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The number of negative pelvic lymph nodes removed does not affect the risk of biochemical failure after radical prostatectomy

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Abstract

OBJECTIVES—To assess patients who had radical prostatectomy (RP) and pelvic lymph node dissection (PLND) for pT2–4 N0M0 prostate cancer, to determine if LN yield affects the risk of biochemical failure (BCF), as the extent of PLND at the time of RP has become increasingly uncertain with the decreasing trend in tumour stage.

PATIENTS AND METHODS—We reviewed the Columbia University Urologic Oncology Database for patients with pT2–4 N0M0 prostate cancer treated with RP from 1990 to 2005. Exclusion criteria included <12 months of follow-up, incomplete clinical and pathological data, and neoadjuvant androgen-deprivation therapy (ADT) or immediate adjuvant ADT or external beam radiotherapy. Unadjusted and adjusted models were used to determine the ability of clinical and pathological variables to predict BCF.

RESULTS—The final dataset included 964 patients, with a mean age of 60.5 years and median preoperative prostate-specific antigen (PSA) level of 6.2 ng/mL. The median (range) LN yield was 7 (1–42) and the median follow-up 59 (12–190) months. In the unadjusted and adjusted models, preoperative PSA, pathological Gleason score, pathological stage, surgical margin status and year of surgery were significant predictors of BCF. The LN group was not a significant predictor of BCF in both the unadjusted and adjusted model ($P = 0.759$ and 0.408 , respectively). When patients were stratified into high and low-risk groups, LN yield remained an insignificant predictor of BCF.

CONCLUSION—A higher LN yield at the time of RP does not increase the chance of cure for patients with pT2–4N0M0 prostate cancer. This lack of a survival advantage holds true for patients with high-risk disease.

Keywords

prostate cancer; lymph node dissection; PSA; retropubic prostatectomy

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CONFLICT OF INTEREST

None declared.

INTRODUCTION

During the PSA era, the tumour stage of prostate cancers has shifted towards more organ-confined disease. This downward trend in tumour stage has been accompanied by a decrease in the nodal involvement for localized prostate cancer [1]. Subsequently, the extent of pelvic lymph node dissection (PLND) required at the time of radical prostatectomy (RP) has become increasingly uncertain. The lymphatic drainage of the prostate is variable and several studies from Europe showed that extended PLND provides more accurate staging by improving the detection of nodal involvement [2,3]. While the primary goal of a PLND is to accurately stage a patient, there might be a secondary therapeutic benefit.

Several studies reported a survival advantage for patients with pN0 breast cancer and bladder cancer who have undergone more extensive LND [4-6]. In these studies, improved survival is directly proportional to the number of LNs examined. This concept of improved survival for patients with pN0 disease who have had a more extensive LND has been examined previously in prostate cancer. While a single-institution study did not show a similar survival advantage for patients with pN0 prostate cancer [1], a Surveillance, Epidemiology and End Results (SEER) Program-based report showed that a more extensive PLND was associated with a reduced risk of death from prostate cancer in pN0 patients [7]. Given the conflicting results in previous reports we examined patients who had RP and PLND at our institution for pT2–4N0M0 prostate cancer to determine if the LN yield affects the risk of biochemical failure (BCF).

PATIENTS AND METHODS

We reviewed the Institutional Review Board-approved Columbia University Urologic Oncology Database for patients with prostate cancer treated with RP. In all, 3198 patients had RP from 1990 to 2005. We identified patients who had undergone a PLND and were found to have LN-negative disease on final pathology. Patients were excluded if they received neoadjuvant androgen-deprivation therapy (ADT) or immediate adjuvant ADT or external beam radiotherapy (EBRT). Patients were excluded for NX status (391), LN-positive disease (55), <12 months of follow-up (413), neoadjuvant or immediate adjuvant ADT or EBRT (181) and incomplete clinical and pathological data (1867). After exclusion criteria were applied, 964 patients comprised the final dataset.

Clinical and pathological data included age, PSA level at diagnosis, biopsy Gleason score, clinical stage, pathological Gleason score, pathological stage, number of LNs examined, surgical margin status, year of surgery and months of follow-up. Patients were stratified according to the number of LNs examined and LN yield served as a surrogate for the extent of PLND [8]. LN groups were based on a previously published series that examined the association between the extent of PLND and prostate cancer outcomes [1]. Prostate specimens were staged using the 1997 American Joint Committee on Cancer TNM staging system [9]. After RP, patients were evaluated with serial PSA tests, DREs and imaging studies as deemed necessary. The primary endpoint was BCF, defined as one PSA value of 0.2 ng/mL.

Differences in mean age among the LN categories were analysed by nonparametric ANOVA. The median PSA levels across LN groups were assessed using the Kruskal–Wallis test. Categorical variables were assessed with the chi-square test. A Cox proportional hazard model was used to identify clinical and pathological variables that were independently predictive of BCF; the significance of the hazard models was then validated with the Wald test.

A separate adjusted Cox proportional hazard model was devised with patients stratified into high- and low-risk subsets, based on the Kattan postoperative nomogram for progression-free probability (PFP), with high-risk defined as a PFP of <75% [10]. Finally, BCF was estimated with patients stratified by LN group using the Kaplan-Meier method. All analyses were conducted using $\alpha = 0.05$ to determine statistical significance.

RESULTS

The final dataset of patients who met the inclusion criteria comprised 964 patients, with a mean (SD, range) age of 60.5 (6.9, 36–77) years and median (interquartile range) preoperative PSA level was 6.2 (4.1) ng/mL. The median (range) number of LNs examined was 7 (1–42); the median follow-up was 59 (12–190) months and the median time to BCF or completion of follow-up with no BCF was 48 months. Table 1 provides a complete description of clinical and pathological characteristics. When LN groups were compared, there was no significant difference in biopsy Gleason score, clinical stage, pathological Gleason score, pathological stage and surgical margin status. Examination of a higher LN yield was more common in patients with higher PSA level and earlier year of surgery. The correlation between earlier year of surgery and examination of more LNs is reflected in the longer follow-up for patients who had 15 LNs examined.

Clinical and pathological variables were then examined to determine their ability to predict BCF (Table 2). In the unadjusted and adjusted models, preoperative PSA level, pathological Gleason score, pathological T stage, surgical margin status and year of surgery were significant predictors of BCF ($P = 0.022$). By contrast, LN group was not a significant predictor of BCF in both the unadjusted and adjusted model ($P = 0.759$ and 0.408 , respectively). Figure 1 is a Kaplan-Meier curve for BCR-free survival with patients stratified by LN yield; there was no significant difference in the curves ($P = 0.76$). When patients were stratified into high- and low-risk groups using PFP derived from the Kattan nomogram, the number of LNs examined was still not a significant predictor of BCF in an adjusted model (Table 3).

DISCUSSION

We sought to determine if the number of LNs removed at the time of RP affects the risk of BCF in patients with localized pT2–4N0M0 prostate cancer. We found that in an unadjusted and adjusted model, preoperative PSA level, pathological Gleason score, pathological stage, surgical margin status and year of surgery were significant predictors of BCF. By contrast, LN group was not a significant predictor of BCF in both the unadjusted and adjusted model ($P = 0.759$ and 0.408 , respectively). When patients were stratified into high- and low-risk

groups, we determined that LN yield remained an insignificant predictor of BCF in an adjusted model.

There is conflicting evidence about the need to perform an extended PLND at the time of RP. Several series from Europe suggest that extended PLND is necessary for accurate LN staging [3,11]. In 2002, Bader *et al.* [3] examined 365 patients with clinically organ-confined prostate cancer who had RP and extended PLND (median number of nodes removed 21). The rate of LN involvement was high, at 24%. A more contemporary study by Briganti *et al.* [11] examined 858 patients with largely organ-confined disease who had RP with extended PLND (median number of nodes removed 14). The number of LNs examined was a significant predictor of LN involvement in an adjusted model. Similar to the study by Bader *et al.* the rate LN involvement was relatively high at 10.3%.

By contrast with the European data, several studies from the USA have questioned the need for an extended PLND when treating organ-confined disease [12,13]. A study conducted by Clark *et al.* [13] randomized 123 patients to unilateral extended PLND in conjunction with a limited PLND on the contralateral side; the rate of LN involvement was 6.5%. In comparison to limited PLND, extended PLND did not detect significantly more patients with nodal disease and the more extensive dissection was associated with a higher rate of complications. Such contradiction between the series of Briganti *et al.* and Clark *et al.* might be accounted for by the difference in disease characteristics, despite both studies examining a contemporary cohort of patients. While the patients of Briganti *et al.* had a preoperative PSA level <10 ng/mL in 67.9% and clinical T3 prostate cancer in 4.0%, the patients of Clark *et al.* had a preoperative PSA level of <10 ng/mL in 84.6% and clinical T3 disease in only 1.3% of patients.

The benefit of an extended PLND certainly depends on a patient's preoperative clinical variables. While the patients included in the study of Bader *et al.* might have warranted an extended PLND, as supported by the 25% rate of LN involvement, the patients include in the study of Clark *et al.* are more reflective of our patient population. Despite our 15-year inclusion period, our patient population only included 0.5% clinical T3 disease and the patients had a median preoperative PSA level of 6.2 ng/mL. To determine if patients with a higher preoperative risk profile would benefit from a more extended PLND, we conducted a separate analysis to determine if the number of LNs removed was a significant predictor of BCF with patients stratified by risk category. In an adjusted model, we determined that even patients with higher risk characteristics did not benefit from extended PLND.

In addition to the debate about the decision to perform a limited vs extended PLND on patients with clinically organ-confined disease, controversy also surrounds the potential benefit of removing more LNs in pT2–4N0M0 patients. A SEER-based study of Joslyn and Konety [7] examined 6516 patients who had RP and PLND as primary therapy for prostate cancer. In an adjusted model, more extensive PLND (> 10 nodes removed) was associated with improved disease-specific survival. By contrast, a large series reported by DiMarco *et al.* [1] examined 7036 patients with pTXN0 prostate cancer who had RP and PLND (median number of LNs was 9) with no adjuvant therapy. Similar to our findings, the adjusted model showed that the number of LNs removed was not significantly associated with BCF. In

addition, the adjusted model indicated that the number of LNs examined was also not a significant predictor of systemic progression or disease-specific survival.

Our analysis had several limitations. Although we are currently capturing the PLND template for each patient, this information was unavailable for the patients included in our dataset. In addition, we make the supposition that the number of LNs removed is a surrogate for the extent of PLND. A previous study by Allaf *et al.* [8] supported this principle by showing that more extensive PLND templates remove more LNs than limited templates.

A higher LN yield does not affect biochemical failure rates in patients undergoing RP for pT2–4N0M0 prostate cancer. This lack of a survival advantage holds true for patients with high-risk disease. There is inconclusive evidence currently to support extended PLND at the time of RP for contemporary patients.

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Abbreviations

P(LN)D pelvic (lymph node) dissection

RP	radical prostatectomy
BCF	biochemical recurrence
SEER	Surveillance, Epidemiology and End Results
ADT	androgen-deprivation therapy
EBRT	external beam radiotherapy
PFP	progression-free probability

FIG. 1.
BCF by LNs examined, with BCF-free survival against time in months.

TABLE 1

Clinical and pathological features by number of LNs examined

Variable	Total	Number of LNs examined					P
		1-4	5-9	10-14	15-19	20	
N(%) patients	964	234 (24.3)	395 (41.0)	198 (20.5)	78 (8.1)	59 (6.1)	
Mean (SD) age, years	60.5 (6.9)	59.5 (7.1)	60.3 (6.9)	61.1 (7.0)	62.5 (6.6)	61.0 (5.5)	0.010 [*]
Median (IQR) PSA level, ng/mL	6.2 (4.1)	5.8 (3.2)	6.2 (4.1)	6.4 (3.9)	7.3 (5.0)	6.9 (5.7)	0.006 [‡]
Mean (median) follow-up, months	62.9 (59.0)	55.2 (48.0)	59.6 (57.0)	65.2 (60.0)	79.9 (77.0)	83.6 (70.0)	<0.001 [*]
Biopsy Gleason score, n (%)							0.649 [‡]
6	612 (63.5)	147 (62.8)	241 (61.0)	128 (64.7)	57 (73.1)	39 (66.1)	
7	277 (28.7)	69 (29.5)	123 (31.1)	55 (27.8)	14 (18.0)	16 (27.1)	
8	75 (7.8)	18 (7.7)	31 (7.9)	15 (7.6)	7 (8.9)	4 (6.8)	
Clinical stage, n (%)							0.238 [‡]
T1	509 (52.8)	129 (55.1)	219 (55.4)	92 (46.5)	43 (55.1)	26 (44.1)	
T2	450 (46.7)	104 (44.4)	173 (43.8)	106 (53.5)	35 (44.9)	32 (54.2)	
T3	5 (0.5)	1 (0.4)	3 (0.8)	0	0	1 (1.7)	
Pathological Gleason score, n (%)							0.110 [‡]
6	424 (44.0)	92 (39.3)	178 (45.1)	85 (42.9)	35 (44.9)	34 (57.6)	
7	440 (45.6)	117 (50.0)	168 (42.5)	98 (49.5)	38 (48.7)	19 (32.2)	
8	100 (10.4)	25 (10.7)	49 (12.4)	15 (7.6)	5 (6.4)	6 (10.2)	
Pathological stage, n (%)							0.963 [‡]
T2	698 (72.4)	172 (73.5)	287 (72.7)	142 (71.7)	54 (69.2)	43 (72.9)	
T3/4	266 (27.6)	62 (26.5)	108 (27.3)	56 (28.3)	24 (30.1)	16 (27.1)	
Surgical margin, n (%)							0.425 [‡]
Negative	747 (77.5)	176 (75.2)	314 (79.5)	155 (78.3)	61 (78.2)	41 (69.5)	
Positive	217 (22.5)	58 (24.8)	81 (20.5)	43 (21.7)	17 (21.8)	18 (30.5)	
Year of surgery							<0.001 [‡]
1990-95	344 (35.7)	44 (18.8)	126 (31.9)	76 (38.4)	53 (68.0)	45 (76.3)	
1996-2000	387 (40.1)	112 (47.9)	166 (42.0)	80 (40.4)	18 (23.1)	11 (18.6)	
2001-2005	233 (24.2)	78 (33.3)	103 (26.1)	42 (21.2)	7 (9.0)	3 (5.1)	

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* nonparametric ANOVA;
Kruskal-Wallis;
\$ chi-square
IQR, interquartile range.

TABLE 2

Unadjusted and adjusted analysis to determine predictors of BCF

Variable	Unadjusted HR (95% CI)	<i>P</i> *	Adjusted HR (95% CI)	<i>P</i> *
Preoperative PSA level, ng/mL				
4	1.0		1.0	
5–9	2.0 (1.1–3.7)	<0.001	1.8 (1.0–3.4)	0.001
10	5.1 (2.8–9.5)		3.4 (1.8–6.4)	
Gleason Score				
6	1.0		1.0	
7	3.1 (2.1–4.7)	<0.001	2.4 (1.6–3.6)	<0.001
8	8.9 (5.7–13.9)		5.1 (3.1–8.4)	
Pathological stage				
T2	1.0		1.0	
T3/T4	3.6 (2.7–4.9)	<0.001	1.9 (1.4–2.7)	<0.001
Surgical margin				
Negative	1.0		1.0	
Positive	2.6 (1.9–3.5)	0.001	1.7 (1.2–2.4)	0.004
Year of surgery				
1990–95	1.0		1.0	
1996–2000	0.63 (0.44–0.88)	0.022	0.52 (0.36–0.76)	0.002
2001–2005	0.71 (0.45–1.1)		0.56 (0.35–0.92)	
LN Group				
1–4	1.0		1.0	
5–9	0.94 (0.6–1.4)	0.759	0.79 (0.5–1.2)	0.408
10–14	0.92 (0.6–1.5)		0.90 (0.6–1.4)	
15–19	0.86 (0.5–1.6)		0.82 (0.5–1.5)	
20	1.3 (0.7–2.3)		1.3 (0.7–2.4)	

* Wald test;

HR, hazard ratio.

TABLE 3

Adjusted analysis to determine predictors of BCF with patients stratified by risk category

LN group	Adjusted HR (95% CI)	
	High-risk	Low-risk
1–4	1.0	1.0
5–9	0.73 (0.43–1.24)	1.23 (0.67–2.27)
10–14	0.51 (0.27–0.98)	1.46 (0.75–2.84)
15–19	0.59 (0.25–1.39)	1.21 (0.51–2.85)
20	1.21 (0.52–2.83)	1.86 (0.83–4.16)
<i>P</i> *	0.299	

* Wald test;

HR, hazard ratio.