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First Nomogram Predicting the Probability of Lymph Node Involvement in Prostate Cancer Patients Undergoing Radioisotope Guided Sentinel Lymph Node Dissection

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Key Words
Prostate cancer · Sentinel lymph node dissection · Lymphadenectomy · Nomogram · Lymph node involvement

Abstract
Introduction: Existing nomograms predicting lymph node involvement (LNI) in prostate cancer (PCa) are based on conventional lymphadenectomy. The aim of the study was to develop the first nomogram for predicting LNI in PCa patients undergoing sentinel guided pelvic lymph node dissection (sPLND). ***Materials and Methods:*** Analysis was performed on 1,296 patients with PCa who underwent radioisotope guided sPLND and retropubic radical prostatectomy (2005–2010). Median prostate specific antigen (PSA): 7.4 ng/ml (IQR 5.3–11.5 ng/ml). Clinical T-categories: T1: 54.8%, T2: 42.4%, T3: 2.8%. Biopsy Gleason sums: ≤6: 55.1%, 7: 39.5%, ≥8: 5.4%. Multivariate logistic regression models tested the association between all of the above predictors and LNI. Regression-based coefficients were used to develop a nomogram for predicting LNI. Accuracy was quantified using the area under the curve (AUC). ***Results:*** The median number of LNs removed was 10 (IQR 7–13). Overall, 17.8% of patients (n = 231) had LNI. The nomogram had a high predictive accuracy (AUC of 82%). All the variables were statistically significant multivariate predictors of LNI (p = 0.001). Univariate predictive accuracy for PSA, Gleason sum and clinical stage was 69, 75 and 69%, respectively. ***Conclusions:*** The sentinel nomogram can predict LNI at a sPLND very accurately and, for the first time, aid clinicians and patients in making important decisions on the indication of a sPLND. The high rate of LN+ patients underscores the sensitivity of sPLND.

Introduction

Pelvic lymph node dissection (PLND) is still the gold standard for lymph node (LN) staging in clinically localized prostate cancer (PCa). The diagnostic accuracy of available imaging procedures is quite inferior to the histological verification of LN metastases. The LN status is a crucial prognostic factor in PCa. Presence and extension of LN involvement (LNI) is associated with an increased risk of systemic dissemination and progression of the disease. A debate is currently underway on the positive therapeutic impact of PLND, especially in patients with minimal LNI [1, 2].

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Numerous nomograms based on preoperative variables have been developed to predict LNI in PCa and to select candidates for PLNDs. The goal is to identify low-risk LNI cases and hinder additional morbidity from a PLND. Without exception, these decision tools were based on conventional PLND techniques. Many of these algorithms and Partin tables [3] were based on series in which the patients underwent a limited degree of PLND (lPLND). The nomograms now available are based on ePLND [4–6], which means they account for the fact that LNI prevalence is directly related to the number of dissected LNs and extent of the PLND [7, 8]. However, the rate of complications rises along with the number of LNs removed [9–11].

Similarly, for radioisotope guided sPLNDs, one can demonstrate a high staging accuracy accompanied by even lower morbidity [11–13]. The sentinel approach allows an individualized extension of LN dissection outside the boarders of ePLND too [14]. Presently, different tracers, such as the near-infrared fluorescent dye indocyanine green, are being tested to mark sentinel LNs (SLNs), especially in connection with robotic [15] and laparoscopic [16] radical prostatectomies (RPs). So far, there is no LNI nomogram based on a sPLND.

We hypothesized that preoperative parameters obtained in patients undergoing sPLNDs can accurately predict LNI in sPLND specimens. To test our hypothesis, we used data collected from men who had undergone a sPLND in combination with a radical retropubic prostatectomy (RRP). Multivariable logistic regression was used to calculate the probability of LNI.

Materials and Methods

Patients

A total of 1,325 consecutive patients with PCa were identified, who underwent sPLNDs in combination with RRPs carried out by 4 highly experienced surgeons, in a single center between January 2005 and April 2010. We excluded patients with incomplete clinical information for prostate specific antigen (PSA), clinical stage or biopsy Gleason score (n = 4, 0.3%). Furthermore, we also excluded patients who had undergone a transurethral resection or laser therapy of the prostate (n = 14, 1.1%) and cT4 tumors (n = 8, 0.6%). An additional 3 patients (0.2%) were also excluded, since no SLN could be detected by the gamma probe. The final sample comprised 1,296 patients.

The clinical stage was classified per the 2002 Union for International Cancer Control TNM staging system. PSA was measured using standard assays. The primary pretherapeutic PSA value was considered in patients who had undergone hormonal therapy prior to operative treatment (n = 12, 0.9%). Prostate biopsies were performed at our hospital, other hospitals and medical offices, which were then examined histopathologically by internal and external uropathology experienced pathologists. All patients were informed orally and in writing about a sPLND and RRP, and they signed a consent form.

SPLND Technique

Using ultrasound guidance, 99mTechnetium nanocolloid was transrectally injected into the prostate 24 h before the surgery [12]. Three injections were administered per prostate lobe. Activity attained about 100 MBq per lobe and total injection volume was about 1.2 ml. A few hours after injection, scintigraphy was carried out. The radioactivity of the LN was intraoperatively measured using 2 different gamma probe systems (C-Trak System, Care Wise, Morgan Hill, Calif., USA; Crystal Probe SG04, Crystal Photonics GmbH, Berlin, Germany). LNs identified as SLNs by the gamma probe were dissected. For surgical reasons, LNs other than SLNs directly adjoining and adhering to SLNs were also removed, if an in situ separation was not possible. Furthermore, if the SLNs are present in the obturator fossa area, the surrounding non-radioactive lymphatic tissue of the fossa was also dissected. However, the lymphatic tissue of the fossa was not resected, if no SLN existed in the fossa area.

Histopathological Examination

All LNs were initially cut into 3-mm transverse sections, routinely processed and completely embedded in paraffin; sections of thickness 4–5 μm were stained with hematoxylin-eosin. Selected cases of serial sections were analyzed. An immunohistochemical study with a pancytokeratin antibody (AE1/AE3) was carried out to confirm or exclude metastatic spread in rare cases with inconclusive conventional histology.

Measurement and Statistical Methods

Univariable and multivariable logistic regression models were carried out to test the association between preoperative tumor characteristics and the probability of LNI. The predictor variables were the preoperative PSA level categorized as 4, 4.1–10, 10.1–20 and >20 ng/ml; clinical T-category as T1, T2 and T3 and biopsy Gleason sum as 5–6, 7 and 8–10.

Regression coefficients were used to develop the nomogram that predicts the probability of LNI at a sPLND. Bootstrapping (9,999 replications) was applied to generate reliable 95% confidence intervals for the predicted probabilities and for internal validation. Predictive accuracy was quantified using the receiver operator characteristics of the AUC. The performance characteristics were evaluated using a calibration plot of predicted probabilities against observed LNI rates.

Statistical analyses were performed using the generalized linear model function of the open-source statistical software R (R Development Core Team 2008) [17].

Results

Table 1 lists the summary of patient characteristics. By definition, details of the Gleason score in the surgical specimen could not be given for 12 patients who previously underwent hormonal treatment. The median number of LNs removed was 10 (interquartile range (IQR)

Table 1. Patient characteristics

	Overall (n = 1,296)	pN0 (n = 1,065, 82.2%)	pN1 (n = 231, 17.8%)
Age at surgery, years	66 (61–70)	66 (61–70)	67 (62–70)
Total PSA, ng/ml	7.4 (5.3–11.5)	6.9 (5.1–10.0)	12.3 (7.3–20.6)
No. of LN removed	10 (7–13)	10 (7–13)	11 (9–15)
No. of positive LN	–	–	2 (1–3)
T-category			
T1c	710 (54.8)	652 (61.2)	58 (25.1)
T2a	171 (13.2)	136 (12.8)	35 (15.2)
T2b	160 (12.4)	127 (11.9)	33 (14.3)
T2c	219 (16.9)	135 (12.7)	84 (36.4)
T3	36 (2.8)	15 (1.4)	21 (9.1)
Biopsy Gleason sum			
≤6	714 (55.1)	670 (62.9)	44 (19.1)
7	512 (39.5)	369 (34.7)	143 (61.9)
≥8	70 (5.4)	26 (2.4)	44 (19.1)
Postoperative Gleason sum, n = 1,284*			
≤6	269 (21.0)	267 (25.3)	2 (0.9)
7	942 (73.4)	772 (73.1)	170 (74.6)
≥8	73 (5.7)	17 (1.6)	56 (24.6)
Pathologic stage			
pT2	841 (64.8)	813 (76.3)	28 (12.1)
pT3a	231 (17.8)	173 (16.2)	58 (25.1)
pT3b	182 (14.0)	68 (6.4)	114 (49.4)
pT4	42 (3.2)	11 (1.0)	31 (13.4)

Data are given as median (IQR) or number (%). * Twelve patients who previously underwent hormonal treatment excluded.

PSA = Prostate specific antigen; LN = lymph nodes; IQR = interquartile range.

7–13), encompassing a median of 6 (IQR 4–8) SLNs. Overall, 17.8% of patients (n = 231) had LNI. The number of positive LNs ranged from 1 to 15 (median 2; IQR 1–3).

In the multivariate logistic regression analysis, all variables (pretherapeutic PSA, clinical T-category and biopsy Gleason sum) were significantly associated ($p < 0.001$) with LNI. The multivariate predictive accuracy (AUC) was 82%, under consideration of the 3 predictors. Univariate analysis also showed a significant ($p < 0.001$) association between each predictor and LNI. In the univariate predictive accuracy analysis, the biopsy Gleason sum was the most accurate predictor of LNI (74.5%), followed by the clinical T-category (69.3%) and the preoperative PSA value (68.9%). The results of the multivariate and univariate logistic regression analyses are detailed in table 2.

Figure 1 illustrates the nomogram tool in a graphical form as generated by the multivariate analysis. The probabilities for LNI, predicted by the multivariate regression analysis, ranged from 3% in low-risk to 88% in high-risk PCa patients. For example, the probability of LNI is 24% for patients with a cT1c tumor, a PSA value of 10 ≤ 20 and a Gleason sum of 7.

The calibration plot of predicted probabilities against observed LNI rates showed a high level of consistency between predicted and actual probabilities in low- and intermediate-predicted probability ranges. Variances from the ideal nomogram are shown in the high-predicted probability ranges (fig. 2).

Discussion

There is general consensus that an ePLND performed on PCa patients achieves the highest staging accuracy. For sPLND, a high staging accuracy has been demonstrated too [12, 13, 18]. LNI predictor ePLND-based nomograms provide PCa patients a crucial basis to decide for or against a PLND [4–6]. Other predictive models are based on series of lPLNDs, and thereby, these models most likely underestimate the risk of a LNI [3, 19]. It was

Table 2. Results of multivariate and univariate logistic regression analyses predicting LN invasion based on preoperative PSA, biopsy Gleason sum and clinical T-category

Predictors	Multivariate model		Univariate model		Univariate predictive accuracy
	OR	p value	OR	p value	
Preoperative PSA	–	<0.001	–	<0.001	68.9%
4–10 ng/ml vs. ≤4	1.076	0.846	0.932	0.842	
10–20 ng/ml vs. ≤4	2.884	0.006	3.396	0.001	
>20 ng/ml vs. ≤4	3.873	0.001	6.606	<0.001	
Biopsy Gleason sum	–	<0.001	–	<0.001	74.5%
7 vs. ≤6	2.586	<0.001	5.901	<0.001	
≥8 vs. ≤6	5.062	<0.001	25.769	<0.001	
Clinical T-category	–	<0.001	–	<0.001	69.3%
T2 vs. T1c	3.786	<0.001	4.293	<0.001	
T3 vs. T1c	12.924	<0.001	15.738	<0.001	
Predictive accuracy	82%				

OR = Odds ratio.

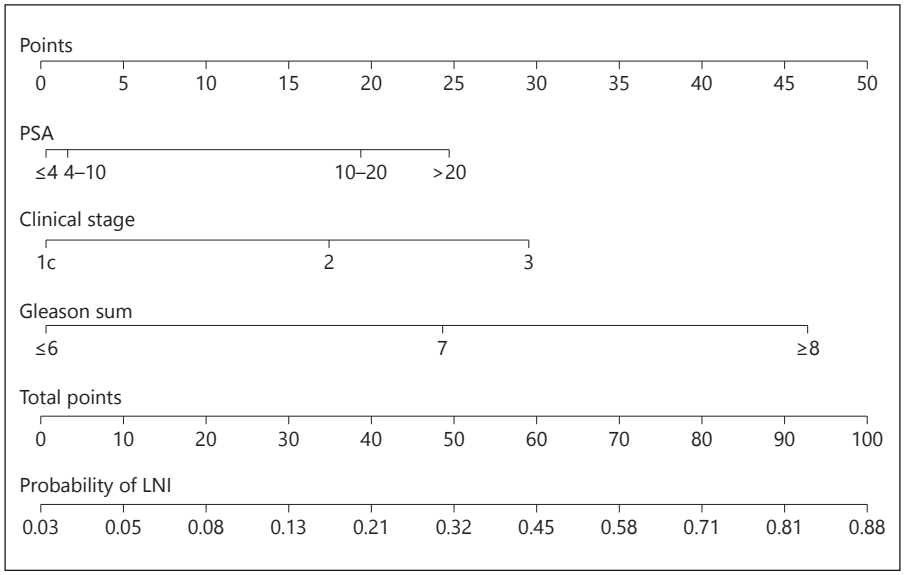

Fig. 1. Nomogram predicting the probability of lymph node involvement (LNI) in patients undergoing sentinel guided pelvic lymphadenectomy based on the preoperative PSA, clinical T-category and biopsy Gleason sum. Instructions: Locate the pretreatment parameters (e.g. PSA, ng/ml) on the respective axis and draw a line straight up to the point axis. Sum the points for each of the predictors and locate the final sum on the total point axis. Draw a line straight down to find the patient's probability of having a LNI.

possible to demonstrate that for a sPLND, the LNI rate was higher in a sentinel cohort than was expected from the European Association of Urology (EAU) guideline nomogram [20]. The validation of a corresponding sentinel-based nomogram is still pending. This study presents the first sPLND-based nomogram.

With an AUC of 82%, the sentinel nomogram presents a comparably accurate model for predicting LNI in patients with PCa. In various lPLND- or ePLND-based nomograms that use the same preoperative parameters as those of predictors of a LNI the reliabilities are 76–86% [3, 4, 6, 19]. Despite the extended approach in these studies, the proportion of LN+ patients was significantly lower than in that of the sentinel series (table 3).

There is no consensus on the risk level of a LNI that would be the ideal cutoff for choosing a PLND in patients with PCa. For instance, the National Comprehensive Cancer Network deems a cutoff acceptable if it leads to waiving about 50% of the PLNDs prior to RP at the expense of proof or removal of LNMs in 12% of the cas-

Table 3. The predictive accuracy of various models predicting LN invasion from PSA, clinical T-category and biopsy Gleason sum

Reference	n	PLND technique	Prevalence of LNI, %	AUC, %
Makarov et al. [3]	5,730	lPLND	5.0	82
Cagiannos et al. [19]	5,510	lPLND	3.7	76
Briganti et al. [4]	602	ePLND	11.0	76
Godoy et al. [6]	4,176	ePLND	5.2	86
Winter et al.	1,296	sPLND	17.8	82

lPLND = Limited pelvic lymph node dissection; ePLND = extended PLND; sPLND = sentinel guided PLND; LNI = lymph node involvement.

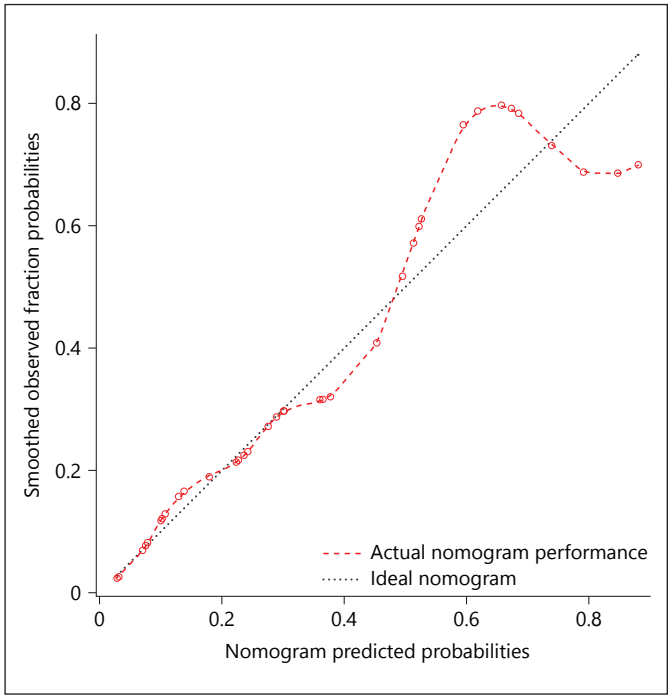

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Fig. 2. Nomogram calibration plot. The dotted line indicates the location of the ideal nomogram in which predicted and actual probabilities are identical. The broken line indicates actual nomogram performance.

es with LNI [21]. The EAU guidelines advise the usage of an LNI nomogram-calculated probability of 5% as a cutoff to perform ePLND, which would allow the avoidance of unnecessary PLND in about 65% of patients at the cost of missing 12% of patients with LNI [5, 22]. Table 4 presents a systematic analysis of a range of nomogram thresholds from 1 to 10% to help in the correct discrimination of patients with or without histologically confirmed LNI taking into account the sentinel model. The number of avoidable sPLNDs versus the number of potentially missed patients with LNI was quantified. Accordingly, a 7% threshold would be regarded as the most favorable cutoff. In our population of 1,296 patients, 406 patients (31.3%) were classified below this threshold. A voidance of sPLND in those 406 cases would have resulted in missing LNI in 7 patients or in 3% of all patients with histologically confirmed LNI. Therefore, approximately one-third of patients could be spared from sPLND. Considerable costs and patient discomfort could be saved.

In view of the low morbidity of sPLNDs in combination with the high sensitivity of proof of metastases [11, 13], we question the ability to define a cutoff. One should also note that patients with minimal LNI especially appear to benefit from removal of LN metastases [23]. Finally, the sPLND nomogram offers PCa patients the first-ever opportunity to make an informative decision about the probability of the sPLND detecting LN metastases, and thereby allows them to weigh the pros and cons of going for a sPLND for themselves.

On the other hand, a high risk of positive LNs may discourage urologists offering a RP. However, increasing evidence suggests that RP and PLND improve survival in LN+ PCa [24]. Besides being a staging procedure, PLND may be curative, or at least beneficial, in a subset of patients with limited LNI [23, 25]. A retrospective observational study has shown a dramatic improvement in cancer-specific survival and overall survival in favor of completed RP versus abandoned RP in patients who were found to be LN+ at the time of surgery [26]. These results suggest that RP may have a survival benefit and the discontinuation of RP in LN+ patients may not be justified [22] or that it is useful to perform RP in such cases. Furthermore, RP and PLND are important components of multimodal strategies for patients with LN+ PCa [22]. Due to these results, we consider the definition of an upper cutoff for PLND as not useful.

No consideration has yet been given to the percentage of positive cores as a predictor, as in other nomograms [3, 5, 6, 19, 27, 28]. In the Update Nomogram of Briganti et al. [5], the percentage of positive cores is the most accurate predictor of LNI. This was also confirmed by external validation studies [29, 30]. On the flip side, the sentinel nomogram reflects the reality of care. One expects better predictability on inclusion of the percentage of positive cores. Yet, the requirements, such as compliance with standards for biopsies and histopathological preparation, have not yet been established fully in most regions.

Table 4. Systematic analysis of thresholds used to discriminate between patients with and without histologically confirmed LN involvement in 1,296 patients treated with radical retropubic prostatectomy and radioisotope guided sentinel lymphadenectomy between 2005 and 2010, at a single institution

Nomogram-calculated probability of LNI (threshold, %)	Patients in whom sPLND is not recommended according to the threshold (below threshold)*	Patients below threshold without histological LNI*	Patients below threshold with histological LNI*	Patients in whom sPLND is recommended according to the threshold (above threshold)*	Patients above threshold without histological LNI*	Patients above threshold with histological LNI*	PPV	NPV
≥1	0 (0.0)	0 (0.0)	0 (0.0)	1,296 (100.0)	1,065 (100.0)	231 (100.0)	17.8	100.0
≥2	0 (0.0)	0 (0.0)	0 (0.0)	1,296 (100.0)	1,065 (100.0)	231 (100.0)	17.8	100.0
≥3	26 (2.0)	24 (2.3)	2 (0.9)	1,270 (98.0)	1,041 (97.8)	229 (99.1)	18.0	92.3
≥4	392 (30.3)	385 (36.2)	7 (3.0)	904 (69.8)	680 (63.9)	224 (97.0)	24.8	98.2
≥5	392 (30.3)	385 (36.2)	7 (3.0)	904 (69.8)	680 (63.9)	224 (97.0)	24.8	98.2
≥6	392 (30.3)	385 (36.2)	7 (3.0)	904 (69.8)	680 (63.9)	224 (97.0)	24.8	98.2
≥7	406 (31.3)	399 (37.5)	7 (3.0)	890 (68.7)	666 (62.5)	224 (97.0)	25.2	98.3
≥8	619 (47.8)	587 (55.1)	32 (13.9)	677 (52.2)	478 (44.9)	199 (86.2)	29.4	94.8
≥9	631 (48.7)	587 (55.1)	32 (13.9)	665 (51.3)	466 (43.8)	199 (86.2)	29.9	93.0
≥10	638 (49.2)	587 (55.1)	32 (13.9)	658 (50.8)	459 (43.1)	199 (86.2)	30.2	92.0

* Data are given as number (%). PPV = Positive predictive value; NPV = negative predictive value; LNI = lymph node involvement.

Another limitation of the study arises from the limitations inherent to unicentric analysis. However, the staging accuracy and the rates of LNI patients detected by sPLNDs in the monitored sample compare well with data from other sPLND-experienced centers [13]. Ideally, one should also externally validate the reliability of the sentinel nomogram [29–31].

No clear statement can be made about the sensitivity of a sPLND, since no additional ePLNDs were performed. However, this was not the aim of our research. In a meta-analysis [18], the pooled detection rate of sPLND was 93.8% with a pooled sensitivity rate of 94%. In the largest study [13] conducted, falsely detected negative results (non-SLNMs found in the absence of SLNMs) were found in <6% of the cases.

One fundamental problem with this technique is that when LNs are fully metastasized or when the lymph pathways blocked, the afferent lymph will be directed to other LNs/non-SLNs [32]. These nodes will not be positive on SLN imaging, resulting in false-negative findings. The false-negative rate was shown to correlate with the Gleason score [13]. Patients with a high-risk disease could thus have both positive SLNs and positive non-SLNs [33]. If the goal in such cases is to remove all pelvic LN metastases high-risk patients have the option of undergoing a combination of sPLND and ePLND. As such, the possibility of an ePLND overlooking a part of the LN metastases, possibly in the pre-sacral region, is overcome by being able to detect it through the sPLND. Reportedly, Joniau et al. [14] did not detect 13% of metastatic LNs by applying only an ePLND.

Conclusions

For radioisotope guided sPLNDs, one can demonstrate a high staging accuracy accompanied by even lower morbidity. We have developed the first nomogram to predict the probability of LNI in patients undergoing a sPLND at a RP. The first sentinel nomogram demonstrates a high degree of accuracy. This means that a nomogram can, for the first time, support clinicians and patients in making a key decision on whether to go for a sPLND. Compared with the ePLND-based nomograms, the higher rate of LN+ patients detected underpins the sensitivity of the sPLND. An external validation of the sentinel nomogram is still pending.

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