity Index (CCI). The ELND group (29.1%) had a higher number of D'Amico high risk patients compared to the LLND group (21.8%). Total operative time was longer in the ELND group with a median of 3.1 h compared with 2.8 h with LLND ($p < 0.0001$). Pathologic stage was ≥ pT3 in 29.9% and 33.7% of ELND and LLND patients, respectively ($p = 0.5$). Additionally, positive surgical margin rate was 20.5% versus 28.5% ($p = 0.03$), favoring ELND patients.

Median LN yield for the LLND cohort was 6 (IQR 3-9). The nodal yield for the ELND cohort was significantly higher with a median of 20 (IQR 16-25) nodes removed ($p < 0.0001$). LN positive rates were 3.4 and 15.1% for LLND and ELND, respectively ($p < 0.0001$). Figure 2 shows the distribution of pathologically positive LNs.

Equal number of patients (n = 16) in both LLND and ELND cohorts underwent adjuvant therapy. Median follow up for patients included in BCR and multivariable analyses (n = 552) was 46 months in the ELND cohort (n = 242) and 54 months in the LLND cohort (n = 310).

For all patients, Table 2a, Figure 3a, BCRFS was higher at 3, 4, and 5 years postoperatively favoring ELND. Three year BCRFS for ELND and LLND was 85% and 75% ($p = 0.01$), respectively and at 4 years was 82% and 69% ($p = 0.001$). Five year BCRFS for ELND and LLND was 76% and 67% respectively though this did not reach statistical significance ($p = 0.10$).

In subgroup analysis, ELND was associated with improved 3 and 5 year BCRFS (90% versus 77%, 84% versus 68%, $p < 0.01$) in node-negative patients, Figure 3b. Additionally, ELND was associated with improved 3 and 5 year BCRFS (93% versus 80%, 91% versus 73%. $P < 0.01$) in intermediate risk patients, Figure 3c. The difference in high risk disease patients was not seen with 3 year BCRFS for ELND and LLND being 63% and 58% ($p = 0.6$) and 5 year BCRFS being 38% and 47% ($p = 0.4$), respectively.

Five year overall survival for all patients who underwent ELND and LLND was 97% and 96% ($p = 0.4$), whereas the 5 year radiographic recurrence-free survival for all patients was 98% and 96% ($p = 0.2$), respectively. When stratifying BCRFS in all patients by the number of positive nodes, the 3 year BCRFS for patients with node negative, one positive LN and > one positive LN was 82.7%, 51.8%, and 25% ($p < 0.0001$), respectively, Figure 4.

Specifically when examining BCRFS with respect to LN yield (< 15 LNs removed versus ≥ 15 LNs removed, Table 2b), regardless of the type of PLND, the 5 year BCRFS in patients who had ≥ 15 LN yield (79%) appeared higher compared to patients that had < 15 LNs removed (67%, $p = 0.02$), but did not reach statistical significance per our 0.01 threshold.

In a multivariable analysis, D'Amico high risk (HR = 2.21, $p = 0.0001$), pathologic Gleason score ≥ 8 (HR = 1.91, $p = 0.007$), positive margins (HR = 2.46, $p < 0.0001$) and pathologic stage ≥ pT3 (HR = 3.28, $p < 0.0001$) were significant predictors of BCRFS in all patients, Table 3a.

TABLE 1. **Patient demographics, perioperative and pathological outcomes**

	ELND (n = 258)	LLND (n = 326)	p value
Median (IQR) age at surgery, years	65.0 (59.0-69.0)	65.0 (60.0-70.0)	0.4
Median (IQR) body mass index	27.7 (25.4-31.1)	27.5 (25.3-30.5)	0.5
Median (IQR) preoperative PSA, ng/mL	6.1 (4.5-9.4)	6.1 (4.6-10.1)	0.5
Median (IQR) non-age adjusted CCI	2 (2-3)	2 (2-3)	0.2
Median (IQR) age adjusted CCI	4 (4-5)	4 (4-5)	0.2
Race, n (%)			0.8
Caucasian	201 (77.9%)	259 (79.4%)	
Black	19 (7.4%)	18 (5.5%)	
Asian	15 (5.8%)	18 (5.5%)	
American Indian	0 (0.0%)	1 (0.3%)	
Hispanic	15 (5.8%)	23 (7.1%)	
Other	8 (3.1%)	7 (2.1%)	
Biopsy Gleason score, n (%)			0.002
≤ 6	6 (2.3%)	30 (9.2%)	
7	194 (75.2%)	237 (72.7%)	
≥ 8	58 (22.5%)	59 (18.1%)	
Clinical stage, n (%)			0.02
T1	165 (64.0%)	243 (74.5%)	
T2	90 (34.9%)	81 (24.8%)	
T3	3 (1.2%)	2 (0.6%)	
D'Amico risk classification, n (%)			0.05
Intermediate	183 (70.9%)	255 (78.2%)	
High	75 (29.1%)	71 (21.8%)	
Median (IQR) operative time, h	3.1 (2.9-3.4)	2.8 (2.6-3.1)	< 0.0001
Median (IQR) estimated blood loss, mL	200 (150-250)	200 (150-300)	0.1
Pathologic Gleason score, n (%)			0.7
≤ 6	20 (7.7%)	24 (7.4%)	
7	198 (76.4%)	261 (80.1%)	
≥ 8	34 (13.1%)	34 (10.4%)	
Pathological stage, n (%)			0.5
pT2a/b	29 (11.2%)	25 (7.7%)	
pT2c	152 (58.9%)	191 (58.6%)	
pT3a/b	76 (29.5%)	109 (33.4%)	
pT4	1 (0.4%)	1 (0.3%)	
Positive surgical margins, n (%)	53 (20.5%)	93 (28.5%)	0.03
Median (IQR) LN yield	20 (16-25)	6 (3-9)	< 0.0001
Patients with positive LNs, n (%)	39 (15.1%)	11 (3.4%)	< 0.0001
Intermediate risk	12 (6.6%)	3 (1.2%)	0.002
High risk	27 (36.0)	8 (11.3%)	0.0005
Median (IQR) positive LNs yield	1 (1-3)	1 (1-1)	0.2
Adjuvant therapy	16 (6.2%)	16 (4.9%)	0.5
Median (IQR) length of stay	1 (1-1)	1 (1-1)	0.02
Median (95%CI) follow up in months*	46 (44-48)	54 (43-60)	< 0.0001

*calculated with reverse Kaplan Meier method
ELND = extended lymph node dissection; LLND = limited lymph node dissection; IQR = interquartile range; PSA = prostate-specific antigen; CCI = Charlson Comorbidity Index

TABLE 2. **Biochemical recurrence free survival prior to adjusting to covariants**

a) BCRFS for all patients

Time (months)	ELND (n = 242) BCRFS [95%CI]	LLND (n = 310) BCRFS [95%CI]	p value*
12	90% [86.3%, 93.9%]	91% [87.6%, 94.3%]	0.8
24	89% [85.1%, 93.2%]	84% [79.8%, 88.6%]	0.1
36	85% [79.9%, 89.6%]	75% [69.9%, 80.9%]	0.01
48	82% [77.0%, 87.5%]	69% [62.4%, 74.8%]	0.001
60	76% [67.8%, 84.3%]	67% [61.0%, 73.7%]	0.1

*p value comparing survival estimates at said time point

b) BCRFS for all patients divided by LN yield

Time (months)	LN < 15 (n = 339) BCRFS [95%CI]	LN > 15 (n = 213) BCRFS [95%CI]	p value*
12	91% [87.9%, 94.2%]	90% [85.7%, 93.9%]	0.6
24	85% [80.3%, 88.7%]	89% [85.0%, 93.5%]	0.1
36	76% [70.3%, 80.8%]	86% [80.7%, 90.6%]	0.006
48	69% [62.9%, 74.8%]	84% [78.2%, 88.9%]	0.0003
60	67% [60.3%, 72.7%]	79% [70.8%, 87.4%]	0.02

*p value comparing survival estimates at said time point

c) Three year BCRFS for all patients stratified by number of positive LNs (p < 0.0001)

Nodal status	3 year BCRFS [95% CI]
Lymph node negative	82.7% [78.6%, 86.0%]
1 positive lymph node	51.8% [29.9%, 69.9%]
> 2 positive lymph nodes	25.0% [6.0%, 50.4%]†

†no events after 4 months

ELND = extended lymph node dissection; LLND = limited lymph node dissection; BCRFS = biochemical recurrence free survival; LN = lymph node

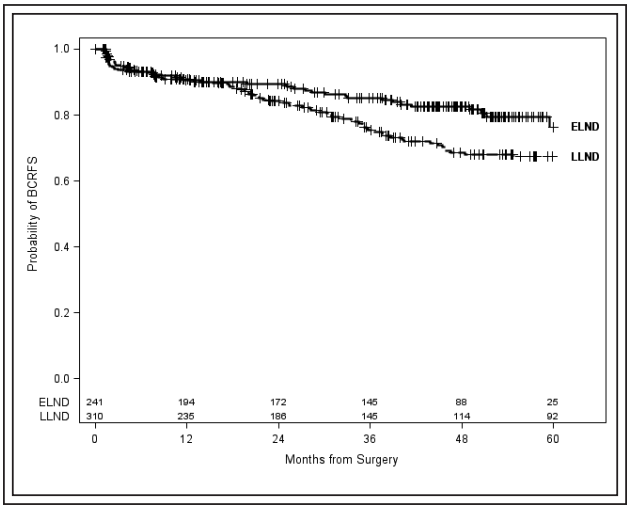

Figure 3a. BCRFS for all patients (log-rank p = 0.058).

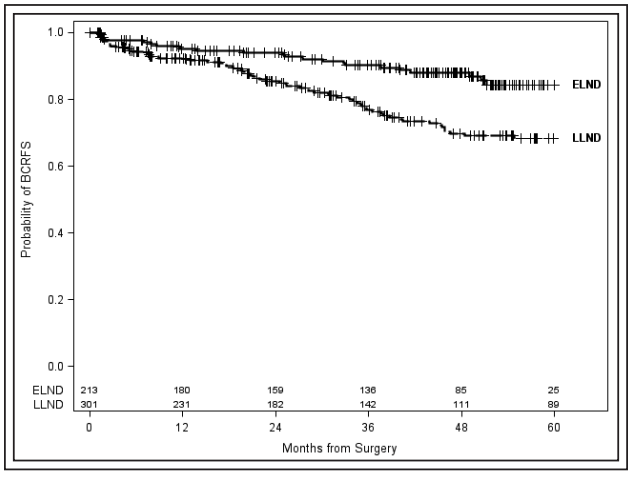

Figure 3b. BCRFS for patients with no evidence of nodal metastases (log-rank p = 0.001).

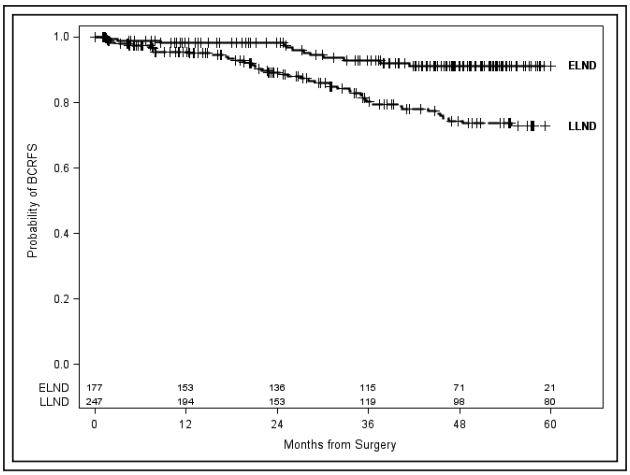

Figure 3c. BCRFS for patients with intermediate risk of prostate cancer (log-rank p = 0.0008).

ELND was a significant predictor of BCRFS in node-negative (HR = 0.59, p = 0.03) patients, along with PSA, positive margins, pathologic stage and pathologic Gleason score, Table 3b. Among intermediate risk patients, ELND (HR = 0.51, p = 0.04) was a significant predictor for BCR even when controlling for PSA, pathologic stage, positive margins, and pathologic Gleason score, Table 3c. Regardless of PLND template, LN yield ≥ 15 was a significant predictor for BCRFS in all patients (p = 0.02).

There were no intraoperative ureteral, vascular or nerve injuries in either the LLND (n = 326) or ELND cohorts (n = 258). In regards to the incidence of symptomatic lymphoceles (90 day), seven patients in the LLND cohort (2.1%) and six patients (2.3%) in the ELND cohort developed a symptomatic lymphocele requiring intervention (Clavien 3a).

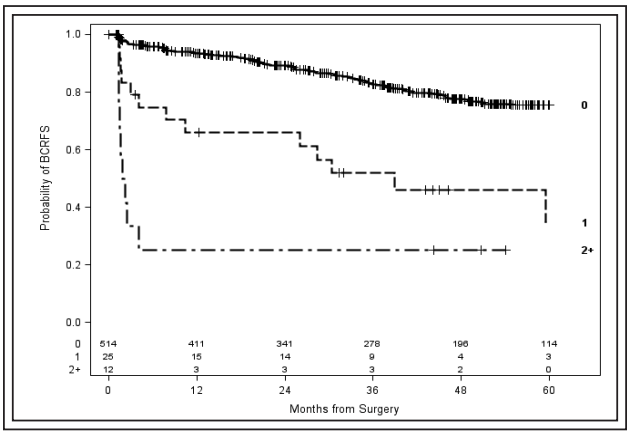

Figure 4. BCRFS stratified by number of positive LNs in all patients.

Discussion

Similar to other pathologic assessments in prostate cancer such as Gleason score, pathologic stage, margin status, and percentage of prostate involved by tumor, LN invasion has shown to negatively affect patient survival.[16] As lymphatic drainage patterns in prostate cancer can be notoriously variable, a systematic PLND is necessary to more thoroughly include potential drainage basins. LLND risks significant under-evaluation of possible drainage sites, as studies have shown internal iliac LNs to be involved up to 58% of the time.[17] Extending the dissection template by including the nodes along the internal iliac decreases the rate of overlooked metastases but not to zero, as at least 10% of LN metastases will still be missed in an ELND.[18] Mattei and colleagues showed that up to 35% of prostatic lymphatic drainage sites still remained outside the extended anatomical template but recommended extending the PLND along the common iliac vessels to the ureteric crossing.[19] To date, an ideal anatomic ELND template has not been widely validated.

A longstanding debate regarding the role of ELND exists in the prostate cancer literature.[9,11,20-22] A factor that may contribute to declining use of ELND in the contemporary era includes the potential for increased complications.[7] Even though major complications from PLND are rare, extending the dissection template may increase minor complications such as lymphocele and lymphedema, which urologists would prefer to avoid in the absence of a proven oncological benefit. Our center previously compared the complication rate of ELND and LLND and found that ELND could be performed safely with no significant difference in the symptomatic lymphocele rate.[23] In the present series we sought to evaluate the therapeutic benefit of ELND, by assessing the impact of extent of PLND on BCR in intermediate and high risk clinically localized prostate cancer patients undergoing RARP.

Several findings are notable. First, 3, 4, and 5 year BCRFS for all patients who underwent an ELND was higher than patients who underwent a LLND. Though statistically significant at 3 and 4 years postoperatively, at 5 years the difference was not, which may be related to length of follow up and/or censoring. Patients who were node-negative from an ELND (84%) experienced a significantly higher 5 year BCRFS compared to those who were node-negative from a LLND (68%, p = 0.0005). As with any study in which the intervention is used to classify patients, our analysis could be influenced by a stage shift (Will Rogers phenomenon) wherein pN0 patients

TABLE 3. **Multivariable cox proportional hazards survival analysis assessing for predictors of biochemical recurrence**

a) All patients

Parameter	Univariable analysis Hazard ratio [95%CI]	p value	Multivariable analysis Hazard ratio [95%CI]	p value
Surgical age (continuous)	1.01 (0.99, 1.04)	0.3		
BMI (continuous)	1.03 (0.99, 1.07)	0.2		
Total CCI (continuous)	1.07 (0.90, 1.23)	0.4		
D'Amico high risk (vs. Interm)*	3.45 (2.42, 4.89)	< 0.0001	2.21 (1.47, 3.29)	0.0001
Positive surgical margins	3.22 (2.27, 4.57)	< 0.0001	2.46 (1.73, 3.541)	<0.0001
Pathologic stage > T3 (vs. < T2c)	4.28 (3.01, 6.13)	< 0.0001	3.28 (2.28, 4.74)	<0.0001
Pathologic Gleason > 8 (vs. ≤ 7)	3.51 (2.26, 5.27)	< 0.0001	1.91 (1.18, 3.05)	0.007
ELND (vs. LLND)	0.70 (0.47, 1.01)	0.06	0.70 (0.48, 1.03)	0.07

*D'amico risk parameter was included in this model to study the effect of high risk disease on BCRFS, and thus clinical characteristics (PSA, t-stage, and Gleason sum) have been removed to eliminate redundancy

b) Node-negative patients

Parameter	Univariable analysis Hazard ratio [95%CI]	p value	Multivariable analysis Hazard ratio [95%CI]	p value
Surgical age (continuous)	1.02 (0.99, 1.05)	0.2		
BMI (continuous)	1.03 (0.99, 1.08)	0.1		
Total CCI (continuous)	1.02 (0.82, 1.21)	0.8		
Clinical T-stage ≥ T2a (vs. ≤ T1c)	1.39 (0.91, 2.08)	0.1		
Clinical Gleason ≥ 8 (vs. < 8)	3.22 (2.10, 4.83)	< 0.0001		
PSA (continuous)	1.04 (1.03, 1.06)	< 0.0001	1.02 (1.00, 1.04)	0.008
Positive surgical margins	3.12 (2.12, 4.59)	< 0.0001	2.43 (1.63, 3.60)	< 0.0001
Pathologic stage > T3 (vs. < T2c)	3.17 (2.52, 5.48)	< 0.0001	3.03 (2.02, 4.54)	< 0.0001
Pathologic Gleason > 8 (vs. ≤ 7)	3.04 (1.72, 5.03)	< 0.0001	2.84 (1.55, 4.85)	0.0003
ELND (vs. LLND)	0.48 (0.30, 0.74)	0.001	0.59 (0.37, 0.93)	0.03

c) Intermediate risk patients

Parameter	Univariable analysis Hazard ratio [95%CI]	p value	Multivariable analysis Hazard ratio [95%CI]	p value
Surgical age (continuous)	1.02 (0.99, 1.06)	0.2		
BMI (continuous)	1.02 (0.96, 1.08)	0.5		
Total CCI (continuous)	0.92 (0.64, 1.21)	0.6		
Clinical T-stage ≥ T2a (vs. ≤ T1c)	1.20 (0.68, 2.00)	0.5		
PSA (continuous)	1.12 (1.06, 1.18)	< 0.0001	1.09 (1.03, 1.15)	0.0007
Positive surgical margins	3.71 (2.31, 5.94)	< 0.0001	2.90 (1.78, 4.72)	< 0.0001
Pathologic stage > T3 (vs. < T2c)	3.24 (2.00, 5.19)	< 0.0001	2.29 (1.39, 3.75)	0.001
Pathologic Gleason > 8 (vs. ≤ 7)	2.96 (0.72, 8.03)	0.07	2.65 (0.61, 7.88)	0.1
ELND (vs. LLND)	0.37 (0.20, 0.66)	0.001	0.51 (0.26, 0.94)	0.04

CCI = Charlson Comorbidity Index; ELND = extended lymph node dissection; LLND = limited lymph node dissection; BMI = body mass index

with higher number of removed LNs were better staged and, thus, more likely to be really free from LN metastases. Conversely, pN0 patients with lower number of removed LNs were possibly less accurately staged, and might actually harbor an undiscovered LN metastasis. Previous observational reports assessing the impact of ELND on BCR and/or survival have been equivocal.[20-22] Murphy et al reported that the number of LNs removed at prostatectomy did not increase the chance of cure for 964 pT2-4 node-negative patients.[20] Similarly, in a study of 7036 RPs by DiMarco and colleagues, the extent of PLND did not appear to affect cancer outcomes in node-negative cases.[21] On the other hand, Bivalacqua et al found that patients undergoing ELND had better oncologic outcomes at 10 year follow up compared to their counterparts receiving a LLND.[24] Furthermore, immunohistologic and molecular analysis from two series have suggested that a significant proportion of men (13%-17%) felt to have N0 disease on standard pathologic evaluation, may actually harbor occult micrometastases.[25,26] These patients were at an increased risk of BCR compared to true N0 disease and therefore ELND minimized the burden of histologically undetectable metastases.[25,26] It can be surmised that the beneficial effect of ELND on BCR in our study may be related both to the removal of micrometastatic disease and to the stage shift.

Second, intermediate risk prostate cancer patients who underwent an ELND (91%) had a higher 5 year BCRFS compared to those who underwent a LLND (73%, p = 0.0006). Even though an anatomic ELND is recommended by guidelines,[3,6] Gandaglia and colleagues evaluated Surveillance, Epidemiology, and End Results (SEER)-Medicare data and revealed that ELND in intermediate risk prostate cancer patients was underutilized as only 21.2% of RARP patients received an ELND.[7] A significant difference in BCRFS seen in our study reinforces that increased efforts should be made to offer ELND in intermediate risk prostate cancer patients.

Third, while a difference in BCRFS was seen in intermediate risk prostate cancer patients who underwent an ELND, a similar benefit was not seen in high risk prostate cancer patients. This surprising observation may be multifactorial. It is possible that ELND offers incrementally less therapeutic benefit over LLND in high risk prostate cancer patients as they simply have a higher risk of systemic disease regardless of PLND. Also, as these patients are less likely to nadir, the notion of BCR may not be as meaningful. Additionally, the lower number of patients with high risk disease in our analysis and lack of long term follow up may also have prevented our study from showing a therapeutic benefit to ELND in this cohort.

Fourth, by separately analyzing by LN number, 5 year BCRFS was higher in patients who had ≥ 15 LNs removed. Studies have shown that a more extensive dissection with various cut offs of LN yield may decrease BCR.[9-11] Joslyn et al reported on SEER database patients experiencing improved survival rates if they had at least 4 excised LNs, and among men who were node-negative, a nodal yield of > 10 was required for a therapeutic benefit.[9] Schiavina et al also noted that patients with > 10 LNs removed had a significantly lower BCR.[10] Of the 213 patients in our study who had ≥ 15 LNs removed, 201 patients (94.4%) underwent an ELND. Thus while following a consistent template for dissection is likely more important than specific nodal counts, by adhering to a standardized ELND, nodal yields exceeding 15 would be almost assured.

This present study's limitations include its retrospective single-center non-randomized design that possibly led to some degree of selection and information bias. Our findings should be considered in the context of retrospective, observational evidence and warrant prospective, randomized validation. To our knowledge, this represents the largest comparative series examining the oncologic effect of robotic ELND. However, with the recent introduction of robotics and subsequently the incorporation of ELND in all intermediate and high risk prostate cancer patients by two surgeons in 2010, our follow up was limited. Further, since patients were unmatched and consecutive, learning curve issues may have impacted results though this is unlikely given the experience level of surgeons. The variability of the reading pathologist could also have affected LN counts between cases. Additionally, even though BCR risk reduction is an important finding, it does not always translate into improved overall survival, which requires longer follow up to fully evaluate. As with any study in which the intervention is used to classify patients, our analysis was prone to selection bias (Will Rogers phenomenon).

Conclusion

The results of the current study demonstrate that ELND is associated with a reduced risk of PSA failures in intermediate risk disease as well as patients with no evidence of LN metastasis. Long term evaluation is necessary to determine definitive impact on survival. Although, a prospective trial is required to confirm our results, an ELND at the time of RARP in all intermediate and high risk patients should be considered. □

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