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Clinical-Prostate cancer

The estimated prevalence of missed positive lymph nodes based on extent of lymphadenectomy at radical prostatectomy

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Abstract

Purpose: To determine practice patterns for the extent of lymphadenectomy at radical prostatectomy and associations with detection of pN1 prostate cancer, as well as the impact of lymphadenectomy extent on underdetection of pN1 disease and overall survival.

Materials and methods: Prostatectomy cases in the NCDB from 2004 to 2013 were included. Lymphadenectomy extent was defined by the number of nodes examined. Logistic regression was used to identify risk factors for the top quartile of lymph node count and pN1 disease. This model was created to estimate the expected prevalence of pN1, and generated observed over expected ratios. A Cox regression model was used to evaluate the effect of lymph node count on overall survival.

Results: Lymphadenectomy was performed in 209,789 (60%) of 358,522 surgeries, with pN1 in 6,428 (3.08%). Increasing quartiles for lymph node count was associated with pN1 (3−5 nodes OR 2.11; 6−8 nodes OR 3.12; ≥9 nodes OR 5.91, all $P< 0.001$). The logistic regression model suggested that 59% of pN1 cases are missed due to low lymph node count. Increased lymph node count was associated with increasing pN1 detection (O/E: 1−2 nodes = 0.18; 3−5 nodes = 0.37; 6−8 nodes = 0.56; ≥9 nodes = 1.01). Cox proportional hazards modeling demonstrated that the top quartile for lymph node count had improved overall survival (HR 0.93, CI 0.87−0.99, $P= 0.03$).

Conclusions: Increasing lymphadenectomy extent was associated with pN1 disease on multivariate analysis, and logistic regression modeling suggested a substantial proportion of pN1 were missed due to low lymphadenectomy extent across all risk groups.

Keywords: Prostate cancer; Lymph node dissection; Lymphadenectomy

1. Introduction

Lymph node (LN) positive (pN1) prostate cancer (CaP) has a reported prevalence of 3.5% to 10% after radical prostatectomy (RP) [1,2,3]. LN dissection (LND) may be diagnostic for pN1 CaP and potentially therapeutic. However, the optimal extent and optimal template of LND is unclear. Many authors have advocated for a more extended LND at RP, yet this has not been established as a standard through randomized clinical trials.

Stage pN1 disease carries poor prognosis both in terms of progression and overall survival (OS) [1,3,4]**.** The ECOG 3886 trial established level 1 evidence for adjuvant treatment of pN1 CaP in which initial observation had inferior OS compared to immediate androgen deprivation therapy [5]**.** Adequate LN sampling is therefore central to identifying pN1 patients who may benefit from adjuvant therapy. Furthermore, single-center studies have demonstrated LND alone may be an effective treatment in some cases, and that increasing LN yield may correlate with improved OS [6−9].

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Touijer et al. reported a cohort of 369 pN1 men treated with surgery alone and the 10-year probability of freedom from biochemical recurrence was 28% [6]. Abdollah et al. also demonstrated in a single institution series that an increasing number of removed LNs was associated with improved cancer-specific survival [7]. However, these findings are driven by high volume centers and may not be generalizable to patients at most treating facilities.

The estimated national prevalence of missed positive LNs due to low LND extent at RP has yet to be reported. Currently there are Commission on Cancer quality standards regarding the minimum number of LNs examined after LND for colon, gastric, bladder, and non−small cell lung cancers [10]. No such quality metric for LN count has been established for CaP.

We hypothesize that pN1 disease is currently underdetected due to low LND extent. Our primary objective is to estimate the number of undetected pN1 cases attributable to low LN count. Our secondary objective is to determine the association between LN count and OS.

2. Materials and methods

2.1. Study population

This study was conducted after approval of the local Institutional Review Board. The analysis set included CaP patients from the National Cancer Database (NCDB) diagnosed from 2004 to 2013. The NCDB includes roughly 70% of cancer cases in the US and are reported by member facilities of the Commission on Cancer. We identified patients who underwent RP as primary treatment for clinical nonmetastatic CaP. Patients were excluded if they underwent radiation, chemotherapy, or hormonal therapy prior to surgery, if the cancer grade was Gleason sum <6, if they were diagnosed on transurethral resection of prostate, or if data were missing on clinical stage, PSA at diagnosis, or biopsy Gleason grade. Details regarding the analysis set creation are displayed in Fig. 1.

2.2. Variables and definitions

LND extent was defined and analyzed using quartiles for the number of LNs that were examined in the surgical specimen. The NCDB generates this data field from pathology reports, and there is no data available regarding the surgeons' intent to perform an LND or the anatomic regions of LND. LN positive disease was defined as a binary outcome (pN1/pN0). Natural log transformation was applied to pretreatment PSA to reduce skewness in distribution. In addition to raw data on clinical risk factors (PSA, clinical stage, Gleason sum), the cases were assigned ISUP Grade Group [11,12], NCCN risk group [13], and the University of California San Francisco Cancer of the Prostate Risk Assessment (CAPRA) score [14]. Other clinical variables included open vs. minimally invasive RP (2010−013 only).

2.3. Statistical analysis

The prevalence of LND and pN1 disease was estimated from the database. The prevalence of LND and the LN count was compared among NCCN risk and CAPRA risk groups. Logistic regression analysis was used to determine risk factors for cases to be in the top quartile for LN count. Univariable and multivariable logistic regression was performed to determine the association between LN count and pN1 after adjusting for independent risk factors for LN count.

The primary objective was to estimate the number of undetected pN1 cases that would have been identified with a higher LN count. A logistic regression model was fit to the top quartile for LN count (≥9 nodes) to estimate pN1 based on statistically significant variables (PSA, primary Gleason grade, secondary Gleason grade, and clinical T stage). This is similar to the methodology in clinically available predictive models [14]. This model was used to calculate the probability of pN1 disease for each patient, as detailed by the formula below:

$$probability\ of\ pN1\ disease = P = \frac{e^x}{1 + e^x}$$

X = 0.0224*PSA + 2.066*GG1 + 0.993*GG2 + 0.509*T2 + 0.906*T3 − 5.004

Note: GG1 is the primary Gleason grade, GG2 is the secondary Gleason grade, T2 and T3 are factor variables indicating the presence or absence of clinical stage T2 or >T2 disease. (Supplemental Table 1)

The expected number of pN1 patients in each LN count group was estimated using the product of the number of patients and the mean estimated probability of pN1 disease in each group. Observed over expected (O/E) ratios were generated for pN1 in each LN count group to demonstrate how many pN1 cases may have been missed. Using the same model, the expected prevalence of pN1 was generated within each CAPRA risk category.

The logistic regression model was assessed with the area under the curve (AUC) from the receiver operating characteristic curve analysis. For internal validation of the model a simple cross-validation was performed with 33% of cohort reserved as the validation set. For external validation the result of our model was compared against the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram [15].

The impact of LN count on OS was analyzed as a secondary endpoint. LN count was examined using a Cox proportional hazards model for OS after adjusting for significant confounders.

Statistical analysis was performed using Stata (version 14.2, StataCorp, College Station, TX) and R: A Language and Environment for Statistical Computing (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria)

3. Results

3.1. Prevalence of pN1 and practice patterns for LN count

The analysis set included 358,791 patients (Figure 1). Among 209,789 (60%) who underwent LND, quartiles for LN count were 1-2, 3-5, 6-8, and ≥9 nodes examined. pN1 was detected in 6,428 cases (3.08%). Patient demographics are detailed in Table 1.

3.2. Associations with LN count

Multivariable logistic regression identified positive associations for LN count ≥9 nodes (Supplemental Table 1), including biopsy Gleason score, PSA, clinical stage, year of treatment, median income of patient county, academic facilities, and facility volume; minimally invasive RP was negatively associated. When categorized by CAPRA score, higher scores demonstrated a larger proportion with higher LN count (Figure 2a).

3.3. Associations with pN1 and logistic regression model for expected pN1

Several variables associated with pN1 were identified on multivariable logistic regression (Table 2). Increasing LN count was significantly associated with pN1, (3-5 nodes OR 2.07; 6-8 nodes OR 3.20; ≥9 nodes OR 6.13, all p<0.001) (Figure 2b).

Expected pN1 counts were estimated using the logistic regression model for the probability of pN1 disease, as

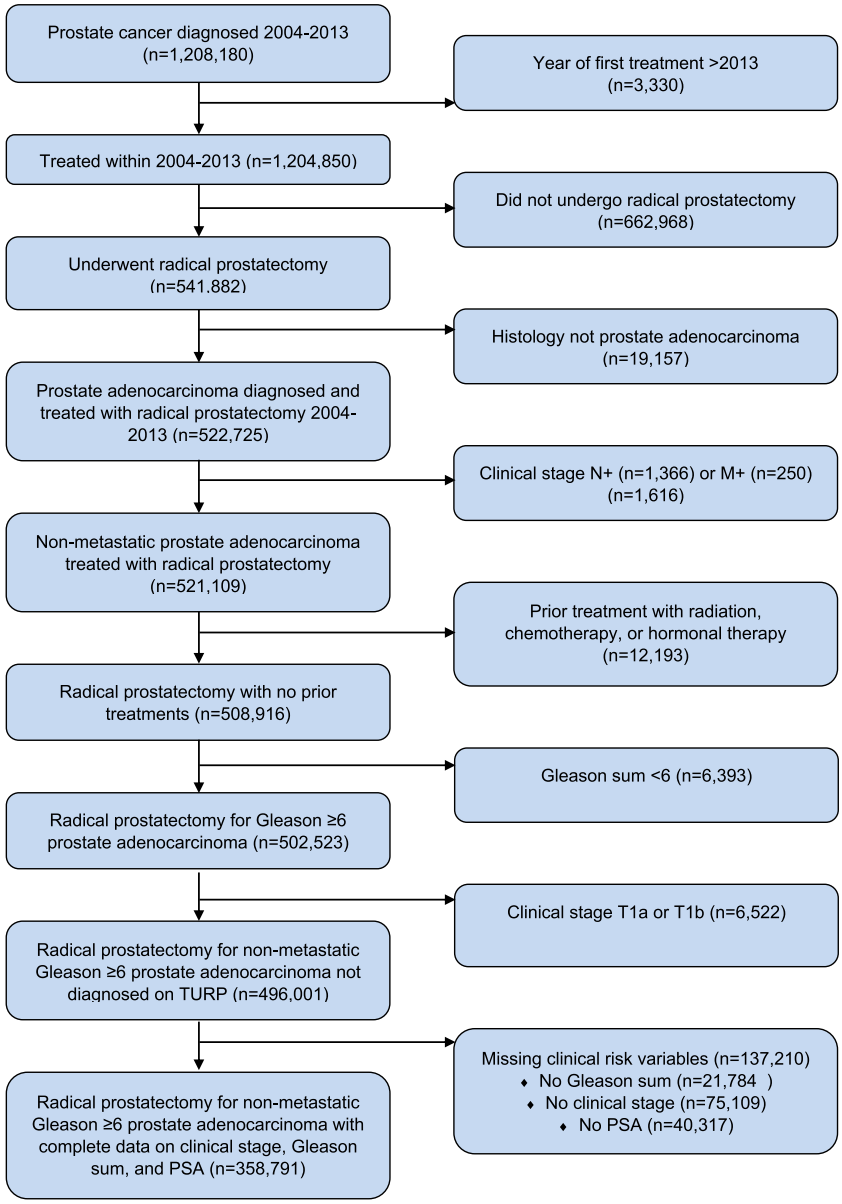

Fig. 1. Study population flow diagram.

Table 1
Patient demographics.

	Overall population $N = 358,791$	pN0 Patients $N = 203,361$	pN1 Patients $N = 6,428$
Age (mean (sd))	61 (7.07)	60.9 (7.09)	61.8 (7.20)
Race (*N* (%))			
White	290,115 (80.86)	170,150 (97.0)	5,279 (3.0)
Black	40,018 (11.15)	23,102 (96.5)	839 (3.5)
Hispanic	12,782 (3.56)	7,277 (96.0)	301 (4.0)
Other	15,876 (4.42)	4,199 (96.8)	141 (3.3)
Insurance type (*N* (%))			
Private insurance	235,229 (65.56)	15,842 (97.2)	3,928 (2.8)
Medicare	103,812 (28.93)	62,939 (96.5)	2,270 (3.5)
Other government	10,559 (2.94)	56,070 (95.9)	260 (4.1)
Uninsured	9,191 (2.56)	5,821 (96.1)	239 (3.9)
County income level (*N* (%))			
<$38,000	46,247 (12.01)	27,005 (96.7)	918 (3.3)
$38,000–47,999	73,080 (20.56)	42705 (96.8)	1,425 (3.2)
$48,000–62,999	96,302 (27.09)	56,102 (96.9)	1,792 (3.1)
≥$63,000	139,904 (39.35)	83,131 (97.1)	2,500 (2.9)
% in County w/o HS degree (*N* (%))			
≥21%	44,132 (12.41)	25,752 (96.6)	920 (3.4)
13–<21%	78,296 (22.01)	45,468 (96.8)	1,501 (3.2)
7–<13%	118,478 (33.31)	69,173 (97.0)	2,172 (3.0)
<7%	114,800 (32.27)	68,660 (97.1)	2,049 (3.9)
Urban/rural (*N* (%))			
Metro	292,310 (83.94)	171,065 (96.9)	5,419 (3.1)
Urban	48,940 (14.05)	29,688 (96.9)	960 (3.1)
Rural	6,933 (2.01)	4,316 (97.0)	136 (3.0)
Facility type (*N* (%))			
Nonacademic	197,156 (55.01)	108,375 (97.3)	3,051 (2.7)
Academic	161,220 (44.99)	102,081 (96.6)	3,640 (3.4)
Facility location (*N* (%))			
Mid Atlantic	52,559 (14.67)	33,847 (96.8)	1,112 (3.2)
New England	20,442 (5.7)	10,164 (97.0)	316 (3.0)
South Atlantic	71,870 (20.05)	37,337 (97.4)	994 (2.6)
East North Central	58,703 (16.38)	34,428 (96.7)	1,173 (3.3)
East South Central	28,862 (8.05)	16,916 (97.4)	451 (2.6)
West North Central	36,088 (10.07)	24,452 (97.4)	650 (2.6)
West South Central	22,863 (6.38)	14,762 (96.9)	467 (3.1)
Mountain	18,581 (5.18)	9,807 (96.4)	364 (3.6)
Pacific	48,408 (13.51)	28,743 (96.1)	1,164 (3.9)
Clinical stage (*N* (%))			
T1c	251,925 (70.21)	145,214 (97.8)	3,277 (2.2)
T2	98,439 (27.44)	60,094 (95.5)	2,825 (4.5)
T3/T4	8.427 (2.35)	5,364 (90.0)	595 (10.0)
ISUP grade group (*N* (%))			
1	143,890 (41.10)	66,596 (99.7)	207 (0.3)
2	126,767 (36.21)	80,711 (98.3)	1,376 (1.7)
3	42,535 (12.15)	30,455 (95.3)	1,507 (4.7)
4	22,202 (6.34)	17,179 (92.6)	1,381 (7.4)
5	14,173 (4.20)	11,022 (84.2)	2,069 (15.8)
PSA (median (IQR))	5.4 (4.2–7.8)	8.4 (10.6)	14.9 (15.9)
Charlson			
0	301,664 (84.08)	176,563 (97.0)	5,490 (3.0)
1	50,897 (14.19)	30,387 (96.6)	1,072 (3.4)
2+	6,230 (1.74)	3,722 (96.5)	135 (3.5)

detailed in the methods section. Receiver operating characteristic curve for the model demonstrated an AUC of 0.817 for the outcome of pN1 among the entire cohort (Supplemental Figure 1). Simple cross-validation was performed using the holdout method with 33% of cohort reserved for the validation set and yielded nearly identical AUC (0.819 vs 0.812).

The logistic regression model was then used to generate expected pN1 case counts for each LN count quartile. From these expected counts O/E ratios were calculated for pN1

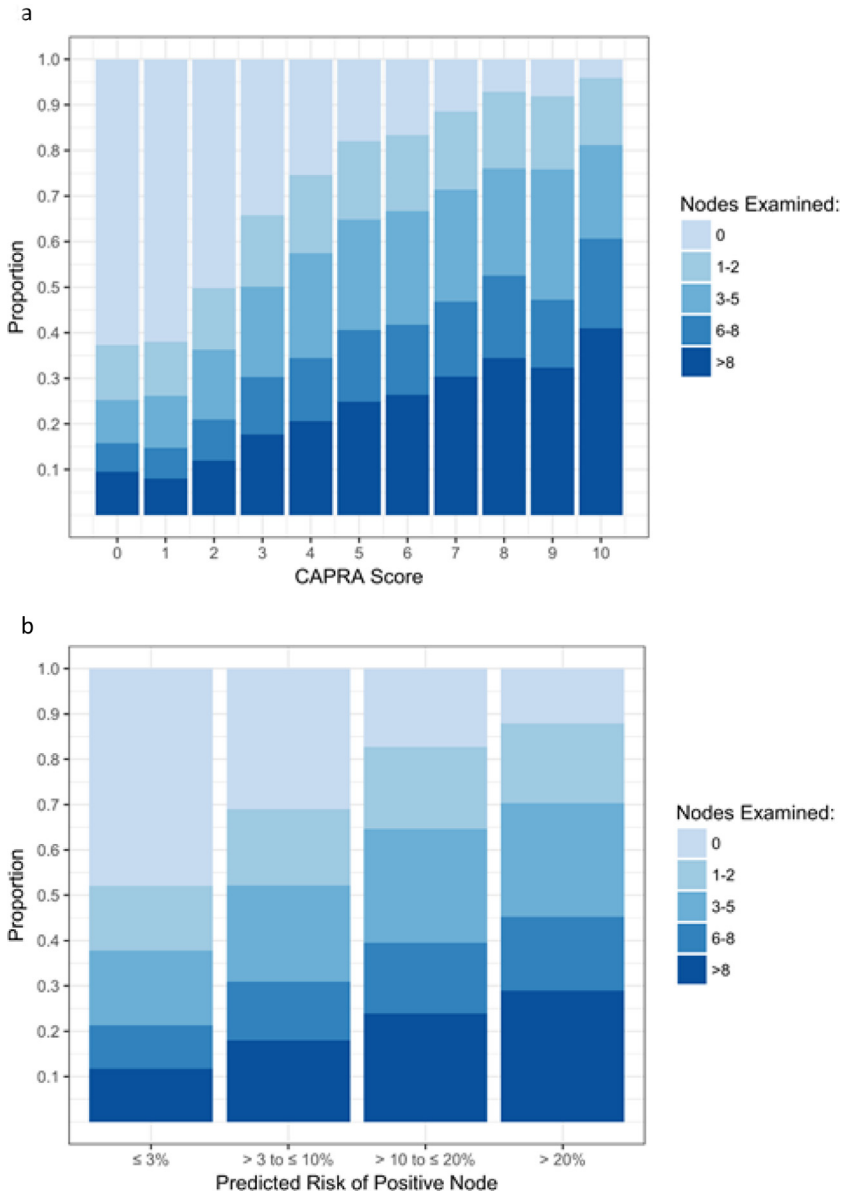

Fig. 2. (**a and b)** Lymph node count stratified by CAPRA score (a) and Predicted Risk of Positive LN (b)

among 6-8 nodes (0.56), 3-5 nodes (0.37), and 1-2 nodes (0.18) (Table 3, Figure 3a). Those without an LND performed were expected to have 2,672 (1.3%) pN1 cases. O/E decreased among lower CAPRA scores, demonstrating a higher proportion of missed pN1 cases (CAPRA 6-10=0.77, CAPRA 3-5=0.57, and CAPRA 0-2=0.34) (Table 3, Figure 3b). When categorized by quartiles of predicted pN1 risk, higher risk categories showed a higher proportion of patients with higher LN counts (Figure 2b). The model estimated that 59% of pN1 were missed due to low LN count.

When this NCDB data was applied to the MSKCC nomogram, the overall O/E trends were similar to our logistic regression model, but with a higher proportion of anticipated missed pN1 in the MSKCC model. Overall the MSKCC model estimated that 72.6% of pN1 patients are missed due to low LN count. (Table 3)

3.4. Survival analysis

Cox regression analysis demonstrated that the highest quartile for LN count was associated with an OS benefit (HR 0.93, CI 0.87−0.99, *P*= 0.03). The survival analysis also showed decreased OS for patients with higher ISUP grade group, higher PSA, more advanced T stage, pN1, and care received at a lower volume or nonacademic center (Table 4).

4. Discussion

In this analysis utilizing national facility-level data from the NCDB and novel prediction methods for expected pN1 prevalence, we estimated that a substantial proportion of pN1 CaP cases in the US are underdiagnosed. This

Table 2
Risk factors for lymph node positive disease.

	OR	95% CI	*P*
LN count (# nodes, Ref. <3)			
3–5	2.07	1.85–2.30	<0.001
6–8	3.2	2.86–3.58	<0.001
9+	6.13	5.53–6.78	<0.001
Age (per 5yr increase)	0.97	0.94–0.99	0.004
Income level (Ref. <25th percentile)			
25th–50th percentile	0.96	0.87–1.05	0.297
50th–75th percentile	0.96	0.87–1.04	0.212
>75th percentile	0.92	0.84–0.998	0.033
Facility type (Ref. Other facility)			
Academic	1.05	0.98–1.11	0.49
Insurance (Ref. Private)			
Medicare	1.05	0.98–1.14	0.14
Other government	1.16	1.00–1.34	0.032
Cash	1.11	0.95–1.29	0.199
WHO/ISUP Grade Group (Ref. 1)			
2	4.57	3.93–5.31	<0.001
3	11.74	10.09–13.65	<0.001
4	17.32	14.86–20.19	<0.001
5	38.03	32.70–44.22	<0.001
PSA (Ref. <10)			
10–20	2.11	1.97–2.25	<0.001
20+	3.19	1.20–2.96	<0.001
Clinical T stage (Ref. T1c)			
T2	1.61	1.52–1.70	<0.001
T3+	2.02	1.82–2.24	<0.001
Facility volume (per 1k pt increase)	1.011	1.00–1.02	0.003
Charlson category (Ref. 0)			
1	1.01	0.94–1.08	0.848
2+	0.99	0.82–1.20	0.944

underdetection of pN1 persisted among patients who were the highest risk, including high-risk CAPRA score and those with a predictive model estimated risk of pN1 greater than 20%. The understaging may have implications for immediate therapeutic benefit of LND [6,7], in addition to selection for adjuvant therapy [5]. Patients with missed positive LNs are likely to have biochemical recurrence, and could theoretically receive salvage radiotherapy to the prostate bed when it is not necessarily indicated.

LN count was highly associated with increased likelihood of pN1. One reason was that higher risk patients were more likely to receive a more extensive LND. This data is consistent with previous literature [16]. To address this confounding factor, a logistic regression model was created to predict the probability of pN1 based on known risk factors. When the model was applied to the entire cohort, the data suggested that the overall rate of missed pN1 due to low LN count was 59%. The likelihood of missed pN1 increased as LN count decreased across all clinical risk groups (Table 3, Fig. 3a).

Underdetection of pN1 was most likely in the lowest risk CAPRA group, though with lower absolute numbers due to a low overall risk of pN1 in this group. Current clinical practice is steering away from surgical management of low-risk CaP, making the analysis of this group less clinically relevant [17–19]. In contemporary practice, patients with disease-risk low enough to warrant exclusion of LND at RP are likely good candidates for active surveillance.

Our model estimated 43% of pN1 cases are missed in the intermediate risk group, as compared to a 23% in the high-risk group (Table 3, Fig. 3b). It is unclear at this time what the optimal number of LNs examined, or the optimal LND template should be for these patients. However, we emphasize that in this analysis an unacceptably high number of patients in the highest risk categories had either zero or very few LNs examined. In patients with an expected pN1 probability of >20%, patients had 2 or fewer LNs examined in approximately 30% of cases.

When this NCDB data was applied to the MSKCC nomogram we found a similar trend for missed pN1 due to low LND extent, with respect to changes in LN count and CAPRA score (Table 3). However, the MSKCC nomogram consistently estimated a higher overall rate of missed pN1, including an overall estimation of 72.6% missed pN1 in the NCDB cohort. The differences between our model, which was derived from NCDB data, and the MSKCC model can be accounted for in multiple ways. The MSKCC model's underlying data likely reflects a higher risk patient population being referred to a highly specialized tertiary care cancer center. Additionally, the surgeons at that institution

Table 3
Estimations of LN Positivity by LN count and CAPRA score using NCDB and MSK models.

Variable	NCDB model					MSK model				
LN Count	Total *N*	pN1	Observed	Expected	O/E	Total *N*	pN1	Observed	Expected	O/E
9+	51843	3504	0.068	0.067	1.01	48985	3267	0.067	0.097	0.69
6–8	38796	1263	0.033	0.058	0.56	36526	1169	0.032	0.084	0.38
3–5	65469	1347	0.021	0.056	0.37	61626	1223	0.020	0.080	0.25
1–2	53811	508	0.009	0.051	0.18	50849	467	0.009	0.074	0.12
0	140324	0	0.000	0.028	0.00	133791	0	0.000	0.044	0.00
CAPRA	Total *N*	pN1	Observed	Expected	O/E	Total *N*	pN1	Observed	Expected	O/E
6–10	13025	1561	0.120	0.156	0.77	12196	1447	0.119	0.252	0.47
3–5	36071	1065	0.030	0.051	0.57	34002	975	0.029	0.068	0.42
0–2	20682	89	0.004	0.012	0.34	19858	87	0.004	0.017	0.26

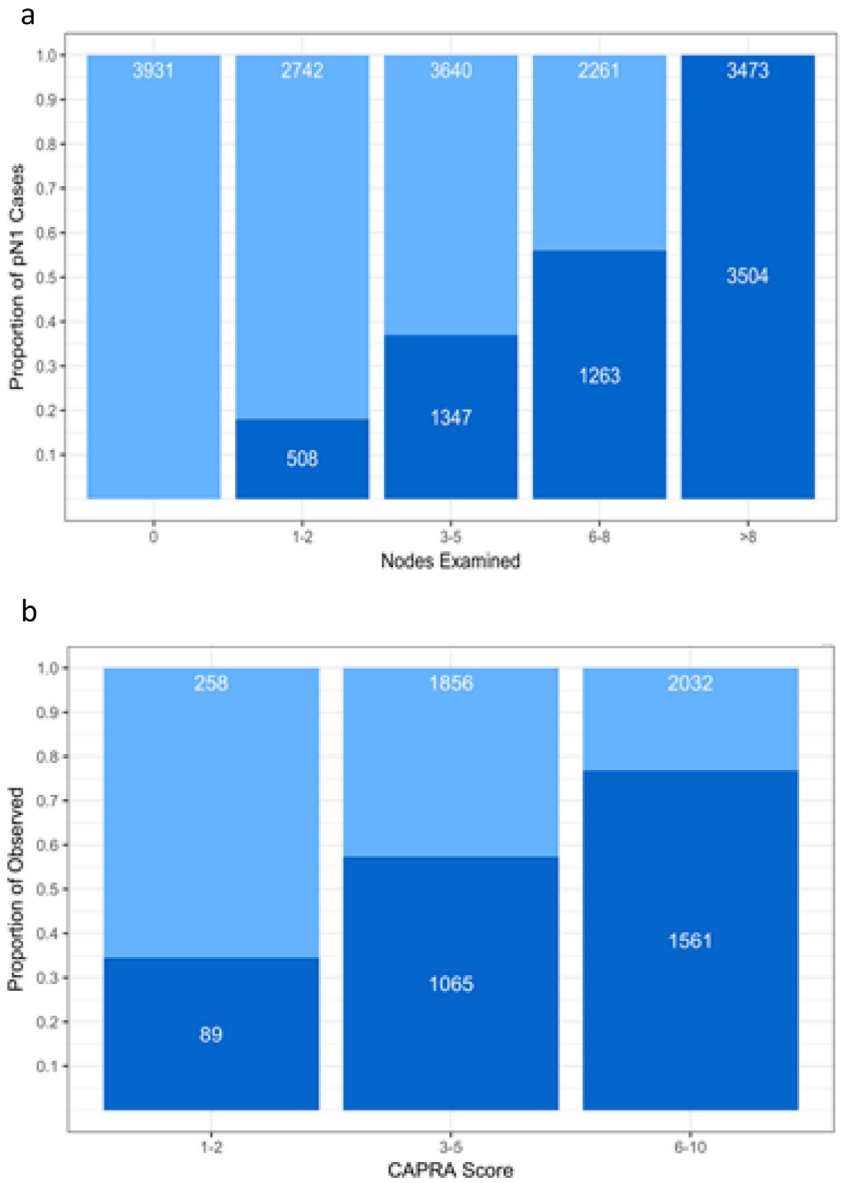

Figure 3. **(a and b)** Observed and expected detection of pN1 disease stratified by LN count (a) and CAPRA risk (b)**.** The dark blue bar represents the proportion of observed cases and the light blue bar represents the proportion of undetected cases, with the total number of expected cases listed on the top of the bar.

may perform a more extensive LND than those that are represented by the NCDB. Both of these factors would be expected to increase the probability of pN1 in their underlying data, and therefore affect the output of the nomogram derived from this data.

A related model described in a 2014 study by Kluth et al. determined that pN0 patients with lower risk preoperative characteristics (PSA, Gleason sum, T stage) were more likely to have accurate nodal staging, presumably due to a lower overall risk of pN1, and that the probability of accurate staging increased with an increasing number of nodes examined [20]. The underlying data was derived from 8 high volume academic centers, which may not reflect that of the general population.

Being in the top quartile for LN count was independently associated with improved OS (Table 4). This finding may reflect the clinical impact of increased detection of pN1 in this group. More extensive LND and increased detection allow for the early diagnosis of systemic disease and initiation of adjuvant androgen deprivation therapy, and may provide therapeutic benefit from removal of the nodes themselves. Although there is no definitive randomized trial to demonstrate a benefit to adjuvant radiotherapy in this setting, there is limited retrospective data that suggests some patients with nodal involvement may benefit [21–23].

The main limitation of this NCDB study is that we do not have anatomic areas of LND, so we cannot determine the surgeons' intent for LND. Also, LND extent is based on

Table 4
Overall survival, Cox regression multivariate analysis[a]

	Hazard ratio	95% CI	*P* value
LN Count (Ref. 1–2 LNs)			
9+	0.93	0.87–0.99	0.031
6-8	0.94	0.87–1.00	0.065
3-5	1.03	0.97–1.09	0.328
WHO/ISUP Grade Group (Ref. group 1)			
2	1.21	1.14–1.29	<0.001
3	1.54	1.43–1.65	<0.001
4	1.9	1.75–2.07	<0.001
5	3.04	2.81–3.29	<0.001
PSA (ng/ml) (Ref. 0–10)			
10–20	1.27	1.29–1.35	<0.001
20+	1.21	1.11–1.31	<0.001
Clinical T stage (Ref. T1c)			
T2	1.11	1.29–1.58	<0.001
T3+	1.42	1.28–1.57	<0.001
Positive LN status (Ref. negative)	1.97	1.79–2.16	<0.001
Facility volume (per 1,000 pt increase)	0.96	0.96–0.97	<0.001
Academic facility (Ref. other facility)	0.81	0.77–0.85	<0.001

[a] The multivariable model included age, race, Charlson score, LN count, WHO/ISUP grade group, PSA, clinical T stage, LN positivity, facility volume, and facility type.

the number of LNs examined, which relies on tissue processing and pathologic examination. However, variability between individual surgeons and pathologists should have minimal impact on the findings given the large number of facilities and patients included in the analysis.

5. Conclusions

In this analysis of the NCDB from 2004 to 2014, LND was only performed in 60% of RP. Increasing LN count was highly associated with pN1 disease. Predictive model estimations indicated that a substantial proportion of pN1 were missed due to low LN count among all risk groups, including those with an estimated risk of nodal involvement >20% or CAPRA high risk. Overall, the model estimated that 59% of pN1 was missed due to low LN count. An OS benefit was demonstrated in the highest quartile of LN count. This data suggests that missed pN1 due to low LN count is highly prevalent and may result in decreased OS.

Conflicts of interest

All the authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.06.008.

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