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

When to Perform Staging Extended Pelvic Lymph Node Dissection for Clinically Localized Prostate Cancer. Development of the First Multivariable Prediction Model in Men Diagnosed with MRI-Targeted Biopsies

Giorgio Gandaglia[1], Guillaume Ploussard[2], Massimo Valerio[3], Agostino Mattei[4], Cristian Fiori[5], Nicola Fossati[1], Armando Stabile[1], Jean-Baptiste Beauval[6], Bernard Malavaud[6], Mathieu Roumiguié[6], Daniele Robesti[1], Paolo Dell'Oglio[1], Stefania Zamboni[4], Arnas Rakauskas[3], Francesco De Cobelli[7,8], Francesco Porpiglia[1], Francesco Montorsi[1,8], Alberto Briganti[1,8]

Unit of Urology/Division of Oncology, URI, IRCCS Ospedale San Raffaele, Milan, Italy Department of Urology, Saint Jean Languedoc/La Croix du Sud Hospital, Toulouse, France Department of Urology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland Klinik für Urologie, Luzerner Kantonsspital, Lucerne, Switzerland
Division of Urology, San Luigi Gonzaga Hospital, Orbassano, Turin, Italy
Department of Urology, Andrology and Renal Transplantation, CHU Rangueil, Toulouse, France
Unit of Clinical Research in Radiology, Experimental Imaging Center, IRCCS Ospedale San Raffaele, Milan, Italy Vita-Salute San Raffaele University, Milan, Italy

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Corresponding author:
Alberto Briganti, MD, PhD
Unit of Urology/Division of Oncology; URI; RCCS Ospedale San Raffaele, Milan, Italy Tel: +39 0226436923
Fax: +39 0226437286
Email: briganti.alberto@hsr.it

ABSTRACT

Background: Available models to predict lymph node invasion (LNI) in prostate cancer (PCa) patients undergoing radical prostatectomy (RP) might not be applicable to contemporary men diagnosed with MRI-targeted biopsies.

Objective: To assess the accuracy of available tools to predict LNI and to develop a novel prediction model in men diagnosed with MRI-targeted biopsies.

Design, setting, and participants: Overall, 497 patients diagnosed with MRI-targeted biopsies treated with RP and extended pelvic lymph node dissection (ePLND) at five European institutions were identified.

Outcome measurements and statistical analyses: Three available models predicting LNI were evaluated using the area under the curve (AUC), calibration plots and decision-curve analyses. A novel coefficient-based nomogram predicti LNI was developed and internally validated.

Results and limitations: Overall, 62 (12.5%) patients had LNI. The median (IQR) number of nodes removed was 15 (11-20). The AUCs of the Briganti 2012, Briganti 2017 and MSKCC nomograms were 82, 82 and 81% and th alibration characteristics were suboptimal. A model including PSA, clinical stage and the maximum diameter of the index lesion at multi-parametric MRI (mpMRI), grade group at targeted biopsy and the presence of clinically significa Ca at concomitant systematic biopsy depicted an AUC of 86% and represented the basis for a coefficient-based nomogram. This tool exhibited a higher AUC, better calibration characteristics and higher net-benefit compared to availab models developed on standard biopsies. Using a cutoff of 7%, 244 (57%) ePLNDs would be spared and a lower number of LNIs would be missed compared to available nomograms (1.6 vs. 4.6 vs. 4.5 vs. 4.2% for the novel vs. Briga 012 vs. Briganti 2017 vs. MSKCC nomograms).
Conclusions: Available models predicting LNI are characterized by suboptimal accuracy and clinical net-benefit in patients diagnosed with MRI-targeted biopsies. We developed and internally validated the first nomogram includi mpMRI and MRI-targeted biopsy data to identify patients who should be considered for ePLND in this setting.

Patient summary: We developed a novel nomogram to predict lymph node invasion (LNI) in prostate cancer (PCa) patients diagnosed with MRI-targeted biopsy undergoing radical prostatectomy (RP). The adoption of this model dentify candidates for an extended pelvic lymph node dissection would allow for sparing up to 60% of the procedures at the cost of missing only 1.6% patients with LNI.
Take home message: Currently available models predicting LNI are characterized by suboptimal characteristics in patients diagnosed with MRI-targeted biopsy. A novel nomogram specifically developed in this setting including mpM nd MRI-targeted biopsy data should be used to identify patients at higher risk of LNI who should be considered for an ePLND.

INTRODUCTION

An anatomically defined extended pelvic lymph node dissection (ePLND) still represents the most accurate method for nodal staging in prostate cancer (PCa) [1]. Even among contemporary patients, up to 15% of men harbor lymph no nvasion (LNI) when treated with ePLND [2]. Although ePLND remains the gold standard for nodal staging, it is a time-consuming procedure not devoid of complications such as lymphocele and lymphedema [3]. Considering an ePLN xclusively in men at higher risk of LNI (above 5% according to the EAU–ESTRO–SIOG guidelines) has been proposed as a reliable approach to minimize the morbidity associated with ePLND while missing only a low proportion of m with nodal metastases [4-7]. Currently available tools to identify ePLND candidates are based on clinical parameters and depict excellent predictive accuracy at internal and external

validation [4, 5, 8]. However, they are all based tandard, systematic biopsies. Recent changes in the diagnostic pathway of clinically localized PCa with the introduction of multi-parametric MRI (mpMRI) and MRI-targeted biopsy might then preclude their applicability to contempora atients for three different reasons. 1. These tools were developed in historic cohorts of men undergoing systematic biopsy and their results might not be generalizable to men diagnosed with MRI-targeted biopsy [9]. 2. The use of mpM nd targeted biopsy provides additional relevant clinical information that are not considered by currently available models predicting LNI [10, 11]. 3. A diagnostic strategy based on mpMRI and MRI-targeted biopsy would result into mo ignificant tumors being identified and reduced risk of detection of insignificant PCa with a consequent change in disease characteristics at radical prostatectomy (RP) [12-14].

We hypothesized that currently available models predicting LNI might be characterized by suboptimal performance characteristics in contemporary patients diagnosed with MRI-targeted biopsy. We aimed at assessing the accuracy vailable models for the identification of LNI in a large contemporary cohort of men diagnosed with MRI-targeted biopsy. Moreover, we sought to develop a novel model including mpMRI and MRI-targeted biopsy data to impro rediction of LNI in order to better identify contemporary candidates for ePLND.

MATERIALS AND METHODS

Study population

After IRB approval, 581 patients who underwent a MRI-targeted biopsy followed by a RP and ePLND between 2016 and 2018 at five European tertiary referral centers were identified. Only patients with a positive MRI-targeted biop were selected (n=516). Among those, we excluded patients with incomplete biopsy or pathologic data (n=19). This resulted in a final population of 497 patients. No patients received neoadjuvant hormonal therapy. An anatomically defin emplate for ePLND that included removal of the obturator, internal iliac and external iliac lymph nodes was applied in all cases [15]. All cases were performed by high-volume surgeons at referral institutions. All specimens were submitt or pathologic evaluation in multiple packages and were evaluated by dedicated uro-pathologists [5].

mpMRI and biopsy technique

All patients underwent a 1.5 or 3-T mpMRI before prostate biopsy with or without an endorectal coil. The imaging protocol consisted of multiplanar T2-weighted images, diffusion-weighted imaging, dynamic contrast-enhanced MRI, a T1-weighted images with fat suppression according to the European Society of Urogenital Radiology guidelines [16]. The mpMRI images were scored and reported according to the Prostate Imaging Reporting and Data System (PI-RAD

.2 by high-volume dedicated radiologists [17]. Patients with a PI-RADS score ≥3 lesion at mpMRI were considered for prostate biopsies. Lesions with a PI-RADS score ≥3 at mpMRI were submitted to targeted biopsy using a softwa egistration system. A minimum of 2 targeted cores was taken for each suspicious lesion at mpMRI. All patients underwent also concomitant systematic biopsy at the time of the targeted biopsy with at least 6 random cores taken. T umber of targeted and systematic cores varied according to the judgment of each treating physician.

Covariates and endpoints

All patients were subjected to a detailed preoperative evaluation that consisted of PSA, clinical stage obtained according to the digital rectal examination performed by the attending urologist and prostate volume at TRUS. Imaging da onsisted of PI-RADS score, extracapsular extension (ECE), seminal vesicle invasion (SVI) and maximum diameter of the index lesion at mpMRI, which was defined as the lesion with the highest PI-RADS score or the one with the larg iameter for lesions with the same PI-RADS score. Biopsy data consisted of grade group, the number of cores taken and the number of positive cores and were collected overall and according to the biopsy approach (targeted vs. systemati The modified Gleason scoring system was adopted according to the International Society of Urological Pathology (ISUP) 2005 and 2014 consensus conferences [18, 19].

The outcome of our study was represented by LNI, which was defined as the presence of positive lymph nodes at final pathology.

Statistical analyses

First, we tested the accuracy of all three available models predicting LNI among ePLND treated men (Briganti 2012, Briganti 2017 and MSKCC nomograms) in our series of men diagnosed with targeted biopsy [5, 15, 20]. The regressi oefficients were used to calculate the individual risk of LNI according to each model and the discrimination accuracy of these models was quantified using the area under the curve (AUC). The extent of over- or underestimation associat with the use of these models was graphically depicted using calibration plots. Moreover, we developed a novel tool predicting LNI in men diagnosed with MRI-targeted biopsy. Three multivariable models were fitted with mp-MRI a argeted biopsy information. The first model was based on preoperative PSA, clinical stage at DRE, the maximum diameter of the index lesion and grade group at targeted biopsy. The second model included information on clinical sta ased on the preoperative imaging (ECE or SVI at mpMRI). A third model including also details on the percentage of cores with clinically significant PCa (defined as a grade group ≥2) outside the target area (i.e., at concomitant systema iopsies) was fitted. The discrimination accuracy of these models was quantified using the receiver operating characteristic-derived AUC. The model with the highest AUC was used to develop a coefficient-based nomogram predicting LN The

extent of overestimation or underestimation of the histologically confirmed vs. nomogram-predicted LNI rates was graphically explored using a calibration plot. The discrimination and calibration were corrected for overfit using eave-one-out cross-validation. A decision-curve analysis (DCA) was then used to determine the clinical net-benefit associated with the use of the novel model as compared to the Briganti 2012, Briganti 2017 and MSKCC nomograms [2 inally, we investigated the clinical implications associated with the use of different cut-offs of the novel nomogram and of the currently available tools. In particular, sensitivity, specificity, the number of LNIs missed and the number PLNDs avoided were calculated.

All statistical tests were performed using the R statistical package v.3.0.2 (R Project for Statistical Computing, www.r-project.org). All tests were two sided, with a significance level set at $P<0.05$.

RESULTS

Baseline characteristics

Overall, 65 (12.5%) patients had LNI (Table 1). The median (IQR) number of lymph nodes removed was 15 (11-20). Preoperative PSA, the median maximum diameter of the index lesion at mpMRI, clinical stage at DRE and mpMR iopsy grade group overall and according to the type of biopsy (MRI-targeted vs. systematic), and the percentage of positive cores overall and at concomitant systematic biopsy significantly differed between patients with pN0 and p isease (all $P<0.001$).

External validation of currently available tools

The AUCs (95% CI) of the Briganti 2012, Briganti 2017 and MSKCC nomograms in our cohort of patients diagnosed with targeted biopsies were 82% (77-88), 82% (76-87) and 81% (76-87), respectively. The Briganti 2012, Briganti 20 nd MSKCC nomograms exhibited suboptimal calibration characteristics in our cohort (Supplementary Figure 1).

Development of a novel nomogram predicting LNI

At univariable analyses, preoperative PSA, clinical stage at DRE and mpMRI, the maximum diameter of the index lesion at mpMRI, biopsy grade group at targeted biopsy and the percentage of cores with clinically significant PCa ystematic biopsy were independent predictors of LNI (all $P\leq0.04$; Table 2). When these covariates were fitted in multivariable models, the one including clinical stage at mpMRI and information on the presence of clinically significant P t systematic biopsy achieved the highest AUC at internal validation (86%) and represented the basis for the novel nomogram predicting LNI. Figure 1 graphically depicts the multivariable effect of each variable on the risk of LNI in t orm of a nomogram (coefficients are shown in Supplementary Table 1). The calibration plot indicated an excellent concordance when the predicted risk of LNI was lower than 15% (Supplementary Figure 2). Table 3 depicts erro ssociated with the use of the novel nomogram when predicting a low risk of LNI.

Using 5 and 7% cut-offs, 217 (51%) and 244 (57%) ePLNDs would be spared and LNI would be missed only in 4 (1.8%) and 4 (1.5%) patients, respective

The novel nomogram improved clinical risk prediction against threshold probabilities of LNI ≤20% at DCA (Figure 2).

Comparison of the novel nomogram with currently available models

In our series the novel nomogram was characterized by the highest net-benefit compared to the Briganti 2012, 2017 and MSKCC models. The use of a 7% cut-off would allow for sparing a slightly lower number of ePLNDs (57%) ompared to the Briganti 2012 (66%), Briganti 2017 (60%) and the MSKCC (62%) nomograms if the same threshold is used (Table 4). However, this would result into a substantially lower number of LNIs missed as compared to the models (1.6 vs. 4.6 vs. 4.5 vs. 4.2% for the novel vs. Briganti 2012 vs. Briganti 2017 vs. MSKCC nomogram, respectively).

DISCUSSION

The EAU–ESTRO–SIOG guidelines recommend the use of predictive tools based on disease characteristics such as the Briganti and MSKCC nomograms to identify individuals at a higher risk of LNI who should be considered for PLND at the time of RP [1, 4-6]. Although these models have been constantly updated over the last few years and exhibited excellent performance characteristics [4-6, 8], they were developed in men diagnosed with systematic biopsy. uch, they might not be applicable to contemporary patients undergoing mpMRI and targeted biopsy. Indeed, the quantity and quality of information for preoperative risk stratification substantially differ in men diagnosed with MRI-target iopsy vs. those receiving systematic biopsy alone [9]. For example, none of the available nomograms predicting LNI account for the type of biopsy cores (targeted vs. systematic) or include mpMRI information. As such, no data a vailable to assist clinicians in the identification of PCa patients diagnosed with MRI-targeted biopsy who should be considered for an ePLND. Given such a paucity of data, we tested the performance characteristics of three mod redicting LNI and we developed a novel nomogram in a cohort of contemporary patients diagnosed with MRI-targeted biopsy.

Our results show that available tools predicting LNI are characterized by suboptimal discrimination, calibration and clinical net-benefit at external validation in men diagnosed with MRI-targeted biopsy. Moreover, the adoption of the omograms to select ePLND candidates in this setting would be associated with a substantially higher risk of missing LNI (up to 5%) as compared to what reported in patients diagnosed with systematic biopsy alone [4, 5]. Given t uboptimal performance characteristics of currently available models we developed a novel nomogram specifically focused on patients diagnosed with MRI-targeted biopsy which achieved excellent discrimination and calibration at intern alidation. Moreover, the use of this nomogram was associated with a higher net-benefit at DCA. Our

novel model presents several elements of novelty as compared to previously published nomograms. First, it considers separately t esults of MRI-targeted and systematic biopsies. Under this light, the assumption that the number of positive cores at targeted biopsy have the same prognostic impact of those at systematic biopsy might lead to an overestimation of tum olume when using the Briganti nomogram and, in turn, of the risk of LNI [4, 5]. For example, a patient with 3 cores with grade group 2 PCa at targeted biopsy and negative random sampling would have the same risk of LNI as compared is counterpart with 3 positive random cores in 3 different areas of the prostate. However, the real tumor volume would differ between the two patients with a substantial impact on the risk of LNI and, in turn, on the selection of ePLN andidates. We tried to overcome this issue by accounting for the different impact of the results of targeted and systematic cores. Moreover, tumor volume of the index lesion at MRI-targeted biopsy was estimated using the maximu iameter at mpMRI. In addition, since information on the presence of clinically significant disease outside the index lesion improved the predictive accuracy of our nomogram, we included a variable to account for the presence of clinical ignificant PCa at concomitant systematic biopsy. Although previous studies demonstrated that adding systematic cores at the time of MRI-targeted biopsy improves the detection rate of clinically significant PCa [22-24], our stu epresents one of the first evidences supporting the concept that systematic cores should be taken in addition to MRI-targeted cores to improve preoperative risk stratification in patients undergoing prostate biopsy. Indeed, the addition ystematic cores to MRI-targeted biopsy would allow to account for PCa multi-focality, eventually reducing the risk of upgrading at final pathology [25]. Finally, while previous nomograms included T stage determined by digital rec xamination, the inclusion of information on the presence of ECE or SVI assessed by mpMRI substantially improved the AUC of our predictive tool. Moreover, a more accurate estimation of tumor burden can be obtained at mpMRI [2 ather than considering the percentage of positive cores at systematic biopsy as a proxy of tumor volume [5]. Of note, although MRI is characterized by a poor sensitivity in the detection of positive nodes in the pelvic area [27], our resul ogether with what observed in previous studies, support the importance of considering parameters obtained at prostatic mpMRI such as tumor volume and T stage to improve our ability to predict the risk of LNI [10, 28, 29].

rom a clinical standpoint, our findings show that currently available nomograms to identify ePLND candidates have sub-optimal performance characteristics when applied to individuals diagnosed with MRI-targeted biopsies. The adopti f a nomogram specifically developed on patients diagnosed with MRI-targeted biopsy would allow for sparing approximately 60% of ePLNDs at the cost of missing only 1.6% LNIs. Of note, our novel nomogram is applicable exclusive o men with a positive MRI-targeted biopsy with concomitant systematic biopsy, as currently indicated by available guidelines [1]. Moreover, the risk of LNI should not be estimated using this model in individuals who were diagnosed

wi ystematic biopsy with a negative MRI-targeted biopsy. In these patients, predictive tools developed in men diagnosed with systematic biopsy such as the 2012, 2017 Briganti and MSKCC nomograms might still be applied.

Despite several strengths, our study is not devoid of limitations. First, the lack of an external validation might preclude generalizability of our results. Under this light, it should be noted that the excellent performance characteristics of o model might be related to the use of an internal validation [30]. Second, the multi-institutional nature of our study might have introduced heterogeneity in mpMRI and biopsy protocols. However, all patients underwent mpMRI and target iopsy at tertiary referral centers, mpMRIs were evaluated by high-volume dedicated radiologists, and MRI-targeted and systematic biopsies were performed by experienced physicians and evaluated by dedicated uro-pathologists. Third, t xtent of nodal dissection varied according to treating institutions and physicians. Nonetheless, the removal of the obturator, internal iliac and external iliac lymph nodes represented the minimum requirement for defining an ePLND a hese stations were dissected free in all patients included in our study.

CONCLUSIONS

Currently available models predicting LNI are characterized by suboptimal accuracy and clinical net-benefit in patients diagnosed with MRI-targeted biopsies. We developed and internally validated the first nomogram specifical eveloped in men undergoing mpMRI targeted and concomitant systematic biopsies in order to identify patients at higher risk of LNI who should be considered for an ePLND. The adoption of this model using a 7% cut-off would allow f paring approximately 60% ePLNDs at the cost of missing only 1.6% LNIs.

FIGURE LEGEND

Figure 1. Novel nomogram predicting the probability of lymph nodes invasion (LNI) in patients diagnosed with targeted biopsies and treated with radical prostatectomy (RP) and extended pelvic lymph node dissection (ePLND).

Figure 2. Decision-curve analyses (DCA) demonstrating the net benefit associated with the use of the novel nomogram on the detection of lymph node invasion (LNI) as compared to currently available ePLND tools (Briganti 2012, Briga 017 and MSKCC nomograms).

Supplementary Figure 1. Calibration plot of observed proportion vs. predicted probability of lymph node invasions (LNI) of the novel nomogram.

Supplementary Figure 2. Calibration plot of observed proportion vs. predicted probability of lymph node invasions (LNI) of the Briganti 2012 (A), Briganti 2017 (B) and MSCKK (C) nomograms.

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Table 1. Descriptive statistics of 497 patients with clinically localized Prostate cancer (PCa) diagnosed with MRI-targeted biopsy and treated with radical prostatectomy (RP) and extended pelvic lymph node dissection (ePLND) between 2016 and 2018.

	Overall (n= 497)	**pN0 (n= 435, 87.5%)**	**pN1 (n= 62, 12.5%)**	**P-value**
Age at surgery (years)				
Median (IQR)	65 (60-70)	65 (60-70)	64 (60-71)	0.8
Preoperative PSA (ng/ml)				
Median (IQR)	7.7 (5.2-11)	7.2 (5.1-11)	11 (6.7-21)	<0.001
Clinical stage (%)				
T1	365 (73)	335 (77)	30 (48)	<0.001
T2	117 (24)	96 (22)	21 (34)	
T3	15 (3)	4 (1)	11 (17)	
Prostate volume (ml)				
Median (IQR)	44 (34-55)	43 (33-55)	48 (34-59)	0.1
PI-RADS score (%)				
3	125 (25)	121 (28)	4 (6)	<0.001
4	261 (53)	235 (54)	26 (42)	
5	111 (22)	79 (18)	32 (52)	
Number of PI-RADS ≥3 lesions at mpMRI				
Median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0.5
Maximum diameter of the index lesion at mpMRI (mm)*				
Median (IQR)	10 (9-15)	10 (9-14)	15 (10-18)	<0.001
Clinical stage at mpMRI (%)				
Organ confined	387 (80)	358 (85)	29 (47)	<0.001
Extracapsular extension	68 (14)	49 (12)	19 (31)	
Seminal vesicle invasion	27 (6)	13 (3)	14 (22)	
Biopsy grade group (%)				
1	56 (11)	55 (13)	1 (2)	<0.001
2	251 (50)	236 (54)	15 (24)	
3	94 (19)	78 (18)	16 (26)	
4	60 (12)	45 (10)	15 (24)	
5	36 (7)	21 (5)	15 (24)	
N. of cores taken				
Median (IQR)	16 (14-18)	16 (14-18)	16 (14-18)	0.2
N. of positive cores				
Median (IQR)	5 (3-8)	5 (3-8)	5 (9-12)	<0.001
Percentage of positive cores				
Median (IQR)	35 (21-53)	33 (20-50)	55 (36-80)	<0.001
Percentage of positive cores with highest-grade PCa**				
Median (IQR)	21 (12-52)	20 (12-38)	40 (24-60)	<0.001
Percentage of positive cores with lower grade PCa**				
Median (IQR)	16 (8-28)	16 (8-27)	21 (10-30)	0.1
Grade group at MRI-targeted biopsy (%)				
1	73 (15)	72 (17)	1 (2)	<0.001
2	240 (48)	225 (52)	15 (24)	
3	88 (18)	72 (17)	16 (26)	
4	63 (13)	46 (11)	17 (27)	
5	33 (7)	20 (5)	13 (21)	
N. of target cores taken				
Median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	0.1
N. of positive cores at MRI-targeted biopsy				
Median (IQR)	2 (2-3)	2 (1-3)	2 (2-3)	0.1
Grade group at systematic biopsy (%)				
Negative	80 (16)	76 (18)	4 (7)	<0.001
1	106 (21)	100 (23)	6 (10)	
2	185 (38)	171 (40)	14 (23)	
3	59 (12)	44 (10)	15 (24)	
4	34 (7)	25 (6)	9 (15)	
5	29 (6)	15 (4)	14 (23)	
N. of systematic cores taken				
Median (IQR)	12 (10-15)	12 (10-15)	12 (10-16)	0.2
Percentage of cores with clinically significant PCa at systematic biopsy				
Median (IQR)	16 (0-41)	12 (0-37)	42 (17-76)	<0.001
Surgical technique (%)				
ORP	43 (8.7)	40 (9.2)	3 (4.8)	0.2
RARP	452 (41)	393 (90)	59 (95)	
Gleason grade group at final pathology (%)				
1	15 (3.0)	15 (3.5)	0 (0)	<0.001
2	221 (45)	218 (50)	3 (4.8)	
3	172 (35)	147 (34)	25 (40)	
4	26 (5.3)	22 (5.1)	4 (6.5)	
5	60 (12)	30 (6.9)	30 (48)	
Pathologic stage (%)				
T2	218 (44)	215 (50)	3 (4.8)	<0.001
T3a	200 (40)	180 (41)	20 (32)	
T3b/4	79 (16)	40 (9.2)	39 (63)	
Positive surgical margins (%)	133 (27)	103 (24)	40 (48)	<0.001
Number of removed lymph nodes				
Median (IQR)	15 (11-20)	15 (10-20)	17 (13-24)	0.01
Number of positive lymph nodes				
Median (IQR)	1 (1-2)	NA	1 (1-2)	NA

*Available for 447 patients; **available for 480 patients

Table 2. Multivariable logistic regression analyses assessing predicting the presence of lymph node invasion (LNI) in patients diagnosed with MRI-targeted biopsy and treated with radical prostatectomy (RP) and extended pelvic lymph node dissection (ePLND).

	Univariable analyses		Model 1		Model 2		Model 3*	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Preoperative PSA	1.06 (1.03-1.08)	<0.001	1.04 (1.02-1.07)	0.002	1.04 (1.01-1.08)	0.004	1.04 (1.01-1.08)	0.01
Clinical stage at DRE					-	-	-	-
T1c	1 (Ref.)		1 (Ref.)					
T2	2.44 (1.33-4.46)	0.004	2.28 (1.14-4.60)	0.02				
T3	30.7 (9.21-87.4)	<0.001	15.6 (3.78-54.4)	<0.001				
Clinical stage at mpMRI			-	-				
Organ confined	1 (Ref.)				1 (Ref.)		1 (Ref.)	
Extracapsular extension	4.78 (2.39-9.17)	<0.001			3.33 (1.56-7.09)	0.002	3.39 (1.56-7.28)	0.002
Seminal vesicle invasion	13.2 (5.71-30.9)	<0.001			5.42 (1.93-15.8)	0.001	4.36 (1.48-12.76)	0.007
Maximum diameter of the index lesion at mpMRI (mm)	1.10 (1.05-1.15)	<0.001	1.06 (1.04-1.12)	0.04	1.04 (0.98-1.1)	0.1	1.03 (0.97-1.09)	0.3
Grade group at MRI-targeted biopsy								
1-2	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
3	4.12 (1.97-8.63)	<0.001	3.43 (1.40-8.37)	0.01	3.39 (1.57-7.10)	0.01	3.33 (1.36-8.12)	0.01
4-5	8.43 (4.34-16.37)	<0.001	8.08 (3.68-17.7)	<0.001	5.51 (1.96-15.5)	<0.001	6.08 (2.74-13.5)	<0.001
Percentage of positive cores with clinically significant PCa at systematic biopsy	1.02 (1.01-1.03)	<0.001	-	-	-	-	1.01 (1.00-1.02)	0.04
AUC of multivariable models, %	-	-	82%	-	83%	-	86%	-

*based on 428 patients with complete available data and 54 events

Table 3. Systematic analyses of the novel nomogram-derived cut-offs used to discriminate between patients with or without histologically confirmed lymph node invasion.

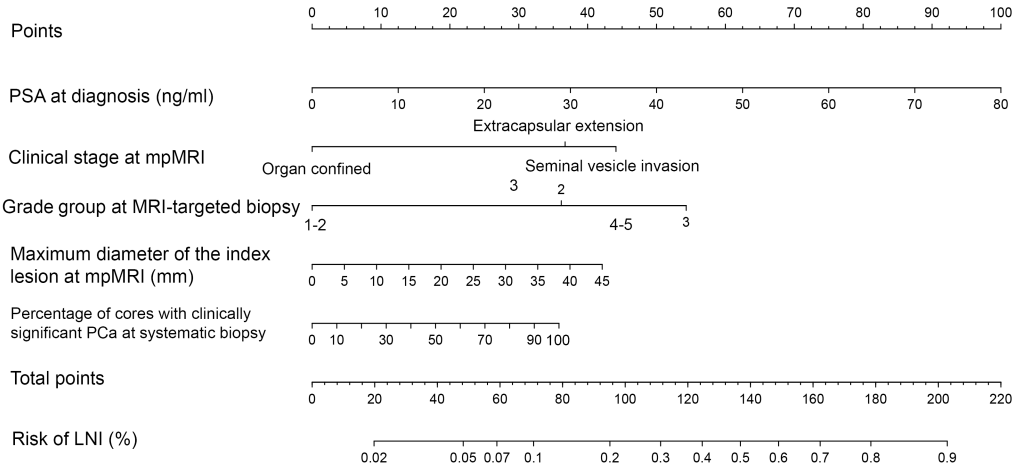
Nomogram calculated probability of LNI, cut-off, %	Patients in whom PLND is not recommended according to the cut-off (below cut-off)	Patients below cut-off without histologic LNI	Patients below cut-off with histologic LNI	Patients in whom PLND is recommended according to the cut-off (above cut-off)	Patients above cut-off without histologic LNI	Patients above cut-off with histologic LNI
2	13 (3.2)	12 (92)	1 (7.7)	415 (97)	362 (87)	53 (13)
3	164 (38)	162 (98)	2 (1.2)	264 (62)	212 (80)	52 (20)
4	200 (47)	197 (98)	3 (1.5)	228 (53)	177 (78)	51 (22)
5	217 (51)	213 (98)	4 (1.8)	211 (49)	161 (76)	50 (24)
6	231 (54)	227 (98)	4 (1.7)	197 (46)	147 (75)	50 (25)
7	244 (57)	240 (98)	4 (1.6)	184 (43)	134 (73)	50 (27)
8	256 (60)	251 (98)	5 (2.0)	172 (40)	123 (71)	49 (29)
9	266 (62)	260 (98)	6 (2.3)	162 (38)	114 (70)	48 (30)
10	283 (66)	276 (97)	7 (2.5)	145 (34)	98 (68)	47 (32)

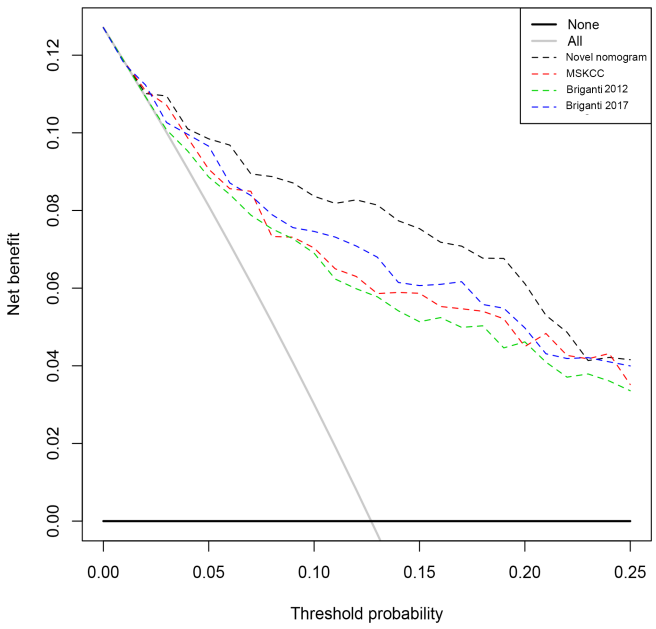
LNI: lymph node invasion

Table 4. Clinical implications according to treatment option (novel nomogram vs. Briganti 2012 vs. Briganti 2017 vs. MSKCC nomograms).

Treatment option	Patients in whom PLND is not recommended according to the cut-off (below cut-off)	Patients below cut-off without histologic LNI	Patients below cut-off with histologic LNI	Patients in whom PLND is recommended according to the cut-off (above cut-off)	Patients above cut-off without histologic LNI	Patients above cut-off with histologic LNI
Novel nomogram, 7%cut-off*	244 (57)	240 (98)	4 (1.6)	184 (43)	134 (73)	50 (27)
Briganti 2012, 7% cut-off**	329 (66)	314 (95)	15 (4.6)	167 (34)	120 (72)	47 (28)
Briganti 2017, 7% cut-off***	290 (60)	277 (95)	13 (4.5)	189 (39)	141 (77)	48 (23)
MSKCC, 7% cut-off****	308 (62)	295 (96)	13 (4.2)	189 (38)	140 (74)	49 (26)

LNI: lymph node invasion
*data available for 428 patients; **data available for 496 patients; ***data available for 479 patients; ****data available for 497 patients


Points
0 10 20 30 40 50 60 70 80 90 100
PSA at diagnosis (ng/ml)
0 10 20 30 40 50 60 70 80
Clinical stage at mpMRI
Extracapsular extension
Organ confined
Seminal vesicle invasion
Grade group at MRI-targeted biopsy
3 2
1-2
4-5
3
Maximum diameter of the index lesion at mpMRI (mm)
0 5 10 15 20 25 30 35 40 45
Percentage of cores with clinically significant PCa at systematic biopsy
0 10 30 50 70 90 100
Total points
0 20 40 60 80 100 120 140 160 180 200 220
Risk of LNI (%)
0.02 0.05 0.07 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9


None
All
Novel nomogram
MSKCC
Briganti 2012
Briganti 2017
Net benefit
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.00
0.05
0.10
0.15
0.20
0.25
Threshold probability