Original Article

Prostate-specific antigen density as a parameter for the prediction of positive lymph nodes at radical prostatectomy

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Abstract

Objective: The aim was to determine the prognostic ability of Partin's tables for a patient collective undergoing radical prostatectomy (RP) and to evaluate the association of prostate-specific antigen (PSA) density (PSAD) and postoperative lymph node status.

Methods: From 1999 to 2006, 393 consecutive patients underwent RP at our Urology department. Patients with Gleason scores <6, clinical stages >T2c or neoadjuvant hormonal therapy were excluded. Preoperative PSA, biopsy results, digital rectal examination, and prostate size at transrectal ultrasound were recorded. Risk stratification according to the Partin scoring system was performed. Postoperative results were compared with preoperative risk estimation. Univariate and multivariate statistical analysis about prediction of postoperative lymph node status was performed.

Results: Lymph node invasion (LNI) was found in 36 patients (9.16%). Kendall's rank correlation analysis revealed a significant association between the number of removed LN and LNI ($P = 0.016$). Patients with LNI had a significantly higher preoperative PSA and PSAD. Preoperative Gleason score was a significant predictor of LNI. The Partin tables' prediction of organ confined stages, extraprostatic extension, and seminal vesicle invasion was in line with the pathological findings in our collective. PSAD was a significant predictor of LNI in univariate and multivariate analysis.

Conclusion: The most widely used nomogram is of high value in therapy decision-making, although it remains an auxiliary means. Considering the performance of lymph node dissection, surgeons should be aware of the specifics of the applied nomogram. PSAD appears as a useful adjunctive parameter for preoperative prostate risk estimation and warrants further evaluation.

Key Words: Lymph node invasion, nomogram, prostate cancer, prostate-specific antigen density, radical prostatectomy

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Received: 12.11.2014, **Accepted:** 28.01.2015

INTRODUCTION

Optimal individual therapy planning for patients with prostate cancer demands a precise preoperative staging and risk estimation. A number of authors have designed nomograms based on a combination of preoperative variables such as age, race, prostate-specific antigen (PSA), %free PSA, digital rectal examination (DRE), prostate volume, ultrasound, International Prostate Symptom Score or family history to improve risk stratification.[1-3] The most widely used tool to predict pathologic stage at radical prostatectomy (RP) are the Partin tables, which allow to calculate the risk of extracapsular tumor extension (ECE), seminal vesical invasion (SVI) and lymph node invasion (LNI) based on the preoperative variables PSA, clinical stage and Gleason

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/0974-7796.152118

score.[1,4] However, there are known limitations of preoperative nomograms in the prediction of side-specific ECE,[5] SVI,[6] and LNI.[3] The last named variable is of special interest referring to the necessity and extent of lymph node dissection (LND). In retrospective series, PSA density (PSAD) has proven to be adjunctive to routine preoperative parameters in the prediction of positive surgical margins, ECE, SVI and biochemical recurrence failure.[7] Moreover, it has been reported to predict the risk of progression of men on active surveillance.[8] In a prospective analysis of 109 patients undergoing RP and limited LND, PSAD and PSAD of the transition zone (PSADT) failed to outperform PSA in preoperative stage prediction.[9] However, the fact that this study enrolled only five patients with positive lymph nodes must be regarded as a limitation towards the prediction of LNI.

To evaluate the predictive quality of the Partin tables for a patient collective undergoing RP and standard LND and to analyze the prognostic ability of PSAD regarding the prediction of LNI, we reviewed data of 393 consecutive patients.

METHODS

We retrospectively analyzed data of 393 consecutive patients who underwent RP at our Urology department from 1999 to 2006.

All patients were screened and underwent transrectal prostate biopsy in an out-patient setting. Before 2000 the majority of patients underwent sextant biopsy, later 10–12 core biopsies were preferentially performed. DRE status is referring to the 2002 TNM classification.[10] Prostate size was preoperatively determined by transrectal ultrasound, performed by urologists at our department.

All patients underwent open RP and a standard LND containing the lymphatic tissue of the ossa obturatoria and the external iliac vessels. Risk stratification according to the Partin scoring system (2007 version) was performed. Postoperative results were compared with the preoperative risk estimation. The postoperative histological analysis was undertaken by four pathologists of our Pathology department.

Univariate statistical analysis was performed using Chi-square test, Fisher's exact test, Wilcoxon-Mann–Whitney-test and Kendall's rank correlation. Multivariate testing was done by step-wise logistic regression analysis. Statistical significance was defined as $P < 0.05$.

RESULTS

We analyzed data of a total of 393 patients after RP. Average patient age at surgery was 64.4 years. Average PSA was 10.74 ng/ml (range: 0.6–114 ng/ml, 68% confidence interval [CI]: 5.1–14.8 ng/ml). Average prostate size was 37.17 cc (range: 14–150 cc, 68%CI: 22.0–51.0 cc). Average PSAD was calculated with 0.34 ng/ml/cc (range: 0.02–2.64, 68%CI: 0.13–0.51). Kendall's rank correlation revealed no significant association between prostate size and PSA in our collective ($P = 0.25$). Prostate size ($P < 0.001$) and elevated PSA level ($P = 0.0097$) were significantly associated with higher patient age, while PSAD ($P = 0.66$) was not. A preoperative Gleason score of 6 was found in 75.34%, Gleason scores ≥8 were rare with only 5.6%. Normal DRE (cT1c) was seen at 47.33% of patients, 12.21% had bilateral palpable carcinoma. Clinical stage ($P < 0.001$) and Gleason score ($P < 0.001$) were significantly associated with higher levels of PSA and elevated PSAD.

A sextant biopsy protocol was performed in 44% of cases. Patients with only a single positive biopsy represented 24.68% of cases. The average number of prostate biopsies was 8.07 (range: 4–16). Perineural invasion was identified in 7% of the biopsy specimen. We observed a significant association of positive biopsies and the number of biopsies in Kendall's rank correlation (tau = 0.11, $P < 0.001$). Elevated PSAD was significantly associated with the presence of more than one positive biopsy ($P = 0.0042$), while PSA alone was not ($P = 0.2$).

Table 1 summarizes the results of pathological staging and grading. In 56.74% of patients, organ confined prostate carcinoma was found.

Positive LN were found in 36 patients (9.16%), median number of removed LN was 10, with a range of 2–26. Univariate analysis revealed a significant association between the number of removed LN and LNI ($P = 0.016$). Patients with LNI had a significantly higher preoperative PSA ($P < 0.001$) and PSAD ($P = 0.0016$). Receiver operating characteristic (ROC) analysis revealed an optimal discrimination for LNI at a cut-off value of 11.9 ng/ml for PSA, and 0.35 ng/ml/cc for PSAD. Here, PSAD showed a sensitivity/specificity of 61%/69%.

Apart from PSA and PSAD, preoperative Gleason score was a significant predictor of LNI in univariate analysis, while clinical stage was not [Table 2].

Table 1: Postoperative pathological stage and Gleason score

T-stage	*n* (%)	Gleason score	*n* (%)
pT2a	20 (5.09)	≤6	193 (49.11)
pT2b	49 (12.47)	7=3+4	118 (30.03)
pT2c	154 (39.19)	7=4+3	38 (9.67)
pT3a	104 (26.46)	8	31 (7.89)
pT3b	29 (7.38)	9	13 (3.31)
pT4	37 (9.41)		

To evaluate the predictive quality of the Partin tables, we performed risk calculation for our patient collective. The results are shown in Table 3. Prediction of organ confined stages, ECE, and SVI is in line with the pathological findings in our patient collective. A difference is seen in lymph node positivity, where Partin tables predict a percentage of 2.29, while LNI was present in 9.16% of our patient collective (95%CI: 6.58–12.56%). In a multivariate model using Partin tables' risk estimation as a base model and integrating the number of positive cores and PSAD, the latter and Gleason score were significant predictors of LNI. The relations of clinical parameters and pathologic determinants in multivariate regression analysis are shown in Table 4.

DISCUSSION

In order to obviate the problem of preoperative prostate cancer risk estimation and to facilitate physicians and patient's decision-making and therapy planning, a number of prediction tools based on statistic models have been created.

Confirmative studies have been undertaken to prove the predictive capability of these nomograms, which showed their superiority in comparison to expert treatment recommendations.[11] The available decision aids consist in nomograms referring to postoperative prognosis, like e.g., the Kattan nomogramm,[12] artificial neuronal networks,[13] risk groupings or probability tables, e.g., the Partin tables[1] which allow a prediction of pathological stages of prostate cancer based on PSA, clinical stage and biopsy Gleason score.

As the Partin tables represent the most widely used risk estimation instrument, several authors have validated the nomogram and discussed its limitations. Graefen *et al*. established a nomogram to circumvent the limitation of side specific prediction of ECE, an important factor in the selection of patients for nerve sparing RP.[2]

In 2006, Briganti *et al*. published a nomogram based on data from patients undergoing extended pelvic LND. The authors reported a predictive accuracy of 76% for LNI.[3] Furthermore they established a tool to predict the presence of positive nonobturatoric lymph nodes for men with localized prostate cancer.[14] The observed accuracy was 80%. In our analysis, 9.16% of patients had LNI in the fossa obturatoria and along the external iliac vessels, correlative to a standard LND template. According to the Partin scoring system, the expected number was lower (2.29%), which is due to the less extensive resection of lymphatic tissue in their nomogram prediction collective at RP. However, the Partin tables sufficiently predicted local staging.

The most frequently used nomograms are mainly based on data from large, relatively homogeneous, data pools of high volume centers. These risk estimation instruments are generally accessible, patients and physicians are able to inform themselves and create a basis for therapy planning. Although most of these tools have passed sophisticated internal and external validation processes, there remains uncertainty about their uncritical general applicability for urological centers performing RP. This is due to the heterogeneity of patient collectives in terms of ethnicity or stage of disease, selection of surgical techniques and especially the choice of LND templates. As the presence of LNI is an important pathological finding at RP on the one hand, LND-associated morbidity on the other hand, should be reduced by identifying individuals where extended LND can be omitted. The Partin tables are based on data of men who underwent RP and limited LND.[1] Briganti *et al*. developed a nomogram for patients undergoing RP with an extended LND template, pointing out the possibilities to identify patients with virtually no risk of positive extraobturator lymph nodes and to avoid extended LND.[3]

In their 2012 update, the authors embedded the number of positive cores into their prediction tool and observed an even higher predictive accuracy of 87.6%.[14]

Table 2: Association of LNI with clinical stage, biopsy Gleason score, number of positive biopsies and perineural carcinosis

	n (%)		*P*
	pN+	pN0	
T-stage			
T1c	12 (6.45)	174 (93.55)	0.30 mp
T2a	18 (11.46)	139 (88.54)	
T2b	0	2 (100.00)	
T2c	6 (12.50)	42 (87.50)	
Gleason score			
≤6	18 (6.08)	278 (93.92)	0.0060c
7=3+4	9 (18.75)	39 (81.25)	
7=4+3	4 (14.81)	23 (85.19)	
8-9	5 (22.73)	17 (77.27)	
Positive biopsies			
One	5 (5.15)	92 (94.85)	0.096c
More than one	31 (10.47)	265 (89.53)	
Perineural invasion			
No	32 (8.74)	334 (91.26)	0.29fy
Yes	4 (14.81)	23 (85.19)	

fy: Fishers exact test, c: Chi-square test, mp: Exact test of metha and patel, LNI: Lymph node invasion

Table 3: Analysis of nomogram prediction

	Reference collective	68% CI	Partin tables prediction
	n (%)		*n* (%)
OC	218 (55.47)	50.40–60.43	244 (62.09)
EPE	122 (31.04)	26.55–35.91	121 (30.79)
SVI	17 (4.33)	2.62–6.97	18 (4.58)
LNI	36 (9.16)	6.58–12.56	9 (2.29)

OC: Organ confined, EPE: Extraprostatic extension, SVI: Seminal vesicle invasion, LNI: Lymph node invasion, CI: Confidence interval

Table 4: Results from stepwise logistic regression analysis for the prediction of organ confined stages and LNI

	Beta	Stratification (β)	OR	95% CI	*P*
Organ confined					
Base	1.047	0.440			
T-stage	−0.605	0.166	0.5462	0.3948-0.7557	<0.0005
+1 positive biopsies	−0.882	0.275	0.4097	0.2389-0.7026	0.001
PSA density	−1.491	0.388	0.2252	0.1053-0.4814	<0.0005
LNI					
Base	−2.229	0.444			
Gleason score	0.493	0.167	1.6369	1.1797-2.2714	0.003
PSA density	1.641	0.571	5.1626	1.6865-15.8037	0.004

LNI: Lymph node invasion, PSA: Prostate-specific antigen, OR: Odds ratio, CI: Confidence interval

One central point of discussion is the fact that the biopsy template in their study consisted in 13–24 biopsy cores, which is beyond the general recommendations of contemporary prostate cancer guidelines.[15] Heidenreich *et al*. showed that the number of positive cores remain predictive of LNI even with an average number of only 8.5 biopsy cores.[16] In our collective, we observed no statistically significant correlation between the number of positive cores and LNI, which is probably caused by the high percentage (44%) of patients who underwent sextant biopsy only and a comparably low average number of only 8.07 cores. This observation underlines the need of guideline conform prostate biopsy prior to the administration of a predictive nomogram integrating the number of positive cores.

In our study, we identified PSAD as a significant predictor of LNI. Interestingly, elevated PSAD was also significantly associated with finding more than one positive core at prostate biopsy. Apart from PSAD, total PSA, and Gleason score were predictive of LNI in univariate analysis. A multivariate model revealed PSAD and Gleason score to be significantly associated with LNI. Moreover, PSAD in our investigation was independent from age in contrast to PSA. We observed no correlation of prostate size and PSA ($P = 0.25$ from Kendall's rank correlation), which might be due to the elevated PSA excretion of prostate carcinoma cells in comparison to normal prostatic tissue.

These findings lead to the assumption that especially for patients with a low number of biopsy cores prior to RP, prediction nomograms may rather involve PSAD than the number of positive cores. In a prospective study, Radwan *et al*. analyzed features of 1327 patients undergoing RP. PSAD here was identified as a significant predictor of positive margins, ECE, SVI and biochemical failure.[17] Recently, another group demonstrated the utility of PSAD in predicting the risk of men progressing on active surveillance.[18] For prostate cancer screening, especially in patients with prior negative biopsies, several authors established nomograms and neuronal networks integrating PSAD and PSADT.[17-19] In our study, PSAD and Gleason score were stable predictors of LNI. In the analogy to Gleason score, the relation of prostate size and carcinoma associated fraction of PSA might be a possible determinant of systemic cancer progression. Giannarini *et al*. demonstrated that PSA, PSAD, and PSADT were significantly related to the percentage of positive biopsy cores, biopsy and surgical Gleason score, and pathological stage ($P < 0.001$), which were equally able to predict higher pathological stage, that is, SVI and lymph node metastases. However, the discrimination of intracapsular from extracapsular tumors was only possible by adding the number of positive cores in multivariate analysis. The authors conclude that the proportion of PSA from nonmalignant prostatic tissue affects the accuracy of PSAD negatively.[9] The study was limited by a low number of patients with positive lymph nodes.

In a prior retrospective series of 285 patients undergoing RP by Sfoungaristos and Perimenis it was shown that PSAD and Gleason score were the statistically significant predictors for positive surgical margins and ECD. In addition, PSAD and PSA were predictive for SVI and only PSAD for LNI.[20] In summary, PSAD appears as a potential additive factor for preoperative risk stratification that warrants further evaluation.

The problem of individual patient cohorts, center specific surgical approaches-especially in terms of LND-and application of risk stratification tools was described by Hinev *et al*. In their external validation study of six widely used nomograms (including the Johns Hopkins, MSKCC and Briganti tools) they found the most accurate prediction of LNI using the first published MSKCC nomogram.[21] Although the reference collective consisted in patients who underwent extended LND, the limited LND based MSKCC nomogram outperformed the Briganti nomogram. Nevertheless, in their ROC analysis all applied nomograms achieved high accuracies. Patient numbers, surgical expertise and open/laparoscopic or robotic approach, individual disease characteristics documented by merely high risk prostate cancer along with high proportions of patients with LNI within the validation cohort (21.5%) were limitations of their study.

Considering our analysis, identical limitations are present, especially in terms of patient numbers and selection. For the

clinical application of our findings, creation of a prediction instrument integrating PSAD was intended. However, patient numbers were insufficient to provide adequate information for all risk classes.

CONCLUSION

Currently, available nomograms are of high value regarding patients' information and therapy selection. Nevertheless, they remain to be considered an auxiliary means. Surgeons should be aware of the underlying specifics of the applied nomogram, especially referring to the risk estimation of positive lymph nodes. With regard to this, PSAD appears to be a useful and easy applicable adjunctive parameter as it showed the ability to improve LNI-prediction in patients undergoing standard LND.

Finally, beyond the validation and specification of the available and new prediction nomograms, the concept of extended LND itself needs to be evaluated on the base of prospective trials.

ACKNOWLEDGMENTS

We thank Dr. Imre Haubitz for her excellent support in planning and performing statistical analysis.

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How to cite this article: Yiakoumos T, Kalble T, Rausch S. Prostate-specific antigen density as a parameter for the prediction of positive lymph nodes at radical prostatectomy. Urol Ann 2015;7:433-7.

Source of Support: Steffen Rausch is supported by a Ferdinand Eisenberger grant of the German Society of Urology, **Conflict of Interest:** None.