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Original Article

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Indications for and complications of pelvic lymph node dissection in prostate cancer: accuracy of available nomograms for the prediction of lymph node invasion

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Objectives

To externally validate the currently available nomograms for predicting lymph node invasion (LNI) in patients with prostate cancer (PCa) and to assess the potential risk of complications of extended pelvic lymph node dissection (ePLND) when using the recommended threshold.

Methods

A total of 14 921 patients, who underwent radical prostatectomy with ePLND at eight European tertiary referral centres, were retrospectively identified. After exclusion of patients with incomplete biopsy or pathological data, 12 009 were included. Of these, 609 had undergone multiparametic magnetic resonance imaging-targeted biopsies. Among ePLND-related complications we included lymphocele, lymphoedema, haemorrhage, infection and sepsis. The performances of the Memorial Sloan Kettering Cancer Centre (MSKCC), Briganti 2012, Briganti 2017, Briganti 2019, Partin 2016 and Yale models were evaluated using receiver-operating characteristic curve analysis (area under the curve [AUC]), calibration plots, and decision-curve analysis.

Results

Overall, 1158 patients (9.6%) had LNI, with a mean of 17.7 and 3.2 resected and positive nodes, respectively. No significant differences in AUCs were observed between the MSKCC (0.79), Briganti 2012 (0.79), Partin 2016 (0.78), Yale (0.80), Briganti 2017 (0.81) and Briganti 2019 (0.76) models. A direct comparison of older models showed that better discrimination was achieved with the MSKCC and Briganti 2012 nomograms. A tendency for underestimation was seen for all the older models, whereas the Briganti 2017 and 2019 nomograms tended to overestimate LNI risk. Decision-curve analysis showed a net benefit for all models, with a lower net benefit for the Partin 2016 and Briganti 2019 models. ePLND-related complications were experienced by 1027 patients (8.9%), and 12.6% of patients with pN1 disease.

Conclusions

The currently available nomograms have similar performances and limitations in the prediction of LNI. Miscalibration was present, however, for all nomograms showing a net benefit. In patients with only systematic biopsy, the MSKCC and Briganti 2012 nomograms were superior in the prediction of LNI.

Keywords

prostate cancer, pelvic lymph node dissection, lymphadenectomy, nomogram, #PCSM, #ProstateCancer, #urooncc

Introduction

Extended pelvic lymph node dissection (ePLND) is the most accurate method for the detection of lymph node invasion (LNI) in prostate cancer (PCa) [1]. Its prognostic role is undeniable, helping to select patients that will benefit from adjuvant treatments [2], whereas its therapeutic value remains controversial [3]. A recent multi-institutional study found no difference in oncological outcomes for patients with high- or intermediate-risk PCa with or without ePLND performed at radical prostatectomy [4].

To date, ePLND is recommended in patients with intermediate- or high-risk PCa, after evaluation of the risk of LNI via available nomograms. Several models are currently available, such as the Briganti and Memorial Sloan Kettering Cancer Center (MSKCC) nomograms, the Partin 2016 tables, and the Yale formula [5–10]. These tools, mainly based on clinical variables, showed good predictive accuracy on internal and external validation, but were still not optimal [11]. According to the European Association of Urology guidelines, a risk of nodal metastases of >5% is an indication to perform ePLND [1]. More recently, the novel Briganti 2019 nomogram was published that uses Gleason score (International Society of Urological Pathology [ISUP] grade) on targeted biopsy and clinical staging by multiparametric MRI (mpMRI). Adoption of this model in patients undergoing mpMRI-targeted and concomitant systematic prostate biopsy using a 7% threshold would avoid approximately 60% of ePLND procedures at the cost of missing only 1.6% of LNI cases [8].

Despite the use of these preoperative tools, several perplexities remain about the indication for ePLND, considering that it is a time-consuming procedure that can lead to complications such as lymphocele and lymphoedema, which are often unpredictable and sometimes difficult to manage. The available nomograms were developed in retrospective cohorts and are far from being infallible. Furthermore, there are no clear recommendations supporting the adoption of one nomogram over another. The routine adoption of new imaging techniques, such as prostate-specific membrane antigen (PSMA) positron-emission tomography (PET)/CT, will probably improve the accuracy of PCa staging [12], but to date we have relied on nomograms to decide whether to perform ePLND or not.

The aims of the present study were to validate externally the MSKCC and Briganti nomograms, the Partin 2016 tables and the Yale formula in a large multicentre European cohort of patients undergoing PLND and to evaluate the potential risk of complications when using the recommended threshold.

Materials and Methods

After institutional review board approval, 14 921 patients who underwent radical prostatectomy with ePLND at eight European tertiary referral centres (Belgium, France, Germany, Italy) from 1992 to 2019 were retrospectively identified. The template for ePLND included the obturator, internal iliac, and external iliac lymph nodes up to the ureteric crossing. All specimens were evaluated by dedicated uropathologists. After exclusion of patients with incomplete biopsy or pathological data, 12 009 were available for analysis. Of these, 609 had undergone mpMRI-targeted and systematic biopsies, targeting lesions with a Prostate Imaging-Reporting and Data System (PI-RADS) score ≥3 [13]. No patients received neoadjuvant hormonal therapy. Examined variables included: PSA, clinical stage according to DRE, mpMRI features (when performed), Gleason score, ISUP grade (on biopsy and pathological specimens), number of positive and negative biopsies, pathological staging, total number of lymph nodes resected, number of positive nodes, and ePLND-related complications. Among ePLND-related complications we included lymphocele, lymphoedema, haemorrhage, infection and sepsis.

Statistical Analysis

The Mann–Whitney test was used to compare the distribution of continuous variables, while Fisher's exact and Pearson chi-squared tests were used to compare proportions of categorical variables. External validation of the performances of the MSKCC [5] and Briganti nomograms [6–8], Partin 2016 tables [9] and Yale formula [10] was conducted according to the TRIPOD recommendations [14]. Previously published regression coefficients were used to calculate the individual risk of LNI [15]. The performance of the models was evaluated in terms of discrimination and calibration. Discrimination was quantified using receiver-operating characteristic curve analysis (area under the curve [AUC]). The extent of over- and underestimation associated with the model was graphically described using calibration plots. Decision-curve analysis was used to evaluate the net benefits of the model according to the threshold. A two-sided P value < 0.05 was taken to indicate statistical significance. Statistical analyses were performed with SPSS version 26.0 (IBM Corp, Armonk, NY, USA) and STATA 14.1 (StataCorp, College Station, TX, USA).

Results

Baseline Characteristics

The characteristics of the main patient cohort are shown in Table 1. Overall, 1158 patients (9.6%) had LNI on final pathological examination, with a mean of 17.7 and 3.2 resected and positive nodes, respectively. Based on the availability of necessary variables and MRI data, the Partin 2016, Briganti 2017 and Briganti 2019 nomograms were tested in subcohorts of 11 626, 585 and 609 patients, respectively.

Table 1 Baseline characteristics of the main cohort.

	Overall	pN0	pN1	*P*
Patients, *n* (%)	12 009	10 851 (90.4)	1158 (9.6)	–
Mean (SD) age at surgery, years	64.4 (6.8)	64.3 (6.8)	65.4 (6.9)	<0.001
ASA score, *n* (%)				
1	2157 (22.7)	1988 (23.1)	169 (18.6)	0.002
2	6199 (65.4)	5589 (65.2)	610 (67.1)	
3	1117 (11.8)	990 (11.5)	127 (14.0)	
4	12 (0.1)	9 (0.1)	3 (0.3)	
Missing	2943			
Mean (SD) preoperative PSA, ng/mL	11.4 (14.0)	10.2 (9.9)	22.3 (31.5)	<0.001
Clinical stage, *n* (%)				
cT1	6739 (56.1)	6439 (59.3)	300 (25.9)	<0.001
cT2	4919 (41.0)	4207 (38.8)	712 (61.5)	
cT3	327 (2.7)	187 (1.7)	140 (12.1)	
cT4	24 (0.2)	18 (0.2)	6 (0.5)	
MRI-targeted biopsy	609	537 (88.2)	72 (11.8)	–
PI-RADS score*, *n* (%)				
3	48 (7.9)	45 (8.4)	3 (4.2)	<0.001
4	317 (52.0)	294 (54.7)	23 (31.9)	
5	244 (40.1)	198 (36.9)	46 (63.9)	
Mean (SD) maximum index lesion diameter on mpMRI†, mm	14.6 (6.9)	13.7 (6.3)	20.7 (8.8)	<0.001
Biopsy grade group, *n* (%)				
1	4295 (35.8)	4208 (38.8)	87 (7.5)	<0.001
2	3676 (30.6)	3412 (31.4)	264 (22.8)	
3	2159 (18.0)	1860 (17.1)	299 (25.8)	
4	1240 (10.3)	986 (9.1)	254 (21.9)	
5	639 (5.3)	385 (3.5)	254 (21.9)	
Mean (SD)cores taken, *n*	12.4 (4.9)	12.4 (4.5)	12.4 (4.9)	0.98
Mean (SD) positive cores taken, *n*	4.7 (3.4)	4.5 (3.2)	7.6 (4.0)	<0.001
Pathological stage, *n* (%)				
pT2	6265 (58.3)	6177 (63.4)	88 (8.7)	<0.001
pT3	4254 (39.6)	3462 (35.5)	792 (78.7)	
pT4	229 (2.1)	103 (1.1)	126 (12.5)	
Missing	1680			
Pathological grade group, *n* (%)				
1	2797 (24.5)	2790 (27.0)	7 (0.6)	<0.001
2	3609 (31.6)	3504 (34.0)	105 (9.6)	
3	2951 (25.9)	2643 (25.6)	308 (28.2)	
4	725 (6.4)	604 (5.9)	121 (11.1)	
5	1327 (11.6)	774 (7.5)	553 (50.5)	
Missing				
Mean (SD) lymph nodes removed, *n*	13.2 (6.9)	12.7 (6.5)	17.7 (8.4)	<0.001
Mean (SD) lymph nodes positive, *n*	–	–	3.2 (6.2)	<0.001

*ASA, American Society of Anaesthesiologists; mpMRI, multiparametric MRI; PI-RADS, Prostate Imaging-Reporting and Data System. *On 609 patients who underwent targeted biopsy. †On 1578 patients who were staged with mpMRI.*

Significant differences were observed between pN0 and pN1 patients concerning age, American Society of Anaesthesiologists score, preoperative PSA, cT, PI-RADS score, maximum index lesion diameter, biopsy grade group, positive cores, pathological stage, pathological grade group, and number of lymph nodes removed.

External Validations

The AUCs for the MSKCC nomogram, the Briganti 2012 nomogram, the Partin 2016 tables, the Yale formula, the Briganti 2017 nomogram and the Briganti 2019 nomogram were 0.83, 0.83, 0.79, 0.81, 0.80 and 0.76, respectively. When comparing directly these models in a subcohort of 444 patients with available data to calculate all models, the AUCs were 0.79, 0.79, 0.78, 0.80, 0.81 and 0.76, respectively, with no significant differences ($P = 0.42$). A direct comparison of the MSKCC nomogram, the Briganti 2012 nomogram, the Partin 2016 tables and the Yale formula was performed in another subcohort of 11 626 patients, resulting in AUCs of 0.82, 0.82, 0.79 and 0.80, respectively, with the MSKCC and Briganti 2012 models performing better than the Yale and Partin 2016 models ($P = 0.001$).

Graphical representation of calibration plots is provided in Fig. 1: the MSKCC and Briganti 2012 nomograms tended to underestimate LNI risk among patients with a probability <20% while overestimating the risk among patients with higher probability. Both the Partin 2016 tables and the Yale formula showed a general tendency to underestimation. By

Fig. 1 Graphical representation of calibration plots. CITL, calibration in the large; E, expected; MSKCC, Memorial Sloan Kettering Cancer Centre; O, observed.

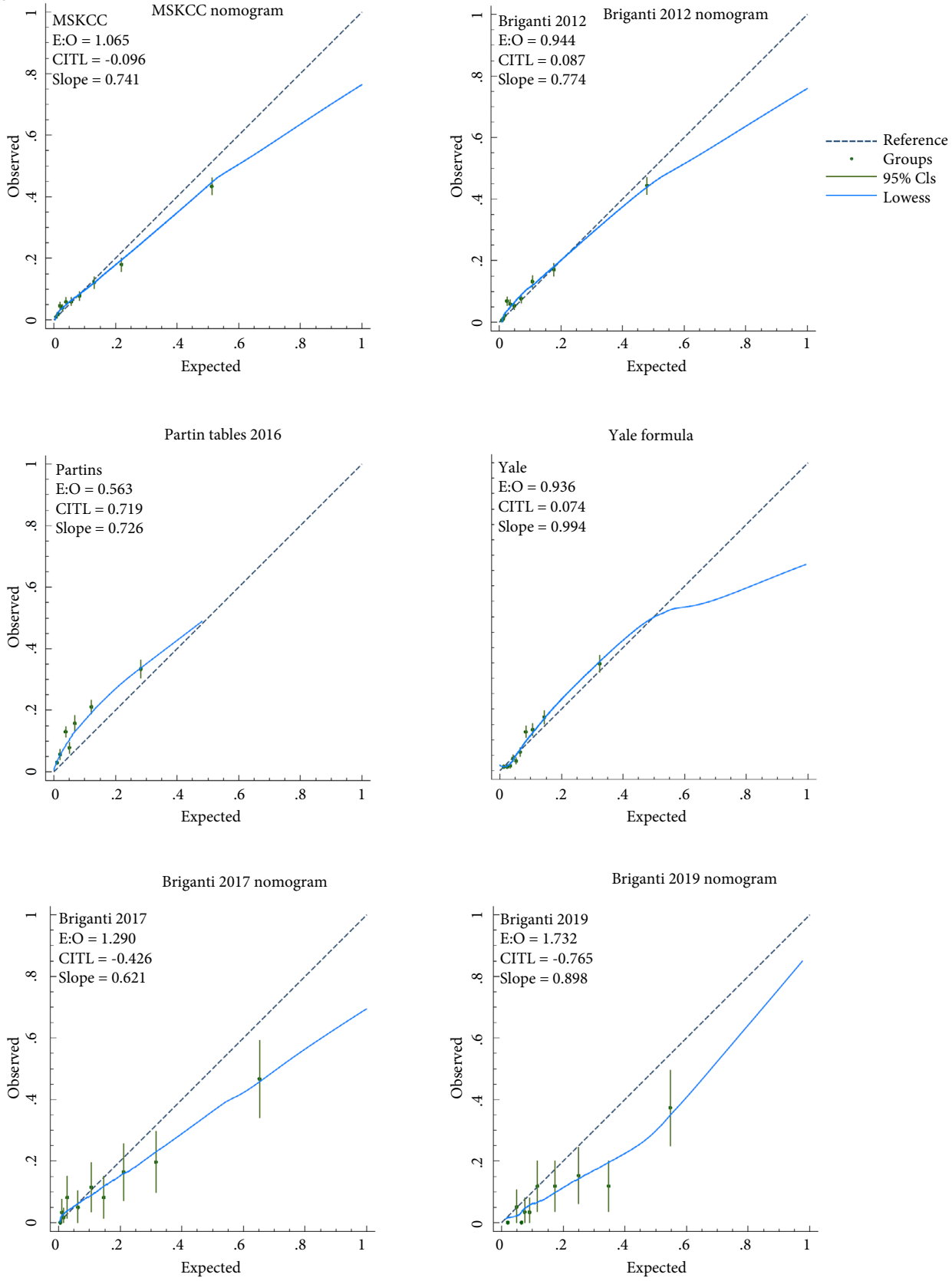
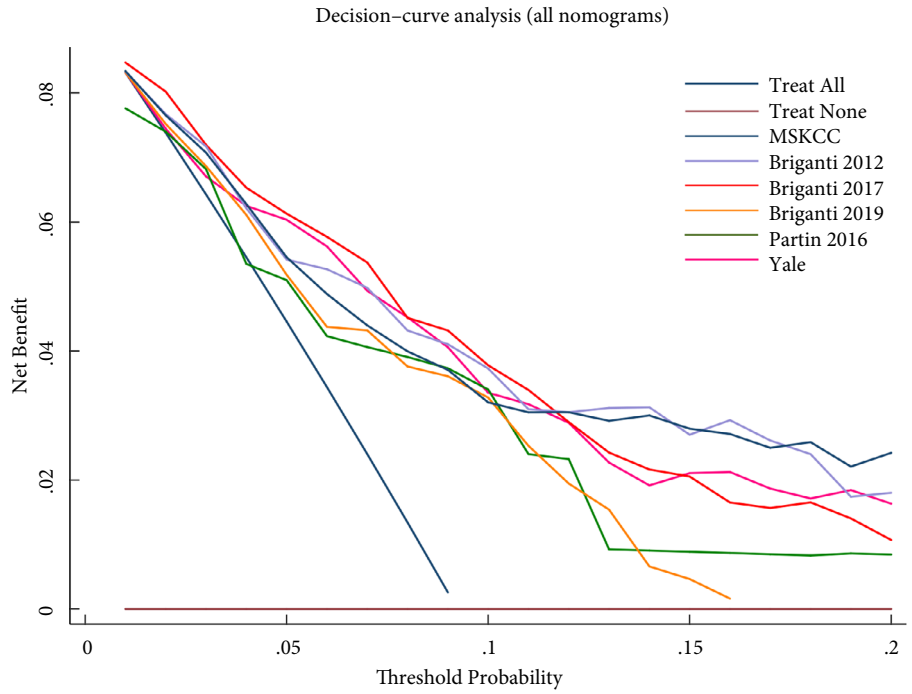
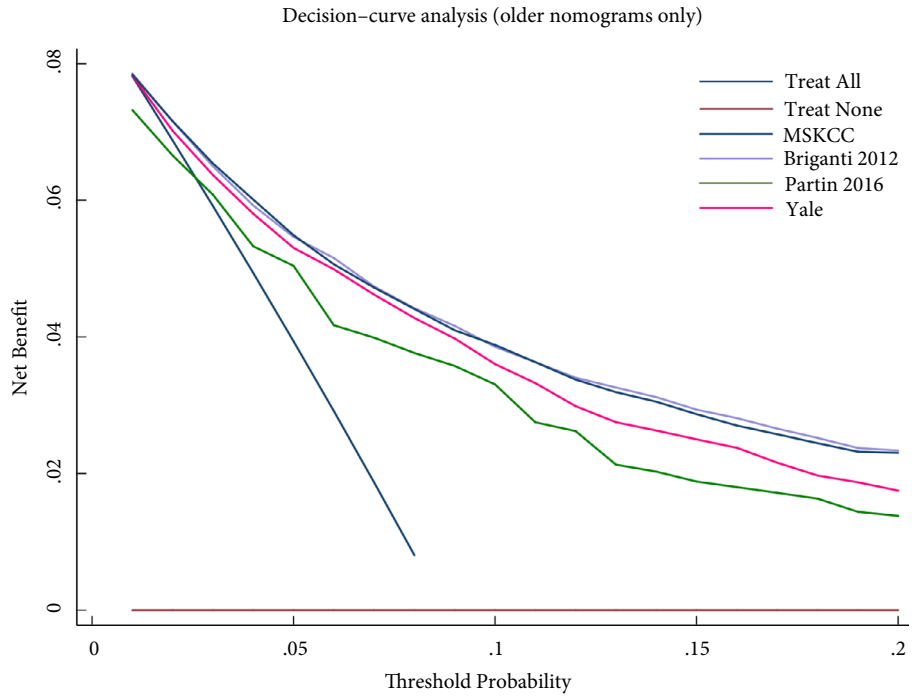


Fig. 2 Decision-curve analysis. MSKCC, Memorial Sloan Kettering Cancer Centre.





contrast, the Briganti 2017 and Briganti 2019 nomograms showed a general tendency to overestimation. Figure S1 shows calibration plots considering only patients with LNI risk below 20% (considered as the range of interest in clinical practice).

According to decision-curve analysis, all models showed a clinical net benefit, with a lower net benefit for the Partin 2016 tables and Briganti 2019 nomogram considering threshold probabilities below 20% (Fig. 2).

Pelvic Lymph Node Disection-Related Complications

Table 2 shows the proportion of patients with and without LNI according to the threshold adopted for each model, and the incidence of PLND-related complications in each subgroup of patients. Complications were experienced by 6.4–11.3% of patients without LNI despite a score above the threshold. Overall, ePLND-related complications were experienced by 1027 patients (8.9%), and 12.6% of pN1 patients. The detailed list of all reported complications is shown in Table 3.

Discussion

The choice of whether to perform ePLND relies on nomograms that estimate the risk of finding LNI. A 5% threshold is generally adopted as an indication to perform ePLND. Recently, a new threshold of 7% was proposed for the Briganti 2019 nomogram that includes mpMRI and mpMRI-targeted biopsy data. Theoretically, a perfect nomogram should have: good accuracy, indicated by a high AUC, discriminating between those with and without disease; good calibration, indicating the agreement between observed outcomes and predictions, to avoid over/underestimation of the actual risk; and good net benefit, weighting the benefit of correct indications over the harms of unnecessary procedures [16]. As of today, however, no comparative data exist to strongly support the routine use of one nomogram over the others. Hueting et al. [11] performed an external validation of 16 predictive models in 1001 Dutch patients with PCa, excluding the Briganti 2017 and 2019 nomograms. The results of that study showed that the Briganti 2012 (AUC 0.76) and MSKCC nomograms (AUC 0.75) were the most accurate, with similar miscalibration with tendency to underestimation. No direct comparison between nomograms, however, was performed.

The present study aimed to validate externally the most commonly used predictive models for LNI in a multicentre, European cohort of patients undergoing ePLND. Strengths of the study include: the large sample size; the heterogeneity of patients, with patients coming from different countries and undergoing surgery in different years being ideal for testing predictive models; the different biopsy techniques adopted, with the majority of patients undergoing only systematic biopsies while only the most recent patients received MRI-targeted biopsies; and the possibility of comparison among different nomograms, taking into account accuracy, calibration and net benefit.

Our results were surprising: the MSKCC and Briganti 2012 nomograms outperformed the Briganti 2019 nomogram, suggesting that mpMRI did not add relevant information with which to predict LNI. In other words, if mpMRI is not

Table 2 Cross-tabulation of patients with lymph node invasion and pelvic lymph node dissection-related complications, stratified according to model's threshold.

Nomogram	Patients, *n*	AUC (95% CI)	Patients below the threshold				Patients above the threshold			
			Without LNI		With LNI		Without LNI		With LNI	
			n (%)	Complications*, *n* (%)	*n* (%)	Complications* (%)	*n* (%)	Complications*, *n* (%)	*n* (%)	Complications*, *n* (%)
MSKCC, threshold 5%	12 009	0.83 (0.81–0.84)	6088 (50.7)	487 (7.9)	140 (0.1)	9 (6.4)	4763 (39.7)	403 (8.4)	1018 (8.5)	128 (12.6)
Briganti 2012, threshold 5%	12 009	0.83 (0.81–0.84)	6479 (53.9)	522 (8.0)	163 (1.3)	13 (7.9)	4372 (36.4)	368 (8.4)	995 (8.2)	124 (12.5)
Partin, threshold 5%	11 626	0.79 (0.78–0.81)	8323 (71.6)	675 (8.1)	332 (2.8)	31 (9.3)	2287 (19.7)	185 (8.1)	684 (5.9)	75 (10.9)
Partin, threshold 15%	11 626	0.79 (0.78–0.81)	9935 (85.4)	791 (7.9)	678 (5.8)	75 (11.1)	675 (5.8)	69 (10.2)	338 (2.9)	31 (9.2)
Yale, threshold 5%	12 009	0.81 (0.80–0.82)	4862 (40.3)	359 (7.4)	96 (0.8)	9 (9.3)	5989 (49.7)	531 (8.9)	1062 (8.8)	128 (12.0)
Yale, threshold 15%	12 009	0.81 (0.80–0.82)	9680 (80.3)	769 (7.9)	566 (4.7)	57 (10.1)	1171 (9.7)	121 (10.3)	592 (4.9)	80 (13.5)
Briganti 2017, threshold 5%	585	0.80 (0.75–0.86)	242 (41.4)	24 (9.9)	7 (1.2)	0 (0)	275 (47.0)	31 (11.3)	61 (10.4)	13 (21.3)
Briganti 2019, threshold 5%	609	0.76 (0.70–0.81)	83 (13.6)	5 (6.0)	2 (0.3)	0 (0)	454 (74.5)	29 (6.4)	70 (11.5)	9 (12.8)
Briganti 2019, threshold 7%	609	0.76 (0.70–0.81)	180 (29.6)	11 (6.1)	4 (0.6)	0 (0)	357 (58.6)	23 (6.4)	68 (11.2)	9 (13.2)

*AUC, area under the curve; LNI, lymph node invasion. *Infection/sepsis, hemorrage, lymphocele/lymphedema.*

Table 3 Pelvic lymph node dissection-related complications.

	Overall	pN0	pN1	*P*
Overall PLND-related complications, *n* (%)	1027 (8.9)	890 (8.5)	137 (12.6)	<0.001
Infection/sepsis, *n* (%)	411 (3.6)	370 (3.5)	41 (3.8)	0.70
Haemorrage, *n* (%)	311 (2.7)	260 (2.5)	51 (4.7)	<0.001
Lymphocele/lymphoedema, *n* (%)	374 (3.2)	316 (3.0)	58 (5.3)	<0.001
Missing, *n* (%)	888 (7.1)	–	–	–

PLND, pelvic lymph node dissection.

capable of detecting small pelvic lymph node metastases, MRI data on the index lesion are not enough for accurate LNI prediction. mpMRI is highly operator-dependent [17], and its misinterpretation could account for the poor performance of the Briganti 2019 nomogram as compared to older nomograms. Only central radiological revision, lacking in the present study, could have provided a definitive answer. With regard to nomogram calibrations, a tendency for underestimation was seen for all the older models, especially the Partin 2016 tables, among patients with a predictive probability <20%, which represents the range of interest. By contrast, the novel nomograms (Briganti 2017 and 2019) tended to overestimate LNI risk. Decision-curve analysis showed a net benefit for all models, and confirming a lower net benefit for the Briganti 2019 nomogram.

Given the fact that the study included mostly patients who underwent surgery before 2015, only the most recent patients received mpMRI-targeted biopsy; therefore, a direct comparison of all nomograms was not possible using the whole cohort of 12 009 patients. The same was applicable for the Briganti 2017 nomogram, which required variables which were available only in a minority of patients. This might explain why this model is generally found quite cumbersome to use. To evaluate the performances of all models and compare them, we singularly tested all nomograms on available patients, and then directly compared them in a smaller subcohort of patients.

Analysis of the baseline features of our patients showed that most of them harboured localized disease, with 58.3% having pT2 disease, and a low biopsy grade group (66.4% of patients with grade 1 or 2). The proportion of patients with LNI was only 9.6%, as compared to 27.6% in the study by Hueting et al. [11], and 11.8% when considering only patients undergoing mpMRI-targeted biopsy. When looking at the number of patients without LNI despite a score above the nomogram thresholds, most patients with an indication for ePLND actually had N0 disease. Adopting a threshold of 5%, the percentage of these patients went from 19.7% (Partin 2016) to 74.5% (Briganti 2019). When using threshold of 7%, as per guidelines [1], the percentage was still 58.6% for the Briganti 2019 model. The question therefore arises of whether we really need to perform so many ePLNDs, given these numbers. The answer will probably come from the widespread adoption of PSMA PET/CT, which has already proven to be superior to conventional imaging for high-risk PCa patients with pelvic nodal metastases [12]. It is likely that, in the future, ePLND will be guided directly by PSMA PET/CT, or nomograms integrating PSMA PET/CT data.

ePLND remains a time-consuming procedure, not without complications which can add relevant morbidity to radical prostatectomy. In the present study, we were not able to calculate the duration of ePLND across centres, but focused instead on ePLND-related complications. We found a 3.2% rate of symptomatic lympoceles/lymphoedemas, in accordance with a systematic review by Ploussard et al. [18] reporting percentages between 0% and 7.9%. The incidence was higher among patients with LNI, where the mean number of resected nodes was higher: this issue could be seen as a bias, but might reflect the anatomical variability reported in the literature [19]. It is also possible that more extended dissections were performed in high-risk cases, or when suspicious nodes were found intra-operatively. Finally, it should be remembered that there is no consensus for the identification, analysis and count of lymph nodes on pathological examination [20]. In line with data in the literature, haemorrhagic and infective complications were quite low, with overall rates of 2.7% and 3.6%, respectively. Given the retrospective nature of the present study, there is a possible underestimation of these complications, especially lymphoceles and lymphoedemas that sometimes become symptomatic after some delay. Considering different nomograms, PLND-related complications were experienced by 6.4–11.3% of patients without LNI despite a score above the threshold, adding unnecessary morbidity to these patients.

The study has some limitations. First, as previously indicated, it was not possible to perform a direct comparison of all nomograms in the whole series, limiting the power of the analysis. Second, there was a lack of central radiological and pathological examination, which could have introduced bias. Third, the number of patients undergoing mpMRI-targeted biopsy was low, with most patients undergoing surgery before 2015. Fourth, patients who did not receive ePLND, irrespective of nomogram score, were not included in this study, possibly generating a selection bias. Finally, the study was retrospective and has the inherent biases of studies of that nature. Nonetheless, our data are drawn from the largest

series published to date, and are likely representative of 'real-life' clinical practice.

In conclusion, our multicentre study shows that the currently available nomograms have similar performances and limitations for the prediction of LNI. Miscalibration was present, however, for all nomograms that showed a net benefit. In patients with only systematic biopsy, the MSKCC and Briganti 2012 nomograms were superior in the prediction of LNI. Nomogram-driven indications for ePLND are still inconsistent in a considerable proportion of patients, who are found to have N0 disease while being at risk of higher morbidity.

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Conflicts of Interest

None declared.

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Abbreviations: AUC, area under the curve; ePLND, extended pelvic lymph node dissection; ISUP, International Society of Urological Pathology; LNI, lymph node invasion; mpMRI, multiparametric MRI; MSKCC, Memorial Sloan Kettering Cancer Centre; PCa, prostate cancer; PET, positron-emission tomography; PI-RADS, Prostate Imaging-Reporting and Data System; PSMA, prostate-specific membrane antigen.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Calibration plots considering only patients with LNI risk below 20%.

