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Prostate Cancer

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

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Abstract

Background: Available models for predicting lymph node invasion (LNI) in prostate cancer (PCa) patients undergoing radical prostatectomy (RP) might not be applicable to men diagnosed via magnetic resonance imaging (MRI)-targeted biopsies.
Objective: To assess the accuracy of available tools to predict LNI and to develop a novel model for men diagnosed via MRI-targeted biopsies.
Design, setting, and participants: A total of 497 patients diagnosed via MRI-targeted biopsies and treated with RP and extended pelvic lymph node dissection (ePLND) at five institutions were retrospectively identified.
Outcome measurements and statistical analyses: Three available models predicting LNI were evaluated using the area under the receiver operating characteristic curve (AUC), calibration plots, and decision curve analyses. A nomogram predicting LNI was developed and internally validated.
Results and limitations: Overall, 62 patients (12.5%) had LNI. The median number of nodes removed was 15. The AUC for the Briganti 2012, Briganti 2017, and MSKCC nomograms was 82%, 82%, and 81%, respectively, and their calibration characteristics were suboptimal. A model including PSA, clinical stage and maximum diameter of the index lesion on multiparametric MRI (mpMRI), grade group on targeted biopsy, and the presence of clinically significant PCa on concomitant systematic biopsy had an AUC of 86% and represented the basis for a coefficient-based nomogram. This tool exhibited a

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higher AUC and higher net benefit compared to available models developed using standard biopsies. Using a cutoff of 7%, 244 ePLNDs (57%) 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 new nomogram vs Briganti 2012 vs Briganti 2017 vs MSKCC).
Conclusions: Available models predicting LNI are characterized by suboptimal accuracy and clinical net benefit for patients diagnosed via MRI-targeted biopsies. A novel nomogram including mpMRI and MRI-targeted biopsy data should be used to identify candidates for ePLND in this setting.
Patient summary: We developed the first nomogram to predict lymph node invasion (LNI) in prostate cancer patients diagnosed via magnetic resonance imaging-targeted biopsy undergoing radical prostatectomy. Adoption of this model to identify candidates for extended pelvic lymph node dissection could avoid up to 60% of these procedures at the cost of missing only 1.6% patients with LNI.

1. 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 node invasion (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 ePLND only for men at higher risk of LNI (>5% according to the European Association of Urology [EAU]-European Society for Radiotherapy & Oncology [ESTRO]-International Society of Geriatric Oncology [SIOG] guidelines) has been proposed as a reliable approach to minimize the morbidity associated with ePLND while missing only a low proportion of men with nodal metastases [4–7]. Tools currently available for identifying ePLND candidates are based on clinical parameters and showed excellent predictive accuracy on internal and external validation [4,5,8]. However, they are all based on standard systematic biopsies. Recent changes in the diagnostic pathway for clinically localized PCa with the introduction of multiparametric magnetic resonance imaging (mpMRI) and MRI-targeted biopsy might preclude their applicability to contemporary patients for three different reasons. (1) These tools were developed using historical cohorts of men undergoing systematic biopsy and the results might not be generalizable to men diagnosed via MRI-targeted biopsy [9]. (2) mpMRI and targeted biopsy provide additional relevant clinical information that is not considered by current models predicting LNI [10,11]. (3) A diagnostic strategy based on mpMRI and MRI-targeted biopsy would result in more significant tumors being identified and could reduce the risk of detection of insignificant PCa with a consequent change in disease characteristics identified on radical prostatectomy (RP) [12–14].

We hypothesized that currently available models predicting LNI might be characterized by suboptimal performance for contemporary patients diagnosed via MRI-targeted biopsy. Our aim was to assess the accuracy of available models for the identification of LNI in a large contemporary cohort of men diagnosed via MRI-targeted biopsy. Moreover, we developed a novel model including mpMRI and MRI-targeted biopsy data to improve the prediction of LNI for better identification of candidates for ePLND.

2. Patients and methods

2.1. Study population

After institutional review board approval, 581 patients who underwent MRI-targeted biopsy and RP with ePLND between 2016 and 2018 at five European tertiary referral centers were retrospectively identified. mpMRI and MRI-targeted biopsies were routinely recommended to patients with a clinical suspicion of PCa according to the judgment of the treating physician. Only patients with a positive MRI-targeted biopsy 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. Surgery was routinely proposed as a treatment option at each center. The decision to perform RP was left to the clinical judgment of the treating physician after discussion with each patient regarding the potential benefits and side effects of all available treatment modalities for the management of localized PCa [1]. Only patients who underwent anatomically defined ePLND with removal of the obturator, internal iliac, and external iliac lymph nodes were included [15]. All procedures were performed by high-volume surgeons at referral institutions. All specimens were submitted for pathologic evaluation in multiple packages and were evaluated by dedicated uropathologists [5].

2.2. mpMRI and biopsy technique

All patients underwent mpMRI using a 1.5- or 3-T scanner with or without an endorectal coil before prostate biopsy. The imaging protocol consisted of multiplanar T2-weighted images, diffusion-weighted imaging, dynamic contrast-enhanced MRI, and 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 Prostate Imaging-Reporting and Data System v.2 (PI-RADS) by high-volume dedicated radiologists [17]. Patients with a PI-RADS score ≥3 lesion on mpMRI were considered for prostate biopsies. Lesions with a PI-RADS score ≥3 on mpMRI were submitted to targeted biopsy. MRI-targeted biopsies were performed by experienced urologists using real-time transrectal ultrasound (TRUS) guidance via a software registration system. A minimum of two targeted cores were taken for each suspicious lesion on mpMRI. All patients also underwent concomitant systematic biopsy at the time of the targeted biopsy, with at least six random cores taken outside the MRI-targeted biopsy area. The number of targeted and systematic cores varied according to the judgment of each treating physician.

Table 1 – Descriptive statistics for 497 patients with clinically localized PCa diagnosed via MRI-targeted biopsy and treated with RP and extended pelvic lymph node dissection between 2016 and 2018

Parameter	pN0	pN1	*p* value [a]
Patients, *n* (%)	435 (87.5)	62 (12.5)	
Median age at surgery, yr (IQR)	65 (60–70)	64 (60–71)	0.8
Median preoperative PSA, ng/ml (IQR)	7.2 (5.1–11)	11 (6.7–21)	<0.001
Clinical stage, *n* (%)			
T1	335 (77)	30 (48)	<0.001
T2	96 (22)	21 (34)	
T3	4 (1)	11 (17)	
Median prostate volume, ml (IQR)	43 (33–55)	48 (34–59)	0.1
PI-RADS score, *n* (%)			
3	121 (28)	4 (6)	<0.001
4	235 (54)	26 (42)	
5	79 (18)	32 (52)	
Number of PI-RADS ≥3 lesions on mpMRI, *n* (%)			
1	299 (69)	38 (62)	0.5
2	91 (21)	20 (32)	
3	27 (6.2)	3 (4.8)	
≥4	18 (4.2)	1 (1.6)	
Median maximum index lesion diameter on mpMRI, mm (IQR) [b]	10 (9–14)	15 (10–18)	<0.001
Clinical stage on mpMRI, *n* (%)			
Organ-confined	358 (85)	29 (47)	<0.001
Extracapsular extension	49 (12)	19 (31)	
Seminal vesicle invasion	13 (3)	14 (22)	
Biopsy grade group overall, *n* (%)			
1	55 (13)	1 (2)	<0.001
2	236 (54)	15 (24)	
3	78 (18)	16 (26)	
4	45 (10)	15 (24)	
5	21 (5)	15 (24)	
Median cores taken overall, *n* (IQR)	16 (14–18)	16 (14–18)	0.2
Median positive cores overall, *n* (IQR)	5 (3–8)	5 (9–12)	<0.001
Median percentage positive cores overall, % (IQR)	33 (20–50)	55 (36–80)	<0.001
Median positive cores with highest-grade PCa, % (IQR) [c]	20 (12–38)	40 (24–60)	<0.001
Median positive cores with lower-grade, % (IQR) [c]	16 (8–27)	21 (10–30)	0.1
Grade group on MRI-targeted biopsy, *n* (%)			
1	72 (17)	1 (2)	<0.001
2	225 (52)	15 (24)	
3	72 (17)	16 (26)	
4	46 (11)	17 (27)	
5	20 (5)	13 (21)	
Target cores taken on MRI-targeted biopsy, *n* (%)			
2	165 (38)	27 (44)	0.1
3	94 (22)	18 (29)	
4	77 (18)	10 (16)	
≥5	99 (23)	7 (11)	
Positive cores on MRI-targeted biopsy, *n* (%)			
1	111 (26)	5 (8.1)	0.1
2	173 (40)	32 (51)	
3	69 (16)	16 (26)	
≥4	82 (18)	9 (15)	
Grade group on systematic biopsy, *n* (%)			
Negative	80 (18)	4 (7)	<0.001
1	100 (23)	6 (10)	
2	171 (40)	14 (23)	
3	44 (10)	15 (24)	
4	25 (6)	9 (15)	
5	15 (4)	14 (23)	
Median systematic cores taken, *n* (IQR)	12 (10–15)	12 (10–16)	0.2
Median cores with csPCa on systematic biopsy, % (IQR)	12 (0–37)	42 (17–76)	<0.001
Surgical technique, *n* (%)			
Open RP	40 (9.2)	3 (4.8)	0.2
Robot-assisted RP	395 (90)	59 (95)	
Gleason grade group on final pathology, *n* (%)			
1	15 (3.5)	0 (0)	<0.001
2	218 (50)	3 (4.8)	
3	147 (34)	25 (40)	
4	22 (5.1)	4 (6.5)	
5	30 (6.9)	30 (48)	

Table 1 (*Continued*)

Parameter	pN0	pN1	*p* value [a]
Pathologic stage, *n* (%)			
T2	215 (50)	3 (4.8)	<0.001
T3a	180 (41)	20 (32)	
T3b/4	40 (9.2)	39 (63)	
Positive surgical margins, *n* (%)	103 (24)	40 (48)	<0.001
Median lymph nodes removed, *n* (IQR)	15 (10–20)	17 (13–24)	0.01
Median positive lymph nodes, *n* (IQR)	–	1 (1–2)	–

PCa = prostate cancer; MRI = magnetic resonance imaging; RP = radical prostatectomy; IQR = interquartile range; PSA = prostate-specific antigen; PI-RADS = Prostate Imaging-Reporting and Data System; mpMRI = multiparametric MRI; csPCa = clinically significant PCa.
[a] The χ^2 test and Mann-Whitney test were used to compare proportions and medians, respectively.
[b] Available for 447 patients.
[c] Available for 480 patients.

2.3. Covariates and endpoints

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

The outcome of interest in our study was LNI, defined as the presence of positive lymph nodes at final pathology.

2.4. Statistical analyses

We first tested the accuracy of all three models available for predicting LNI among men treated with ePLND (Briganti 2012 [5], Briganti 2017 [15] and MSKCC [6] nomograms) in our series of men diagnosed with targeted biopsy. The regression coefficients 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 receiver operating characteristic curve (AUC). The extent of over- or underestimation associated with the use of these models was graphically depicted using calibration plots. Since the current models for predicting LNI do not allow for differentiation between MRI-targeted and systematic cores, we relied on the total number of positive cores obtained by adding the number of positive cores on MRI-targeted and systematic biopsy to estimate the risk of LNI according to these tools. Second, we developed a novel tool for predicting LNI among men diagnosed with MRI-targeted biopsy. Five multivariable models were fitted with mpMRI and targeted biopsy information. The first model was based on preoperative PSA, clinical stage at DRE, maximum diameter of the index lesion, and grade group on targeted biopsy. The second model included information on clinical stage based on preoperative imaging (ECE or SVI on mpMRI). The third model also included the number of positive cores on targeted biopsy. The fourth model included only MRI information and details on the percentage of cores with clinically significant PCa (defined as grade group $\geq$2) outside the target area (ie, on concomitant systematic biopsies). Finally, a model including MRI, MRI-targeted biopsy, and the presence of significant PCa on systematic biopsy was fitted. The discrimination of these models was quantified using AUC. Decision curve analysis (DCA) was used to compare the clinical net benefit associated with the use of these models [20]. The model with the highest AUC and highest clinical net benefit was used to develop a coefficient-based nomogram predicting LNI. Discrimination was corrected for overfitting using leave-one-out cross-validation. DCA was then used to determine the clinical net benefit associated with the use of the novel model in comparison to the Briganti 2012 [5], Briganti 2017 [15], and MSKCC [6] nomograms [20]. Finally, we investigated the clinical implications of using different cutoff points for the novel nomogram and the currently available tools. In particular, the sensitivity, specificity, number of LNI cases that would be missed, and number of ePLND procedures that would be avoided were calculated.

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

3. Results

3.1. Baseline characteristics

Overall, 65 patients (12.5%) had LNI (Table 1). The median number of lymph nodes removed was 15 (interquartile range 11–20). Preoperative PSA, median maximum diameter of the index lesion on mpMRI, clinical stage on DRE and mpMRI, biopsy 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 pN1 disease (all $p < 0.001$).

3.2. External validation of currently available tools

The AUC was 82% (95% confidence interval [CI] 77–88%) for the Briganti 2012 nomogram [5], 82% (95% CI 76–87%) for the Briganti 2017 nomogram [15], and 81% (95% CI 76–87%) for the MSKCC nomogram [6] in our cohort of patients diagnosed via targeted biopsies. The Briganti 2012, Briganti 2017, and MSKCC nomograms exhibited suboptimal calibration characteristics in our cohort (Supplementary Fig. 1).

3.3. Development of a novel nomogram predicting LNI

On univariable analyses, preoperative PSA, clinical stage on DRE and mpMRI, maximum diameter of the index lesion on mpMRI, biopsy grade group on targeted biopsy, and the percentage of cores with clinically significant PCa on

Table 2 – Multivariable logistic regression analyses assessing the prediction of LNI among patients diagnosed with MRI-TBx and treated with radical prostatectomy and extended pelvic lymph node dissection

	Model 1		Model 2		Model 3		Model 4		Model 5 [a]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Preoperative PSA	1.04 (1.02–1.07)	0.002	1.04 (1.01–1.08)	0.004	1.04 (1.01–1.07)	0.005	1.04 (1.02–1.08)	0.002	1.04 (1.01–1.08)	0.01
Clinical stage at DRE			–	–	–	–	–	–	–	–
T1c	1 (reference)									
T2	2.28 (1.14–4.60)	0.02								
T3	15.6 (3.78–54.4)	<0.001								
Clinical stage at mpMRI	–	–								
Organ-confined			1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Extracapsular extension			3.33 (1.56–7.09)	0.002	3.29 (1.60–6.75)	0.001	3.56 (1.66–7.64)	0.001	3.39 (1.56–7.28)	0.002
Seminal vesicle invasion			5.42 (1.93–15.8)	0.001	5.01 (1.84–13.2)	<0.001	4.69 (1.66–13.2)	0.003	4.36 (1.48–12.76)	0.007
Maximum diameter of mpMRI IL	1.06 (1.04–1.12)	0.04	1.04 (0.98–1.1)	0.1	1.03 (0.97–1.10)	0.2	1.05 (0.98–1.11)	0.1	1.03 (0.97–1.09)	0.3
Grade group at MRI-TBx							–	–		
1–2	1 (reference)		1 (reference)		1 (reference)				1 (reference)	
3	3.43 (1.40–8.37)	0.01	3.39 (1.57–7.10)	0.01	3.48 (1.41–8.59)	0.01			3.33 (1.36–8.12)	0.01
4–5	8.08 (3.68–17.7)	<0.001	5.51 (1.96–15.5)	<0.001	6.32 (2.85–14.1)	<0.001			6.08 (2.74–13.5)	<0.001
Number of positive cores at the target lesion	–	–	–	–	0.91 (0.67–1.22)	0.5	–	–	–	–
Percentage positive cores with csPCa on SBx	–	–	–	–	–	–	1.01 (1.00–1.02)	0.01	1.01 (1.00–1.02)	0.04
Model AUC (%)	82		83		84		79		86	

LNI = lymph node invasion; MRI = magnetic resonance imaging; OR = odds ratio; CI = confidence interval; PSA = prostate-specific antigen; DRE = digital rectal examination; mpMRI = multiparametric MRI; IL = index lesion; TBx = targeted biopsy; csPCa = clinically significant prostate cancer; SBx = systematic biopsy; AUC = area under the receiver operating characteristic curve.

[a] Based on 428 patients with complete available data and 54 events.

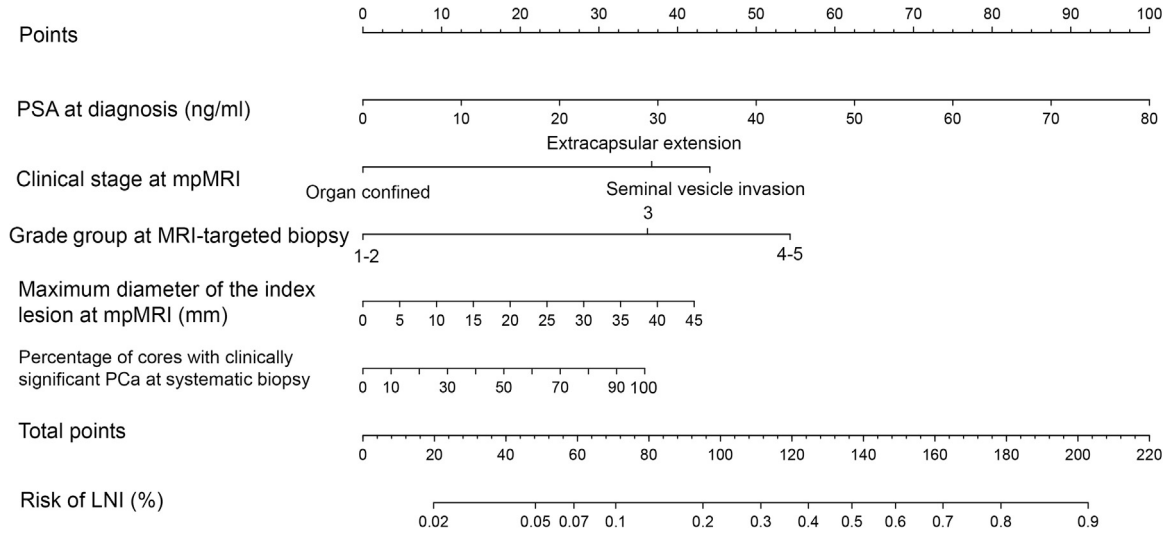

Fig. 1 – Novel nomogram predicting the probability of lymph node invasion (LNI) for patients diagnosed via targeted biopsies and treated with radical prostatectomy and extended pelvic lymph node dissection. mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PSA = prostate-specific antigen.

Table 3 – Systematic analyses of the novel nomogram-derived cutoffs used to discriminate between patients with or without hLNI

Nomogram cutoff	Number of patients, *n* (%)					
	Below the cutoff (PLND not recommended)			Above the cutoff (PLND recommended		
	Total	Without hLNI	With hLNI	Total	Without hLNI	With hLNI
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; hLNI = histologically confirmed LNI; PLND = pelvic lymph node dissection.

systematic biopsy were independent predictors of LNI (all $p \leq 0.04$; Table 2). Conversely, the number of positive cores on targeted biopsy was not associated with the risk of LNI on final pathology ($p = 0.7$). When these covariates were fitted in multivariable models, the one including clinical stage on mpMRI and information on the presence of clinically significant PCa on systematic biopsy achieved the highest AUC on internal validation (86%) and a slightly higher clinical net benefit below the 10% threshold probability (Supplementary Fig. 2). Therefore, this model was used as the basis for the novel nomogram predicting LNI. Figure 1 graphically depicts the multivariable effect of each variable on the risk of LNI in the form of a nomogram (coefficients are shown in Supplementary Table 1). Table 3 lists errors associated with the use of the novel nomogram when predicting a low risk of LNI. Using cutoffs of 5% and 7%, 217 (51%) and 244 (57%) ePLND procedures would be avoided and LNI would be missed in only four (1.8%) and four (1.5%) patients, respectively. DCA revealed that the novel nomogram improved clinical risk prediction against LNI threshold probabilities of ≤20% (Fig. 2).

3.4. *Comparison of the novel nomogram and currently available models*

In our series the novel nomogram had the highest net benefit when compared to the Briganti 2012 [5], Briganti 2017 [15] and MSKCC [6] models. Use of a 7% cutoff would avoid a slightly lower number of ePLNDs (57%) in comparison to the Briganti 2012 (66%), Briganti 2017 (60%), and MSKCC (62%) nomograms (Table 4). However, this would result in a substantially lower number of LNI cases missed in comparison to these 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).

4. 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 ePLND at the time of RP [1,4–6]. Although these models have been

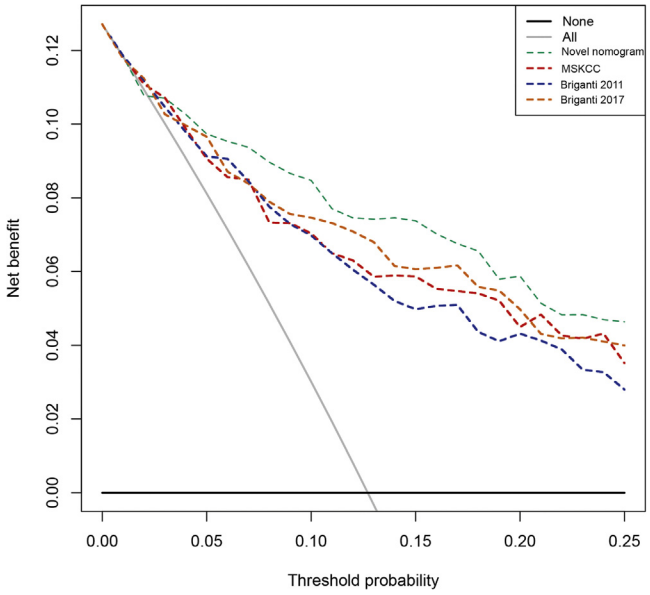

Fig. 2 – Decision curve analysis demonstrating the net benefit associated with use of the novel nomogram for detection of lymph node invasion in comparison to currently available tools (Briganti 2012 [5], Briganti 2017 [15], and MSKCC [6] nomograms).

constantly updated over the last few years and exhibited excellent performance characteristics [4–6,8], they were developed using data for men diagnosed via systematic biopsy. Thus, they might not be applicable to contemporary patients undergoing mpMRI and targeted biopsy. The quantity and quality of information for preoperative risk stratification substantially differ between men diagnosed via MRI-targeted biopsy and those undergoing 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. Thus, there are no data to assist clinicians in identifying PCa patients diagnosed via MRI-targeted biopsy who should be considered for ePLND. Given this paucity of data, we tested the performance characteristics of three models predicting LNI and developed a novel nomogram using data for a cohort of contemporary patients diagnosed via MRI-targeted biopsy.

Our results show that available tools predicting LNI are characterized by suboptimal discrimination, calibration, and clinical net benefit on external validation for men diagnosed via MRI-targeted biopsy. Moreover, adoption of these nomograms for selection of ePLND candidates in this setting would be associated with a substantially higher risk of missing LNI (up to 5%) in comparison to results reported for patients diagnosed via systematic biopsy alone [4,5]. Given the suboptimal performance characteristics of currently available models, we developed a novel nomogram specifically focused on patients diagnosed via MRI-targeted biopsy that achieved excellent discrimination on internal validation. Moreover, use of this nomogram was associated with a higher net benefit according to DCA. Our model has several novel elements compared to previously published nomograms. First, it considers results from MRI-targeted and systematic biopsies separately. In this light, the assumption that the number of positive cores in a targeted biopsy has the same prognostic impact as the number in a systematic biopsy might lead to overestimation of tumor volume when using the Briganti nomogram and, in turn, overestimation of the risk of LNI [4,5]. For example, a patient with three cores of grade group 2 PCa on targeted biopsy and negative random sampling would have the same risk of LNI as a man with three positive random cores in three 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 thus on the selection of ePLND candidates. We tried to overcome this issue by accounting for the different impact of the results for targeted and systematic cores. Moreover, the tumor volume of the index lesion in MRI-targeted biopsy was estimated using the maximum diameter on 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 clinically significant PCa on 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 [21–23], our study findings represent one of the first pieces of evidence supporting the concept that systematic cores should be taken in

Table 4 – Clinical implications of the novel and currently available nomograms using a cutoff of 7%

Nomogram	Patients, *n* (%)					
	Below the cutoff (PLND not recommended)			Above the cutoff (PLND not recommended)		
	Total	Without hLNI	With hLNI	Total	Without hLNI	With hLNI
Novel [a]	244 (57)	240 (98)	4 (1.6)	184 (43)	134 (73)	50 (27)
Briganti 2012 [5] [b]	329 (66)	314 (95)	15 (4.6)	167 (34)	120 (72)	47 (28)
Briganti 2017 [14] [c]	290 (60)	277 (95)	13 (4.5)	189 (39)	141 (77)	48 (23)
MSKCC [6] [d]	308 (62)	295 (96)	13 (4.2)	189 (38)	140 (74)	49 (26)

hLNI = histologically confirmed lymph node invasion; PLND = pelvic lymph node dissection.
[a] Data available for 428 patients.
[b] Data available for 496 patients.
[c] Data available for 479 patients.
[d] Data available for 497 patients.

addition to MRI-targeted cores to improve preoperative risk stratification in patients undergoing prostate biopsy. Addition of systematic cores to MRI-targeted biopsy would be in line with the multifocal nature of PCa, and could reduce the risk of upgrading at final pathology [24]. Finally, while previous nomograms included T stage determined via DRE, the inclusion of information on the presence of ECE or SVI as assessed via mpMRI substantially improved the AUC of our predictive tool. Moreover, more accurate estimation of tumor burden can be obtained on mpMRI [25] rather than considering the percentage of positive cores at systematic biopsy as a proxy for tumor volume [5]. Although MRI is characterized by poor sensitivity in detecting positive nodes in the pelvic area [26], our results, together with those observed in previous studies, support the importance of considering parameters obtained during prostate mpMRI such as tumor volume and T stage to improve our ability to predict the risk of LNI [10,27,28]. Nonetheless, MRI-derived data should be considered together with MRI-targeted biopsy information to achieve the highest predictive accuracy in preoperative estimation of the risk of LNI.

From a clinical standpoint, our findings show that currently available nomograms for identifying ePLND candidates have suboptimal performance when applied to individuals diagnosed via MRI-targeted biopsies. The adoption of a nomogram specifically developed using data for patients diagnosed via MRI-targeted biopsy could avoid approximately 60% of ePLND procedures at the cost of missing only 1.6% LNI cases. Of note, our novel nomogram is applicable exclusively to men with a positive MRI-targeted biopsy with concomitant systematic biopsy, as currently indicated by guidelines [1]. Moreover, the risk of LNI should not be estimated using this model for individuals who were diagnosed via systematic biopsy with a negative MRI-targeted biopsy. For these patients, predictive tools developed using data for men diagnosed with systematic biopsy such as the Briganti 2012 [5], Briganti 2017 [15], and MSKCC [6] nomograms are more suitable.

Despite several strengths, our study is not devoid of limitations. First, the excellent performance characteristics of our nomogram might be related to the use of internal validation [29]. Therefore, formal external validation is needed before implementation of this model in clinical practice. Moreover, the relatively small sample size and number of events might limit its generalizability. It should also be highlighted that our model was developed using data for patients treated at high-volume European institutions, where the majority of men are Caucasians. Thus, caution is needed when generalizing our results to other races. Second, our study is limited by its retrospective nature and thus potentially influenced by patient selection biases typical of all retrospective series. Third, the multi-institutional nature of our study might have introduced heterogeneity in mpMRI and biopsy protocols. However, all patients underwent MRI-targeted biopsy at tertiary referral centers included in this multi-institutional study, mpMRI scans were evaluated by high-volume dedicated radiologists, and MRI-targeted and systematic biopsies were performed by experienced physicians and evaluated by dedicated uropathologists. Finally, the extent of nodal dissection varied according to the treating institutions and physicians. Nonetheless, removal of the obturator, internal iliac, and external iliac lymph nodes represented the minimum requirement for defining ePLND and these stations were dissected free in all patients included in our study.

5. Conclusions

Currently available models predicting LNI are characterized by suboptimal accuracy and clinical net benefit for patients diagnosed via MRI-targeted biopsies. A novel nomogram specifically focused on men undergoing mpMRI targeted and concomitant systematic biopsies should be used to identify patients at higher risk of LNI who should be considered for ePLND. Adoption of this model using a 7% cutoff would avoid approximately 60% of ePLND procedures at the cost of missing only 1.6% of LNI cases.

Author contributions: Alberto Briganti 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.

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Analysis and interpretation of data: Gandaglia, Briganti.
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Statistical analysis: Gandaglia, Dell'Oglio, Briganti.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.10.012.

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