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External Validation of Models Predicting the Probability of Lymph Node Involvement in Prostate Cancer Patients

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Abstract

Background: Multiple statistical models predicting lymph node involvement (LNI) in prostate cancer (PCa) exist to support clinical decision-making regarding extended pelvic lymph node dissection (ePLND).
Objective: To validate models predicting LNI in Dutch PCa patients.
Design, setting, and participants: Sixteen prediction models were validated using a patient cohort of 1001 men who underwent ePLND. Patient characteristics included serum prostate specific antigen (PSA), cT stage, primary and secondary Gleason scores, number of biopsy cores taken, and number of positive biopsy cores.
Outcome measurements and statistical analysis: Model performance was assessed using the area under the receiver operating characteristic curve (AUC). Calibration plots were used to visualize over- or underestimation by the models.
Results and limitations: LNI was identified in 276 patients (28%). Patients with LNI had higher PSA, higher primary Gleason pattern, higher Gleason score, higher number of nodes harvested, higher number of positive biopsy cores, and higher cT stage compared to patients without LNI. Predictions generated by the 2012 Briganti nomogram (AUC 0.76) and the Memorial Sloan Kettering Cancer Center (MSKCC) web calculator (AUC 0.75) were the most accurate. Calibration had a decisive role in selecting the most accurate models because of overlapping confidence intervals for the AUCs. Underestimation of LNI probability in patients had a predicted probability of <20%. The omission of model updating was a limitation of the study.
Conclusions: Models predicting LNI in PCa patients were externally validated in a Dutch patient cohort. The 2012 Briganti and MSKCC nomograms were identified as the most accurate prediction models available.
Patient summary: In this report we looked at how well models were able to predict the risk of prostate cancer spreading to the pelvic lymph nodes. We found that two models performed similarly in predicting the most accurate probabilities.

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1. Introduction

Prostate carcinoma (PCa) is the second most frequently diagnosed cancer among males worldwide, with the highest incidence rates in the USA (168.3/100 000 cases), followed by France (132.1/100 000 cases) and Australia (111.1/100 000 cases) [1]. The incidence rate in the Netherlands is 92.4/100 000 cases [2]. Incidence rates vary highly between countries because of an increase in the use of prostate-specific antigen (PSA) testing since the late 1980s [3]. The treatment options and prognosis for patients with PCa strongly depend on the presence of metastasis. Metastases are predominantly located in bone and the lymph nodes. The risk of lymph node involvement (LNI) depends on tumor aggressiveness and tumor volume, which is estimated using digital rectal examination (DRE) of the prostate (cT stage), serum PSA, and tissue patterns (ie, Gleason score) determined on prostate biopsies [4]. Most lymphogenic metastases occur in the pelvic lymph nodes, which are readily accessible for surgical removal [5].

An extended pelvic lymph node dissection (ePLND) is the most accurate method for detecting LNI. However, ePLND is invasive and has a risk of complications such as lymph leakage, lymph edema, and thromboembolic events [6,7], and is therefore only offered in selected cases such as patients scheduled for radical prostatectomy (RP) or before external beam radiotherapy with curative intent.

To limit the impact of the potential morbidity of ePLND for all patients with localized PCa, selection of candidates has been suggested by using cutoff values for the risk of LNI. The current European PCa guideline states that the indication for ePLND is based on a risk estimation of lymph node metastasis >5% according to a prediction model [4], whereas the Dutch guideline recommends a 10% threshold [8] and the American guideline a 2% threshold [9].

Several models have been developed to predict the probability of LNI in PCa patients. Predicting LNI is possible using, for example, artificial neural networks, logistic regression, classification and regression trees (CART), and simple linear formulas. Most of the prediction models have been updated to reflect recent clinical practice and new insights regarding ePLND.

Predictive models such as the nomograms reported by Briganti and the Memorial Sloan Kettering Cancer Center (MSKCC), Partin tables, and the Roach formula are recommended in several guidelines [4,8,9]. However, no external validation has yet been performed in the Netherlands. Therefore, we aimed to externally validate existing models predicting LNI in a Dutch PCa patient cohort in this study.

2. Patients and methods

Patient data were collected retrospectively in Canisius Wilhelmina hospital (CWZ; Nijmegen, The Netherlands) for patients who underwent ePLND and concomitant RP between October 2008 and December 2016, and in Ziekenhuisgroep Twente hospital (ZGT; Hengelo, The Netherlands) for patients who underwent ePLND (either with or without concomitant RP) between December 2014 and May 2017. In addition, data from ProZIB, an initiative to gain insight into clinical practice for PCa care in the Netherlands and to evaluate the quality of care, were used. Patients diagnosed with PCa between October 2015 and April 2016 were identified in the population-based Netherlands Cancer Registry (NCR). The ProZIB database contains information on patients who underwent ePLND either with or without concomitant RP. Patients treated in CWZ or ZGT were removed from the ProZIB database to avoid duplicates.

Patient pseudonimity was guaranteed. Patients were included in the validation cohort if they had undergone ePLND and had histopathological results available (PSA, cT-stage, Gleason score, biopsy cores, harvested lymph nodes, and positive lymph nodes). Patients with less than ten harvested lymph nodes were excluded to ensure that only data for adequate PLND procedures were included. The ePLND template applied involved removal of nodes overlying the external iliac vessels and internal iliac artery, and nodes located within the obturator fossa. As an option, areas of the common iliac artery and the presacral area can be included. Patients for whom data on biopsy cores taken were missing the corresponding positivity were included for validation, but could not be used for validation in certain models using biopsy core information as a predictor.

Every validated model used at least preoperative PSA (ng/ml), cT stage, and Gleason score as predictors. cT stage was defined according to the International Union Against Cancer TNM classification (edition 7.0) [10]. For Gleason scores, either the Gleason sum score was used as a predictor, or the primary and secondary patterns were used as separate predictors. Some models also used measures based on biopsy cores taken, such as percentage of positive cores or total number of positive and negative cores. One model used the total number of lymph nodes excised as a predictor. The CWZ, ZGT, and ProZIB databases contained information on 270, 109, and 622 patients, respectively. Patient data regarding biopsy cores was missing for 18, one, and 57 patients (total 76; 7.6%). After merging the three databases, a total of 1001 patients were eligible for validation of models without biopsy core predictors and 925 patients for models including biopsy core predictors.

Descriptive statistics were reported in terms of the frequency for categorical variables, the mean with standard deviation for normally distributed continuous variables, and the median with interquartile range for continuous variables that did not follow a normal distribution. Characteristics for patients with and without histologically proven LNI were reported separately. Significant differences ($p < 0.05$) between groups were assessed using Fisher's exact test for categorical variables, an independent sample t test for normally distributed continuous variables, and a Mann-Whitney U test for continuous variables that did not follow a normal distribution.

A total of 16 models were validated; methods for selection of the models are included in the Supplementary material. Model coefficients were derived and made available on www.evidencio.com for validation purposes. Evidencio is an online platform that allows researchers to translate prediction models into user-friendly online calculators, facilitating the application and (external) validation of prediction models. The area under the receiver operating characteristic (ROC) curve (AUC) was used to quantify model accuracy. Model over- and underestimation were assessed using calibration plots showing the agreement between predicted and observed LNI. Characteristics of the calibration are described in terms of calibration slope and intercept. The slope reflects how well a prediction fits the observed outcome over the range of predicted risks and is ideally equal to 1. The intercept (ie, calibration-in-the-large) is a measure of whether the average predicted risk corresponds to the average observed outcome, and is preferably equal to 0 [11]. Given the extent of the validation, only the four best-performing models are fully described here complete with ROC curves and calibration plots. These four models were assessed more thoroughly by looking at the calibration in a subset of patients with a predicted low

Table 1 – Baseline characteristics for the validation cohort with comparison of differences between the group with positive and negative lymph nodes

	Positive LNs	Negative LNs	Total	*p* value
Patients, *n* (%)	276 (27.6)	725 (72.4)	1001 (100)	
Treatment, *n* (%)				
Radical prostatectomy	169 (61.2)	621 (85.7)	790 (78.9)	
No radical prostatectomy	107 (38.8)	104 (14.3)	211 (21.1)	
Mean age, yr (SD)	66.5 (6.2)	66.5 (5.8)	66.5 (5.9)	0.95
Median PSA, ng/ml (IQR)	14.7 (7.6–28.0)	9.9 (6.7–16.4)	10.6 (7.0–19.6)	<0.0001
Mean total biopsy cores, *n* (SD)	10.0 (2.2)	10.2 (2.6)	10.2 (2.5)	0.18
Mean positive biopsy cores, *n* (SD)	7.2 (2.9)	5.2 (2.8)	5.7 (3.0)	<0.0001
Median harvested LNs, *n* (IQR)	17 (13–22)	15 (12–20)	16 (12–21)	0.0005
Clinical T stage, *n* (%)				
cT1	32 (11.6)	229 (31.6)	261 (26.1)	0.0005
cT2	128 (46.4)	335 (46.2)	463 (46.3)	
cT3	109 (39.5)	156 (21.5)	265 (26.5)	
cT4	7 (2.5)	5 (0.7)	12 (1.2)	
Primary Gleason pattern, *n* (%)				
≤3	92 (33.3)	380 (52.4)	472 (47.2)	<0.0001
≥4	184 (66.7)	345 (47.6)	529 (52.8)	
Secondary Gleason pattern, *n* (%)				
≤3	73 (26.4)	229 (31.6)	302 (30.2)	0.12
≥4	203 (73.6)	496 (68.4)	699 (69.8)	
Gleason score, *n* (%)				
≤6	11 (4.0)	103 (14.2)	114 (11.4)	0.0005
7 (3 + 4)	70 (25.4)	237 (32.7)	307 (30.7)	
7 (4 + 3)	56 (20.3)	117 (16.1)	173 (17.3)	
8	62 (22.5)	163 (22.5)	225 (22.5)	
9	68 (24.6)	95 (13.1)	163 (16.3)	
10	9 (3.3)	10 (1.4)	19 (1.9)	

LN = lymph node; IQR = interquartile range; PSA = prostate-specific antigen; SD = standard deviation.

probability of LNI (<20%), as the question of whether or not to perform ePLND is particularly relevant in these patients [4,8]. Validation was based on the intercepts and coefficients for the original models, that is, no model update was performed for the current validation cohort.

3. Results

Baseline characteristics for the validation cohort are listed in Table 1. There were significant differences between patients with and without LNI in PSA, positive biopsy cores, primary Gleason score, cT stage, and Gleason sum.

An overview of all the validated models, including predictors and accuracy estimates from the validation cohort, is presented in Table 2 [12–25]. The more recently updated models performed better than the corresponding original models. The model by Briganti et al published in 2012 performed better than the Briganti models from 2006–2007. The MSKCC model including biopsy core information as predictors performed better than the Godoy nomogram and the MSKCC model without biopsy core information. The most recent update of the Partin tables by Tosoian et al performed slightly better than the Makarov and the Eifler Partin tables. Of the three formulas reported by Roach, Nguyen, and Yu (Yale formula), the most recent (Yale formula) performed best.

ROC plots showing the AUC for the best-performing of each of the four model types are presented in Fig. 1. Fig. 2 shows calibration plots for these four models, including separate plots for a subgroup of patients with predicted risk of <20%.

The Briganti and MSKCC models showed comparable calibration performance: both underestimated the risk of LNI among patients with an observed LNI probability of <25–40% and overestimated the risk of LNI among patients with a higher observed probability of LNI. The Tosoian and Yale models underestimated of the risk of LNI. All four models underestimated the predicted probabilities among patients with an observed probability of <20%.

4. Discussion

The purpose of this study was to validate available models for predicting LNI in Dutch PCa patients. Three databases were combined to validate 16 models predicting LNI. The most recent updates to the prediction models achieved higher AUCs than the older versions. The most recent update of the Briganti model showed the highest AUC (0.76) and the MSKCC nomogram including biopsy cores achieved a comparable AUC (0.75). However, the 95% confidence intervals for several validated models overlap with the confidence intervals for the models by Briganti and the MSKCC. Thus, it remains uncertain if either of these two models truly predicts LNI better than the other validated models.

The validation cohort included data from the ProZIB initiative (62%). The ProZIB data contained patient information collected from all Dutch hospitals treating PCa patients. Therefore, the outcome of this study is likely to be representative for the Dutch population. In the period for which data were collected, it was already known that PLND could be omitted for PCa patients with a low risk of LNI

Table 2 – Results for the validated models and their updates, if applicable

Model and updates	Predictors	AUC (95% CI)
Briganti nomogram		
2006 [12]	PSA, cT stage, Gleason sum	0.69 (0.65–0.72)
2006 [13]	PSA, cT stage, Gleason sum, # LNs removed	0.70 (0.66–0.73)
2007 (% BCs) [14]	PSA, cT stage, Gleason sum, % positive BCs	0.72 (0.69–0.76)
2007 (# BCs) [14]	PSA, cT stage, Gleason sum, # positive BCs	0.71 (0.67–0.74)
2012 [15]	PSA, cT stage, primary Gleason, secondary Gleason, % positive BCs	0.76 (0.73–0.79)
Formulas		
Roach formula [16]	PSA, Gleason sum	0.66 (0.63–0.70)
Nguyen formula [17]	PSA, cT stage, Gleason sum	0.68 (0.64–0.71)
Yale formula [18]	PSA, cT stage, Gleason sum	0.70 (0.66–0.74)
Partin tables		
Makarov [19]	PSA, cT stage, Gleason sum	0.69 (0.66–0.73)
Eifler [20]	PSA, cT stage, Gleason sum	0.69 (0.66–0.73)
Tosoian [21]	PSA, cT stage, Gleason sum	0.70 (0.67–0.74)
MSKCC models		
Godoy [22]	PSA, cT stage, Gleason sum	0.70 (0.66–0.74)
Web calculator (excl. BCs) [23]	PSA, cT stage, primary Gleason, secondary Gleason	0.71 (0.67–0.74)
Web calculator (incl. BCs) [23]	PSA, cT stage, primary Gleason, secondary Gleason, # positive BCs, # negative BCs	0.75 (0.72–0.78)
Yonsei nomogram [24]	PSA, cT stage, Gleason sum	0.69 (0.65–0.72)
Winter [25]	PSA, cT stage, Gleason sum	0.69 (0.66–0.73)

AUC = area under the receiver operating characteristic curve; BCs = biopsy cores; CI = confidence interval; # = number of; LNs = lymph nodes; MSKCC = Memorial Sloan Kettering Cancer Center; PSA = prostate-specific antigen.

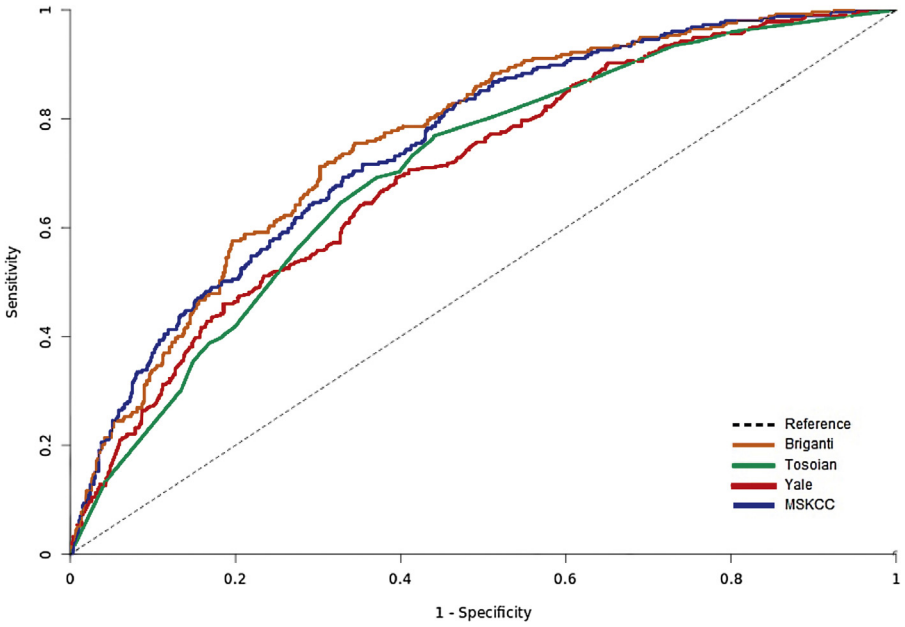

Fig. 1 – Receiving operator characteristic curve for the four best-performing prediction models. MSKCC = Memorial Sloan Kettering Cancer Center.

[8]. Therefore, one might assume that quite a large proportion of, predominantly low-risk, patients did not undergo PLND and thus were not included for validation. This may be reflected by the fact that LNI was present in 27.6% of our patients, while this was 8% for the Briganti 2012 nomogram. The Dutch guideline advises omission of PLND for PCa patients with a calculated LNI probability of <10%. However, it is known that several Dutch hospitals (including CWZ) follow the European guideline, which recommends a 5% threshold for PLND. ZGT applied a 10% threshold for patients undergoing RP, and a 15% threshold for patients undergoing radiation therapy. Of the 925 patients with a risk of <10% according to the Briganti 2012 nomogram, 338 (33.7%) still underwent PLND. If the Dutch guideline had been followed in all cases, PLND would have been incorrectly omitted in 27 patients with positive LNI (false negatives). In addition, the morbidity and costs associated with PLND could have been avoided for 311 patients with negative LNI for whom PLND could be safely omitted (true negatives). Among patients with a predicted probability of <5%, 189 (18.9%) still received PLND, of whom 12 patients had LNI and 177 patients did not. It should be noted that treating physicians might have had alternative reasons that led to a well-considered decision to

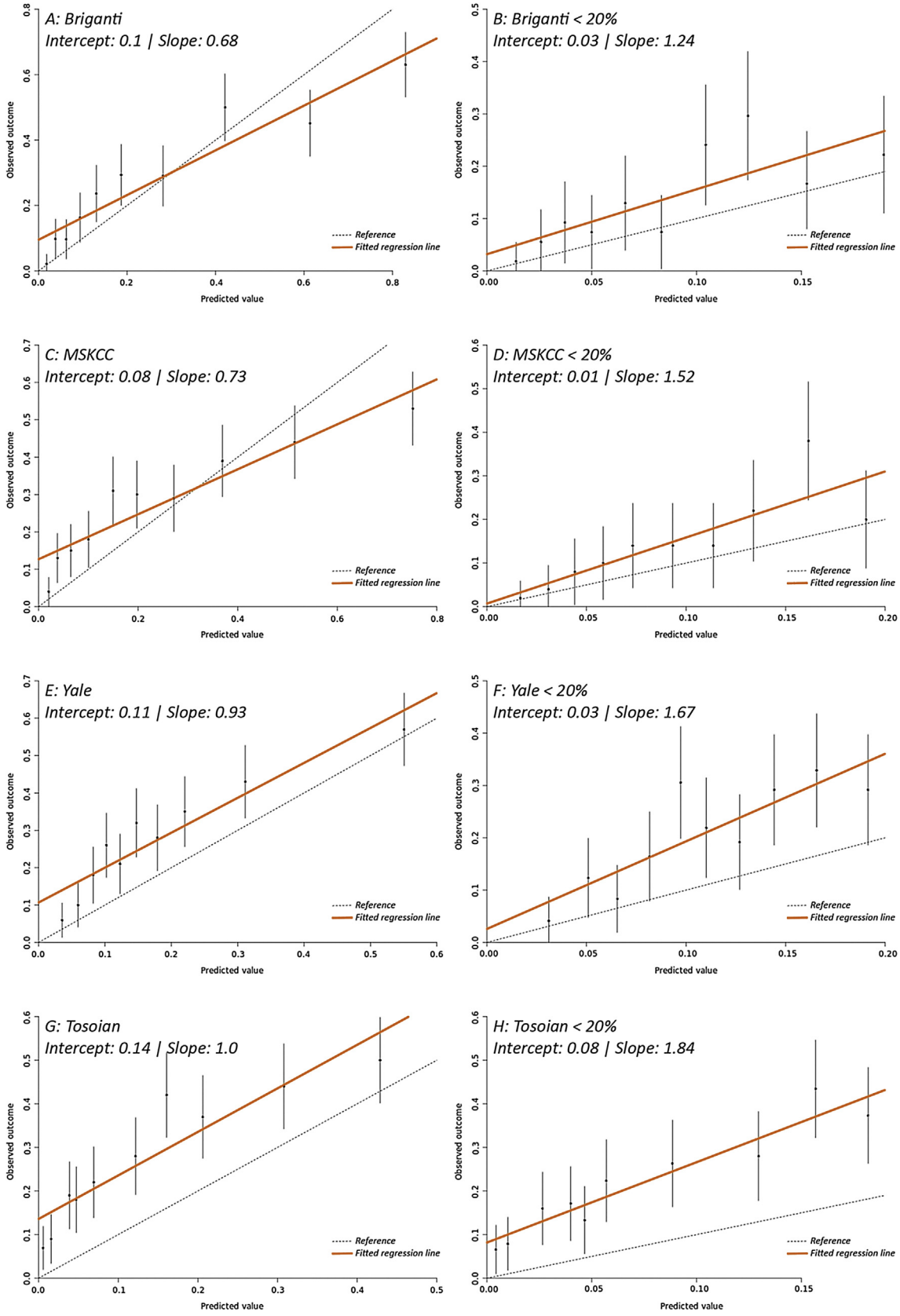

Fig. 2 – Calibration plots for the four best-performing prediction models. (A) Briganti nomogram for the full cohort (intercept 0.1 and slope 0.68). (B) Briganti nomogram for patients with a predicted risk of <20% (intercept 0.03 and slope 1.24). (C) Memorial Sloan Kettering Cancer Center (MSKCC) calculator for the full cohort (intercept 0.08 and slope 0.73). (D) MSKCC calculator for patients with a predicted risk of <20% (intercept 0.01 and slope 1.52). (E) Yale formula for the full cohort (intercept 0.11 and slope 0.93). (F) Yale formula for patients with a predicted risk of <20% (intercept 0.03 and slope 1.67). (G) Tosoian model for the full cohort (intercept 0.14 and slope 1.0). (H) Tosoian model for patients with a predicted risk of <20% (intercept 0.08 and slope 1.84).

perform PLND in patients who were not recommended to receive the procedure. However, since the data were collected retrospectively, it cannot be determined what the basis of such as decision was.

To the best of our knowledge, this is the first validation study on LNI in PCa patients in the Netherlands. However, several other external validations have been performed. An overview of previous validation studies is provided in Supplementary Table 1.

Updating the validated models might have improved the outcomes of our validation. For a proper update, all of the validated models should be updated and then validated again. Although this could be of interest for future research, it was considered not feasible for all the validated models and fell outside the scope of the current study.

Notably, the AUCs in our validations were lower than the AUCs reported in previous external validations. The highest AUC in our validation was 0.76 for the Briganti nomogram. Differences found between the current validation and other validation studies could be caused by several factors. Most external validation cohorts consist of patients receiving PLND with concomitant RP. The current cohort contains both patients undergoing RP with PLND as well as PLND alone. Robot-assisted surgery has been increasingly used to perform RP and PLND in recent years. As our cohort included patients from 2008 to 2016, methods used for lymph node dissection may have been different (robot-assisted, laparoscopic, or open), but information on the surgical method used was not available in the databases. Moreover, the locations of dissected lymph nodes were not registered, making it unclear if there may have been differences in the ePLND templates applied. It is also possible that there were differences in the methods used to take biopsy cores. The article by Briganti et al does not state whether a certain method of performing biopsies influences risk predictions, nor is this indicated for the MSKCC web calculator. For instance, the number of cores and percentage of positive cores can differ if biopsies are guided by magnetic resonance imaging (MRI). Another explanation for the underestimation could be that physicians may have based the choice to perform PLND on other factors than the predicted risk alone, such as enlarged lymph nodes at staging MRI or positron emission tomography/computed tomography. Overestimation of the predictions was often found in higher risk groups and may partly be explained by the inclusion of patients with high serum PSA (>50 ng/ml), who were often excluded in the development cohorts [18]. The combination of underestimation for lower predicted risks and overestimation for higher predicted risks may also explain why our AUC values were notably lower than in most external validation studies.

There has been no consensus on the suggested thresholds described by the different developers of the models, validations, and international guidelines. It seems that the thresholds advised were based on expert opinions on clinically acceptable sensitivity and specificity without a thorough quantitative analysis of the impact of using different risk threshold values [26]. Therefore, the outcomes of the current validation were used as an input for a new study applying cost effectiveness analysis to identify the optimal risk threshold for performing or omitting PLND.

Recently, Gandaglia et al [27] published a novel model for predicting LNI risk. This model uses the number of biopsy cores containing high-grade PCa and the number containing lower-grade PCa. These data were not available for the current cohort and therefore this model could not be validated. The new model seems to be an update of the 2012 Briganti nomogram, which showed the best performance in this validation. Collecting data on the number of biopsy cores with specific primary and secondary Gleason scores may be useful for future validations, and potentially more accurate predictions regarding LNI.

5. Conclusions

Among the 16 validated models, the Briganti nomogram from 2012 showed the best performance, with an AUC of 0.76. The MSKCC nomogram showed comparable results, with an AUC of 0.75. The confidence intervals for the AUC of these models overlap with AUCs of multiple other validated models; however, the Briganti and MSKCC nomograms showed adequate calibration. On the basis of these results, we advise use of either the Briganti or the MSKCC nomogram to predict the risk of LNI in PCa patients.

Author contributions: Tom A. Hueting had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Koffijberg, van der Palen, Pleijhuis, Korthorst, Cornel.
Acquisition of data: Hueting, Somford, Jansen, Cornel.
Analysis and interpretation of data: Hueting, Cornel, Somford, Jansen, van Basten, Pleijhuis, Korthorst, van der Palen, Koffijberg.
Drafting of the manuscript: Hueting.
Critical revision of the manuscript for important intellectual content: Cornel, Somford, Jansen, van Basten, Pleijhuis, Korthorst, van der Palen, Koffijberg.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.euo.2018.04.016.

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