Indications and complications of pelvic lymph node dissection for prostate cancer: are currently available nomograms accurate to predict lymph node invasion?

Marco Oderda, Romain Diamand, Simone Albisinni, Giorgio Calleris, Antonio Carbone, Marco Falcone, Gaelle Fiard, Giorgio Gandaglia, Alessandro Marquis, Giancarlo Marra, et al.

TITLE PAGE

TITLE: Indications and complications of pelvic lymph node dissection for prostate cancer: are currently available nomograms accurate to predict lymph node invasion?

AUTHORS: Marco Oderda [1], Romain Diamand [2], Simone Albisinni [3], Giorgio Calleris [1], Antonio Carbone [4], Marco Falcone [1], Gaelle Fiard [5], Giorgio Gandaglia [6], Alessandro Marquis [1], Giancarlo Marra [1,7], Cinzia Parola [1], Antonio Pastore [4], Alexandre Peltier [2], Guillaume Ploussard [8], Thierry Roumeguère [3], Rafael Sanchez-Salas [7], Giuseppe Simone [9], Salvatore Smelzo [10], John H. Witt [11], Paolo Gontero [1]

AFFILIATIONS:

1] Division of Urology, Città della Salute e della Scienza, Molinette Hospital, University of Turin, Torino, Italy

2] Urology Department, Hôpital Erasme, University Clinics of Brussels, Université Libre de Bruxelles, Brussels, Belgium

3] Urology Department, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

4] Department of Medico-Surgical Sciences and Biotechnologies, Urology Unit, Sapienza University of Rome, Latina, Italy

5] Urology Department, CHU de Grenoble, Grenoble, France

6] Unit of Urology/Department of Oncology, URI, IRCCS San Raffaele Hospital, Milan, Italy

7] Department of Urology, Institut Mutualiste Montsouris, Université Paris Descartes, Paris, France

8] La Croix du Sud Hospital, Quint Fonsegrives and Institut Universitaire du Cancer, Toulouse

9] Urology Department, Regina Elena National Cancer Institute, Rome, Italy

10] Urology Unit, San Raffaele Turro, Milan, Italy

11] Dept of Urology, St Antonius Hospital Gronau, Germany

CORRESPONDING AUTHOR: Marco Oderda, MD, FEBU, Department of Surgical Sciences, Division of Urology, Città della Salute e della Scienza - Molinette Hospital, University of Turin, Turin, Italy. Phone number: +393479383465. E-mail address: marco.oderda@libero.it.

KEYWORDS: prostate cancer, pelvic lymph node dissection, lymphadenectomy, nomogram

MANUSCRIPT WORDS COUNT: 2196 words.

ABSTRACT WORDS COUNT: 291 words.

DR. MARCO ODERDA (Orcid ID : 0000-0003-4681-888X)
DR. GIORGIO CALLERIS (Orcid ID : 0000-0003-3831-1632)
DR. MARCO FALCONE (Orcid ID : 0000-0003-1101-892X)
DR. GIORGIO GANDAGLIA (Orcid ID : 0000-0002-5052-721X)
DR. ALESSANDRO MARQUIS (Orcid ID : 0000-0002-6808-148X)
DR. GIANCARLO MARRA (Orcid ID : 0000-0003-2363-026X)
DR. GUILLAUME PLOUSSARD (Orcid ID : 0000-0002-6004-2152)
DR. GIUSEPPE SIMONE (Orcid ID : 0000-0002-4868-9025)

Article type : Original Article

MANUSCRIPT

ABSTRACT

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

Methods: 14.921 patients who underwent radical prostatectomy with ePLND at eight European tertiary referral centers were retrospectively identified. After exclusion of patients with incomplete biopsy or pathologic data, 12.009 were included. Of these, 609 had undergone mpMRI-targeted biopsies. Among ePLND-related complications we included lymphocele, lymphedema, hemorrhage, infection, and sepsis. The performances of MSKCC, Briganti 2012, Briganti 2017, Briganti 2019, Partin 2016 and Yale models were evaluated using the receiver operated characteristic curve (AUC), calibration plots, and decision curve analysis (DCA).

Results: overall, 1158 (9.6%) patients had LNI with a mean of 17.7 and 3.2 resected and positive nodes, respectively. No significant differences in AUCs were observed between MSKCC (0.79), Briganti 2012 (0.79), Partin 2016 (0.78), Yale (0.80), Briganti 2017 (0.81) and Briganti 2019 (0.76). A direct comparison of older models showed a better discrimination for MSKCC and Briganti 2012 nomograms. A tendency for underestimation was seen for all the older models, whereas Briganti 2017 and 2019 nomograms tended to

overestimate LNI risk. DCA analysis showed a net benefit for all models, with a lower net benefit for Partin 2016 and Briganti 2019 models. ePLND-related complications were experienced by 1027 patients (8.9%), and 12.6% of pN1 patients. Conclusions: currently available nomograms have similar performances and limitations for the prediction of LNI. Miscalibration was present for all nomograms that showed however a net benefit. In patients with only systematic biopsy, MSKCC and Briganti 2012 nomograms are better to predict LNI.

1. INTRODUCTION

Extended pelvic lymph node dissection (ePLND) is the most accurate method to detect lymph node invasion (LNI) in prostate cancer (PCa) **[1]**. Its prognostic role is undeniable, helping to select patients that benefit from adjuvant treatments **[2]**, whereas its therapeutic value remains controversial **[3]**. A recent multi-institutional study found no difference in oncologic 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 Briganti and Memorial Sloan Kettering Cancer Center (MSKCC) nomograms, Partin 2016 tables, and Yale formula **[5-10]**. These tools, mainly based on clinical parameters, showed good predictive accuracy on internal and external validation, but still not optimal **[11]**. According to the European Association of Urology guidelines, a risk of nodal metastases over 5% is an indication to perform ePLND **[1]**. More recently, a novel nomogram (Briganti 2019) was published using Gleason score (Internatonal 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% cutoff 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 on the indication for ePLND, considering that it is a time-consuming procedure not devoid of complications such as lymphocele and lymphedema, often unpredictable and sometimes difficult to manage. Available nomograms were developed on retrospective cohorts and are far from being infallible. Furthermore, there are no clear recommendations supporting the adoption of a nomogram over another. The routine adoption of new imaging modalities such PSMA

PET/CT will probably improve the accuracy of PCa staging **[12]**, but to-date we still rely on nomograms to decide whether to perform ePLND or not.

The aim of our study was to externally validate MSKCC and Briganti nomograms, Partin 2016 tables and Yale formula in a large multicentric European cohort of PLND patients and to evaluate the potential risk of complications when using the recommended cut-off.

2. MATERIALS AND METHODS

After institutional review board approval, 14.921 patients who underwent radical prostatectomy with ePLND at eight European tertiary referral centers (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 ureteral crossing. All specimens were evaluated by dedicated uropathologists. After exclusion of patients with incomplete biopsy or pathologic data, 12.009 were available for analysis. Of these, 609 had undergone mpMRI-targeted and systematic biopsies, targeting lesions with a PIRADS score ≥3 **[13]**. No patients received neoadjuvant hormonal therapy. Examined variables included: PSA, clinical stage according to digital rectal examination (DRE), mpMRI features (when performed), Gleason score, ISUP grade (on biopsy and pathologic 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, lymphedema, hemorrhage, infection, and sepsis.

2.1. Statistical analysis

Mann-Whitney test was used to compare the distribution of continuous variables, while the Fisher exact and Pearson chi-square tests were used to compare proportions of categorical variables. External validation followed the TRIPOD recommendations **[14]**, validating the performances of MSKCC **[5]** and Briganti nomograms **[6-8],** Partin 2016 Tables **[9]** and Yale formula **[10]**. Previously published regression coefficients were used to calculate the individual risk of LNI **[15]**. Performance of the model was evaluated in terms of discrimination and calibration. Discrimination was quantified using the area under the curve (AUC) from the receiver operated characteristic curve (ROC). The extent of over- and underestimation associated with the model was graphically described using calibration plots. Decision curve analysis (DCA) was used to evaluate the net benefice of the model according to the cut-off. A two-sided $p < 0.05$ defined statistical significance. Statistical analyses were

performed with SPSS version 26.0 (IBM Corp, Armonk, NY, USA) and STATA 14.1 (StataCorp, Texas, USA).

3. RESULTS

3.1 Baseline characteristics

The characteristics of the main patient cohort are shown in **Table 1**. Overall, 1158 (9.6%) patients had LNI on final pathologic 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, Partin 2016 model, Briganti 2017 and Briganti 2019 nomograms were tested in subcohorts of 11.626, 585 and 609 patients, respectively.

Significant differences were observed between pN0 and pN1 patients concerning age, ASA score, preoperative PSA, cT, PIRADS score, maximum index lesion diameter, biopsy grade group, positive cores, pathologic stage, pathologic grade group, and number of lymph nodes removed.

3.2 External validations

The AUCs of MSKCC nomogram, Briganti 2012 nomogram, Partin 2016 tables, Yale formula, Briganti 2017 nomogram and 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, AUCs were 0.79, 0.79, 0.78, 0.80, 0.81, and 0.76, respectively, without observing significant differences (p 0.42). A direct comparison of MSKCC nomogram, Briganti 2012 nomogram, Partin 2016 tables and 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 MSKCC and Briganti 2012 performing better than Yale and Partin 2016 models (p 0.001).

Graphical representation of calibration plots is reported in **figure 1**: 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 Partin 2016 tables and Yale formula showed a general tendency to underestimation. On the contrary, Briganti 2017 and Briganti 2019 nomograms showed a general tendency to overestimation. **Supplementary figure 1** shows calibration plots considering only patients with LNI risk below 20% (considered as the range of interest in clinical practice).

According to DCA, all models showed a clinical net benefice, with a lower net benefit for Partin 2016 tables and Briganti 2019 nomogram considering threshold probabilities below

20% (**figure 2**).

3.3 PLND-related complications

Table 2 shows the proportion of patients with and without LNI according to the cut-off adopted by each model, and the incidence of PLND-related complications in each subgroup of patients. Complications were experienced by 6.4% to 11.3% of patients without LNI despite a score above the cut-off. 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 whether to perform ePLND relies on nomograms that estimate the risk of finding LNI. A 5% cut-off is generally adopted as an indication to perform ePLND; recently, a new cut-off at 7% was proposed for Briganti 2019 nomogram that includes mpMRI and mpMRI-targeted biopsy data. Theoretically, a perfect nomogram should have good accuracy, indicated by 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 a nomogram over the others. Hueting et al performed in 1.001 Dutch PCa patients an external validation of sixteen predictive models, excluding Briganti 2017 and 2019 nomograms. Results of study showed that Briganti 2012 (AUC 0.76) and MSKCC nomograms (AUC 0.75) were apparently the most accurate, with similar miscalibration with tendency to underestimation. No direct comparison between nomograms, however, was performed **[11]**.

The present study aimed to externally validate the most commonly used predictive models for LNI in a multicentric, European cohort of ePLND patients. Among the strengths of our study, we acknowledge: the large sample size; the heterogeneity of patients, coming from different countries and years of surgery, ideal feature to test predictive models; the different biopsy techniques adopted, with the majority of patients undergoing only systematic biopsies while only the most recent receiving MRI-targeted biopsies; and, finally, the possibility of a comparison between different nomograms, taking into account accuracy, calibration, and net benefit.

Our results were surprising: MSKCC and Briganti 2012 nomograms outperformed Briganti

2019 nomogram, suggesting that mpMRI did not add relevant info to predict LNI. In other words, if mpMRI is not capable of detecting small pelvic lymph node metastases, MRI data on index lesion are not enough for an accurate LNI prediction. mpMRI is highly operator-dependent **[17]**, and its misinterpretation could account for the poor performance of Briganti 2019 nomogram as compared to older nomograms. Only central radiologic revision, lacking in this study, could have given a definitive answer. As for nomogram calibrations, a tendency for underestimation was seen for all the older models, especially Partin 2016 tables, among patients with a predictive probability <20%, which represents the range of interest. On the contrary, the novel nomograms (Briganti 2017 and 2019) tended to overestimate LNI risk. DCA analysis showed a net benefit for all models, confirming a lower net benefit for Briganti 2019 nomogram.

Given the fact that our study included mostly patients operated before 2015, only the most recent ones received mpMRI-targeted biopsy: therefore, a direct comparison of all nomograms was not possible on the whole cohort of 12.009 patients. The same went for Briganti 2017 nomogram, needing variables which were available only in a minority of patients; this might explain the reason why this model is generally found quite cumbersome to use. In order to evaluate the performances of all models and compare them, we singularly tested all nomograms on available patients, and then we directly compared them on a smaller subcohort of patients.

Analyzing baseline features of our patients, most of them harbored localized disease, with 58.3% of pT2, and low biopsy grade group, with 66.4% of grade 1 or 2. The proportion of LNI patients was only 9.6%, as compared to 27.6% of Hueting **[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 cut-offs, most patients with indication for ePLND were actually N0. Adopting a cut-off of 5%, the percentage of these patients went from 19.7% (Partin 2016) to 74.5% (Briganti 2019). When using a cut-off of 7% as per guidelines **[1]**, the percentage was still 58.6% for Briganti 2019. The question is, do 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 than 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 devoid of complications, which can add relevant morbidity to radical prostatectomy. In our study, we were not able to calculate the

duration of ePLND across centers, but focused instead on ePLND-related complications. We found a 3.2% of symptomatic lympoceles/lymphedemas, in accordance with a systematic review by Ploussard et al reporting percentages between 0 and 7.9% **[18]**. The incidence was higher among LNI patients, where mean number of resected nodes was higher: this issue could be intended as a bias but could likely 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 intraoperatively found. Finally, it has to be reminded that there is no consensus for identification, analysis and count of lymph nodes on pathological examination **[20]**. In line with data of the literature, haemorrhagic and infective complications were quite low, with an overall 2.7% and 3.6%, respectively. Given the retrospective nature of this study, there is a possible underestimation of these complications, especially lymphoceles and lymphedemas that sometimes become symptomatic with some delay. Considering different nomograms, PLND-related complications were experienced by 6.4% to 11.3% of patients without LNI despite a score above the cut-off, adding unnecessary morbidity to these patients.

We must acknowledge the study limitations. First, as previously indicated, the impossibility to perform a direct comparison of all nomograms in the whole series, limiting the power of analysis; second, the lack of central radiologic and pathologic examination, which could have introduced biases. Third, the low number of patients undergoing mpMRI-targeted biopsy, with most patients undergoing surgery before 2015. Fourth, patients who did not receive ePLND, irrespectively of nomogram score, were not included in this study, possibly generating a selection bias. Finally, the retrospective nature of study, with all its inherent biases. Nonetheless, our data are drawn from the largest series published to date, being likely representative of "real life" clinical practice.

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

ACKNOWLEDGEMENTS/FUNDING

Giancarlo Marra's a research work at Institut Mutualiste Montsouris has been supported by a scholarship from the European Urological Scholarship Programme (EUSP).

CONFLICTS OF INTEREST

None declared.

REFERENCES

1] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment With Curative Intent. Eur Urol 2017 Apr;71(4):618-629.

2] Fossati, N, Willemse PM, Van den Broeck T, et al. The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A Systematic Review. Eur Urol, 2017; 72: 84-109.

3] Withrow DR, DeGroot JM, Siemens DR, et al. Therapeutic value of lymph node dissection at radical prostatectomy: a population-based case-cohort study. BJU Int. 2011; 108: 209-216.

4] Preisser F, van den Bergh RCN, Gandaglia G, et al. Effect of Extended Pelvic Lymph Node Dissection on Oncologic Outcomes in Patients With D'Amico Intermediate and High Risk Prostate Cancer Treated With Radical Prostatectomy: A Multi-Institutional Study. J Urol 2020; 203: 338-343.

5] Memorial Sloan Kettering Cancer Center. Pre-radical prostatectomy tool to predict probability of lymph node involvement in prostate cancer patients. www.mskcc.org/nomograms/prostate/pre_op.

6] Briganti A, Larcher A, Abdollah F, et al. Updated nomogram pre-dicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. Eur Urol 2012; 61: 480–7.

7] Gandaglia G, Fossati N, Zaffuto E, et al. Development and Internal Validation of a Novel Model to Identify the Candidates for Extended Pelvic Lymph Node Dissection in Prostate Cancer. Eur Urol; 2017: 72: 632-640.

8] Gandaglia G, Ploussard G, Valerio M, Mattei A, et al. A Novel Nomogram to Identify Candidates for Extended Pelvic Lymph Node Dissection Among Patients with Clinically Localized Prostate Cancer Diagnosed with Magnetic Resonance Imaging-targeted and Systematic Biopsies. Eur Urol 2019; 75; 3: 506–514.

9] Tosoian J, Chappidi M, Feng Z, et al. Prediction of Pathological Stage Based on Clinical Stage, Serum Prostate-Specific Antigen, and Biopsy Gleason Score: Partin Tables in the Contemporary Era. BJU International 2017; 119: 676-683.

10] Yu BJ, Makarov DV, Gross C. A New Formula for Prostate Cancer Lymph Node Risk. Int J Radiat Oncol Biol Phys; 2011; 80: 69-75.

11] Hueting TA, Cornelb EB, Somford DM, et al. External Validation of Models Predicting the Probability of Lymph Node Involvement in Prostate Cancer Patients. European Urology Oncology 2018 ; 5: 411-417.

12] Hofman MS, Lawrentschuk N, Francis RJ. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020; 395: 1208‑16.

13] Padhani AR, Weinreb J, Rosenkrantz AB, Villeirs G, Turkbey B, Barentsz J. Prostate Imaging-Reporting and Data System Steering Committee: PI-RADS v2 Status Update and Future Directions. Eur Urol. 2019; 75: 385-396.

14] Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD Statement. Eur Urol. 2015; 67: 1142-1151.

15] Evidencio Medical Decision Support. www.evidencio.com.

16] Schoots IG, Padhani AR. Personalizing prostate cancer diagnosis with multivariate risk prediction tools: how should prostate MRI be incorporated? World Journal of Urology 2020; 38: 531-545.

17] Tay KJ, Gupta RT, Brown AF, et al. Defining the Incremental Utility of Prostate Multiparametric Magnetic Resonance Imaging at Standard and Specialized Read in Predicting Extracapsular Extension of Prostate Cancer. European Urology 2016; 70: 211-213.

18] Ploussard G, Briganti A, de la Taille A, et al. Pelvic Lymph Node Dissection During Robot-Assisted Radical Prostatectomy: Efficacy, Limitations, and Complications-A Systematic Review of the Literature. European Urology 2014; 65: 7-16.

19] Weingartner K, Ramaswamy A, Bittinger A, et al. Anatomical Basis for Pelvic Lymphadenectomy in Prostate Cancer: Results of an Autopsy Study and Implications for the Clinic. J Urol 1996; 156: 1969-71.

20] Mhaolcatha SN, Power E, Mayer N, et al. Optimal Sampling of Pelvic Lymphadenectomy Specimens Following Radical Prostatectomy: Is Complete Tissue Submission Justified? J Clin Pathol 2019; 72: 712-715.

FIGURE LEGENDS

Figure 1. Graphical representation of calibration plots

Figure 2. Decision curve analysis

Supplementary figure 1. Calibration plots considering only patients with LNI risk below 20%

TABLE 1. Baseline characteristics of the main cohort

	Overall	**pN0**	**pN1**	***p* value**
Patients, n (%)	12009	10851 (90.4%)	1158 (9.6%)	-
Mean age at surgery, yrs (SD)	64.4 (6.8)	64.3 (6.8)	65.4 (6.9)	<0.001
ASA score, n (%)				0.002
- 1	2157 (22.7%)	1988 (23.1%)	169 (18.6%)	
- 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 preoperative PSA, ng/ml (SD)	11.4 (14.0)	10.2 (9.9)	22.3 (31.5)	<0.001
Clinical stage, n (%)				<0.001
- cT1	6739 (56.1%)	6439 (59.3%)	300 (25.9%)	
- 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%)	-
PIRADS score*, n (%)				<0.001
- 3	48 (7.9%)	45 (8.4%)	3 (4.2%)	
- 4	317 (52.0%)	294 (54.7%)	23 (31.9%)	
- 5	244 (40.1%)	198 (36.9%)	46 (63.9%)	
Mean maximum index lesion diameter on mpMRI*, mm (SD)	14.6 (6.9)	13.7 (6.3)	20.7 (8.8)	<0.001
Biopsy grade group, n (%)				<0.001
- 1	4295 (35.8%)	4208 (38.8%)	87 (7.5%)	
- 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 cores taken, n (SD)	12.4 (4.9)	12.4 (4.5)	12.4 (4.9)	0.98
Mean positive cores taken, n (SD)	4.7 (3.4)	4.5 (3.2)	7.6 (4.0)	<0.001
Pathologic stage (n (%)				<0.001
- pT2	6265 (58.3%)	6177 (63.4%)	88 (8.7%)	

- pT3 - pT4 - Missing	4254 (39.6%) 229 (2.1%) 1680	3462 (35.5%) 103 (1.1%)	792 (78.7%) 126 (12.5%)	
Pathologic grade group, n (%) - 1 - 2 - 3 - 4 - 5 - Missing	 2797 (24.5%) 3609 (31.6%) 2951 (25.9%) 725 (6.4%) 1327 (11.6%)	 2790 (27.0%) 3504 (34.0%) 2643 (25.6%) 604 (5.9%) 774 (7.5%)	 7 (0.6%) 105 (9.6%) 308 (28.2%) 121 (11.1%) 553 (50.5%)	<0.001
Mean lymph nodes removed, n (SD)	13.2 (6.9)	12.7 (6.5)	17.7 (8.4)	<0.001
Mean lymph nodes positive, n (SD)	-	-	3.2 (6.2)	<0.001

***on 609 patients who underwent targeted biopsy. **on 1578 patients who were staged with mpMRI**

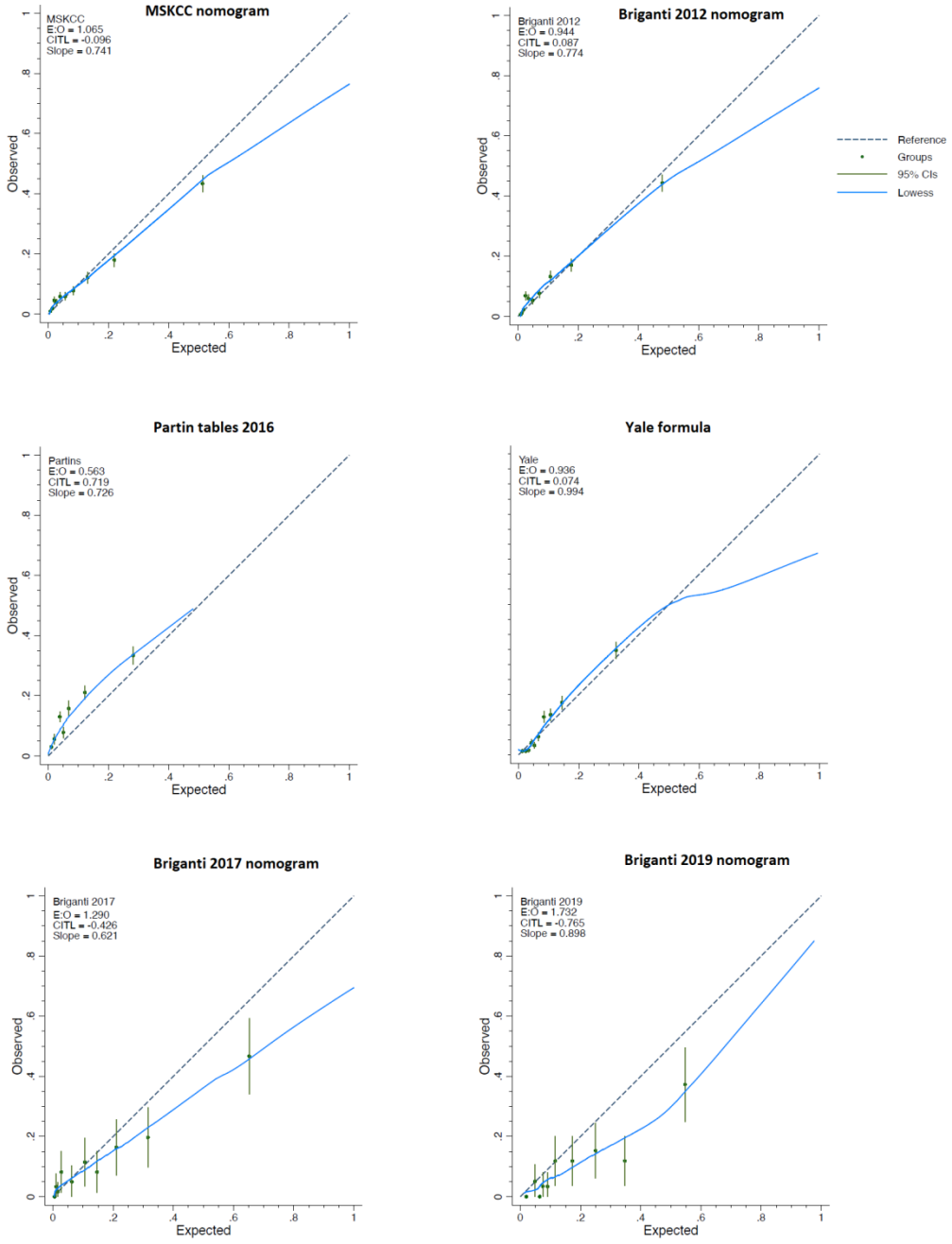
TABLE 2. Cross-tabulation of patients with LNI and PLND-related complications stratified according to model's cut-off

			No. of patients below the cut-off, n (%)				No. of patients above the cut-off, n (%)			
Nomogram	**Patients, n**	**AUC (95% CI)**	**Without LNI, n (%)**		**With LNI, n (%)**		**Without LNI, n (%)**		**With LNI, n (%)**	
			#	**Complications ***	**#**	**Complications ***	**#**	**Complications ***	**#**	**Complications ***
MSKCC, cut-off 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 cut-off 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 cut-off 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 cut-off 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 cut-off 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 cut-off 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	585	0.80	242	24	7	0	275	31	61	13

cut-off 5%		(0.75-0.86)	(41.4%)	(9.9%)	(1.2%)	(0%)	(47.0%)	(11.3%)	(10.4%)	(21.3%)
Briganti 2019 cut-off 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 cut-off 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%)

TABLE 3_ PLND-related complications

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



bju_15220_f1.tif