Research article

External validation of the Briganti nomogram to predict lymph node invasion in prostate cancer - setting a new threshold value.

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Abstract: *Introduction*: The aim of the study was to test and validate the performance of the 2012 Briganti nomogram as a predictor for pelvic lymph node invasion (LNI) in men who underwent radical prostatectomy (RP) with extended pelvic lymph node dissection (PLND), to examine their performance and to analyse the therapeutic impact of using different nomogram cut-off . *Material and methods:* The study group consisted of 222 men with clinically localized prostate cancer (PCa) who underwent RP with ePLND between 01/2012 and 10/2018. Measurements included: preoperative PSA, clinical stage (CS), primary and secondary biopsy Gleason pattern and percentage of positive cores. The area under curve (AUC) of the receiver operator characteristic analysis was appointed to quantify accuracy of the primary nomogram model to predict LNI. The extent of estimation associated with the use of this model was graphically depicted using calibration plots. *Results:* The median number of removed lymph nodes was 16 (IQR 12-21). A total of 53 of 222 patients (23,9%) had LNI. Preoperative clinical and biopsy characteristics differed significantly (all $p<0.005$) between men with and without LNI. A nomogram-derived cut-off of 7% could lead to a reduction of 43% (95/222) of lymph node dissection, while missing 19% (10/53) of patients with LNI. The sensitivity, specificity, and negative predictive value associated with the 7% cut-off were 81.1%, 50.3%, and 96.3%, respectively. *Conclusions:* Analysed nomogram demonstrated high accuracy for LNI prediction. A nomogram-derived cutoff of 7% confirmed good performance characteristics within a first external validation cohort from Poland.

Keywords: prostate cancer; radical prostatectomy; pelvic lymph node dissection; lymph node invasion; preoperative nomogram

1. Introduction

In Europe, prostate cancer (PCa) is the most common cancer in men, accounting for 24% of all cancers diagnosed in 2018, equivalent to 450,000 new cases [1]. Poland ranks first in the incidence rates for men and second in the list of causes of cancer deaths (approx. 9.5%) [2]. Despite the widespread use of screening tests by determining PSA's level, some patients are still diagnosed with a high local stage at diagnosis and are referred to as high risk on the D'Amico scale [3]. There is no doubt that radical treatment brings a much more significant benefit in overall survival and cancer-specific survival. Moreover, radical prostatectomy was found to be most beneficial in patients with localised and locally-advanced PCa [4,5]. Pelvic lymph node dissection (PLND) represents the important staging procedure in identifying patients with LNI and should be performed in patients with intermediate or high-risk PCa with ommiting patients with low-riskdisease [6].It allows selecting lymph nodes affected by the neoplastic invasion out of all the collected ones [7]. However, this procedure carries the risk of complications; therefore, it should be avoided if the risk of LNI is low. The decision to undertake a given treatment strategy depends on the preoperative PSA level, clinical stage, Gleason grade, and histopathological examination. Since the primary tumor is the source of growth factors most likely responsible for the localization of distant metastases, it should be treated as effectively as possible while minimizing any complications.

Several studies have shown that the use of extended lymphadenectomy (ePLND) is recommended for each PLND indication [8–10]. To date, a number predictive models have been developed to determine the risk of LNI in patients undergoing ePLND. Two most used (2021 Briganti and MSKCC) of them have been externally validated [11,12]. The developed predictive models require periodic checks to ensure their current patients' accuracy. The result is a very accurate nomogram after internal validation. However, the lack of external validation is an obstacle to implementing the nomogram into wide clinical practice [13,14]. It is also impossible to obtain older patient data due to the use of different, more favorable grading of PCa in modern patients [15,16]. Finally, according to the European Association of Urology guidelines, ePLND should be performed for patients when the predicted probability of LNI exceeds 5% in Briganti calculation, but in a few recent reports 7% was suggested as an optimal cut-off with a similar sensitivity and specificity and higher number of patients for whom PLND could be safely omitted [6,17]. Our study aimed to update and verify the nomogram predicting LNI on a different external patient data set and to find the most accurate cut-off for performing ePLND.

2. Materials and Methods

Data of 638 patients who underwent radical prostatectomy with ePLND due to a high-risk prostate cancer according to the d'Amico scale (PSA> 20ng/ml, clinical stage ≥T2c or biopsy Gleason sum 8-10) have been retrospectively studied. The collected data comes from 01/2012 to 10/2018 from the Clinical Department of Urology and Urology Oncology in Wrocław. 222 patients met the criteria - they had information on preoperative PSA, age, Gleason score, clinical stage, and had at least 8 fully described sections taken during ePLND.

The clinical stage of the tumor was assessed according to the updated TNM classification from 2016, the prostate biopsy was obtained by TRUS guided systemic

biopsy, and PSA was determined before the DRE examination [18]. Pathologic analysis of the biopsy and post-operative specimens was performed by dedicated uropathologists following the International Society of Urological Pathology's modifications in 2014 [19,20]. All specimens were collected and tested under the Stanford protocol guidelines, and their staging was determined according to the American Committee's guidelines for the Staging System for Prostate Cancer [21,22]. Patients were preoperatively examined for metastases using abdominal CT with contrast and bone scintigraphy. An updated Briganti nomogram was calculated for each subject in this group based on age, PSA, TNM stage, Gleason score, and percentage of samples taken [23].

Extended pelvic lymphadenectomy (ePLND) involves removal of fatty tissue from the obturator fossa area (along the obturator nerve and the external iliac vein) along the internal and external iliac arteries, extending to the distal segment of the common iliac artery. The lateral border is the pelvic wall, and the middle is the perivesical fat. The distal margin is the deep femoral vein. Each stations are collected separately according to their anatomical location for selective histopathological examination [24].

This retrospective study was conducted in agreement with the declaration of Helsinki of 1975, revised in 2013 and approved by the Ethics Committee of Wrocław Medical University (KB/217/20).

3. Statistical analysis

Descriptive statistics focus on the frequencies and proportions of categorical variables. Means, medians, and interquartile ranges are presented for continuously coded variables. The Chi-square and t-tests for the independent sample were used to compare the statistical significance of differences, respectively, of proportions and means. Analyzes focused on testing the accuracy and calibration of a previously updated and internally validated nomogram to predict the likelihood of LNI in ePLND. Therefore, this nomogram was externally validated using predefined regression coefficients. The area under the curve (AUC) of the receiver operator characteristic analysis was used to quantify the model accuracy for LNI prediction. The extent of the overestimation or underestimation was investigated graphically in random calibration plots. Like Briganti, the specificity, sensitivity, and negative predictive value (NPV) were systematically assessed for each LNI probability threshold obtained from the nomogram [25].

All tests were two-sided with statistical significance set at $P < 0.07$. The analyzes were performed using the statistical package for R (R base for statistical calculations, version 2.1.13).

4. Results

The characteristics of 222 patients and the primary cohort on the basis of which the nomogram was created are presented in comparative Table 1. Additionally, the table's data has been divided according to the occurrence of lymph node involvement (LNI) in the study group. Overall, LNI was found in 23.9% of patients (n = 53). The mean PSA value for patients with lymph node involvement was 24 ng/ml compared to 12.2 ng/ml without LNI, IQR: 12.7 - 33.8 vs. 7.2 - 17.6, respectively, with $p < 0.001$. Overall, patients with LNI had a higher clinical stage (T3) than those without, 41,5 vs 13,1% respectively ($p < 0.001$).

Measurement of the biopsy secondary Gleason pattern also showed higher values in patients with LNI (52.8%) than without (21.9%, p <0.001). The mean number of positive cores (6 vs. 5, p = 0.001) as well as the mean percentage of positive cores (50% vs. 42%, p <0.001) were significantly higher in patients with LNI. The description of other clinico-pathological features is also listed in Table 1.

Table 1. Descriptive Perioperative Characteristics of the External Validation Cohort of the Updated Lymph Node Invasion Nomogram, As Well As of the Development Cohort are Displayed [25]

	Comparison of preoperative variables between development and external validation cohort			Comparison within the external validation cohort		
	Updated nomogram development cohort (2006–2010) [25]	External validation cohort (2012–2018)	*p*	Absence of LNI	Presence of LNI	*p*
No (%)	588 (-)	222 (-)		169 (76.1)	53 (23.9)	
Age, years						
Median	66	65	**<0.001**	64	66	**0.045**
IQR	60-70	60-68		59-68	62-70	
PSA, ng/ml						
Median	6.3	13.6	**<0.001**	12.2	24.0	**<0.001**
IQR	4.8-8.9	7.6-21.1		7.2-17.6	12.7-33.8	
No. of biopsy cores taken						
Median	17	12	**<0.001**	12	12	0.639
IQR	13-24	12-12		12-12	10-12	
No. of positive biopsy cores						
Median	6	5	**<0.001**	5	6	**0.001**
IQR	3-10	3-8		3-7	4-10	
Perc. of positive biopsy cores						
Median	36	42	0.296	42	50	**<0.001**
IQR	17-61	25-66		25-58	33-91	
Clinical stage:						
T1	373 (63.4)	10 (4.5)	**<0.001**	8 (4.7)	2 (3.8)	**<0.001**
T2	184 (31.3)	168 (75,7)		139 (82,2)	29 (54,7)	
T3	31 (5.3)	44 (19,8)		22 (13,1)	22 (41,5)	
Primary biopsy Gleason pattern:						
≤3	488 (83.0)	155 (69.8)	**<0.001**	130 (76.9)	25 (47.2)	**<0.001**
≥4	100 (17.0)	67 (30.2)		39 (23.1)	28 (52.8)	
Secondary biopsy Gleason pattern:						
≤3	406 (69.0)	157 (70.7)	0.707	132 (78.1)	25 (47.2)	**<0.001**
≥4	182 (31.0)	65 (29.3)		37 (21.9)	28 (52.8)	

Clinical risk classification:						
Low		16 (7.8)		15 (9.6)	1 (2.0)	**<0.001**
Intermediate		45 (22.0)		44 (28.2)	1 (2.0)	
High		144 (70.2)		97 (62.2)	47 (96.0)	
Pathological stage:						
pT2	431 (73.3)	108 (48.6)	**<0.001**	103 (60.9)	5 (9.4)	**<0.001**
pT3a	97 (16.5)	48 (21.6)		33 (19.5)	15 (28.3)	
pT3b	58 (9.9)	66 (29.7)		33 (19.5)	33 (62.3)	
pT4	2 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)	
Pathological primary Gleason pattern:						
≤3		141 (63.5)		119 (70.4)	25 (47.2)	**0.003**
≥4		81 (36.5)		50 (29.6)	28 (52.8)	
Pathological secondary Gleason pattern:						
≤3		142 (64.0)		119 (70.4)	23 (43.4)	**<0.001**
≥4		80 (36.0)		50 (29.6)	30 (56.6)	
Number of positive lymph nodes						
Median	2	2	**<0.001**	0	2	**<0.001**
IQR	1-3	1-5		0-0	1-5	
Number of lymph nodes removed						
Median	19	16	**<0.001**	15	20	**<0.001**
IQR	15-25	12-21		10-20	16-26	
Biopsy Gleason Grading Group						
1		76 (34.2)		64 (37.9)	12 (22.7)	**<0.001**
2		52 (23.4)		46 (27.2)	6 (11.3)	
3		29 (13.1)		22 (13.0)	7 (13.2)	
4-5		65 (29.3)		37 (21.9)	28 (52.8)	
Pathological Gleason Grading Group						
1		26 (11.7)		26 (15.4)	0 (0.0)	**<0.001**
2		58 (26.1)		49 (29.0)	9 (17.0)	
3		58 (26.1)		44 (26.0)	14 (26.4)	
4-5		80 (36.1)		50 (29.6)	30 (56.6)	

n (%) or median [IQR], PSA, prostate-specific antigen; LNI, lymph node invasion; IQR, interquartile range

The accuracy of the external validation performed was estimated at 0.734 (n = 222). Figure 1 shows the ROC calibration curve, demonstrating the dependence of specificity (X-axis) on sensitivity (Y-axis). A designated segment at an angle of 45° defines the ideal relationship between specificity and sensitivity for a given test. Points above this segment suggest that sensitivity is superior to specificity, which means that there are too many false positives versus false negatives. The opposite dependence occurs in the case of points located below this section. The entire calibration curve for our external validation of the

nomogram runs above it, which means that at the moment, with the help of the nomogram, we are incorrectly finding too many false LNIs. However, the degree of over-detection is low due to the entire assay's high accuracy.

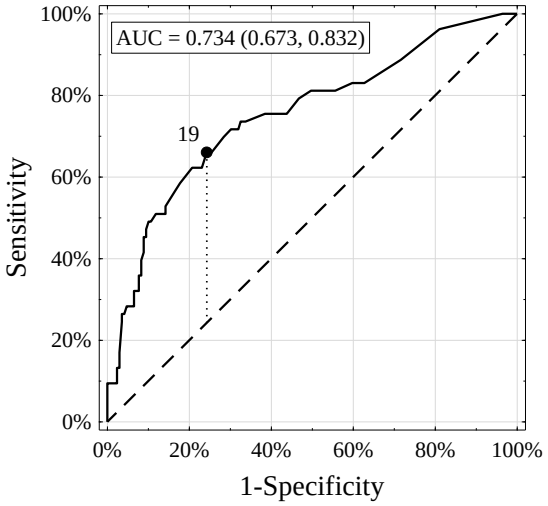

Figure 1. Receiver-operator characteristic (ROC) and area under curve of the nomogram described by Briganti et al. in 222 patients with risk of LNI.

Table 2 shows the probability of LNI occurrence resulting from applying the Briganti nomogram in the cohort where external validation was performed. For each cut-off point of the nomogram, the actual number of men with and without LNI was calculated. In addition, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the individual cut-off values of the nomogram were characterized. ePLND could be omitted in 95 men (42.8%), but this group would include 10 patients with LNI (18.9% of all LNI patients) using the nomogram cut-off of 7%. The sensitivity and specificity of the 7% cut-off were 81.1% and 50.3%, respectively, and NPV and PPV were 96.3% and 33.9%, respectively.

Table 2. Analyses of the Nomogram-Derived Cut-Offs of the Externally Validated Updated LNI Nomogram

Cut-off, %	TN+FN	TN	FN	TP+FP	FP	TP	NPV	PPV	**TPR**	**TNR**
1	6 (3.6)	6 (3.6)	0 (0)	216 (97.3)	163 (96.4)	53 (100)	100	24.5	100	3.6
2	34 (15.3)	32 (18.9)	2 (3.8)	188 (84.7)	137 (81.1)	51 (96.2)	94.1	27.1	96.2	18.9
3	54 (24.3)	48 (28.4)	6 (11.3)	168 (75.7)	121 (71.6)	47 (88.7)	88.9	28.0	88.7	28.4
4	73 (32.9)	64 (37.9)	9 (17.0)	150 (67.6)	106 (62.7)	44 (83.0)	97.4	29.3	83.0	37.6
5	77 (34.7)	68 (40.2)	9 (17.0)	145 (65.3)	101 (59.8)	44 (83.0)	97.2	30.3	83.0	40.2
6	85 (38.3)	75 (44.4)	10 (18.9)	137 (61.7)	94 (55.6)	43 (81.1)	96.9	31.4	81.1	44.4

7	95 (42.8)	85 (50.3)	10 (18.9)	127 (57.2)	84 (49.7)	43 (81.1)	96.3	33.9	81.1	50.3
8	101 (45.5)	90 (53.3)	11 (20.8)	121 (54.5)	79 (46.7)	42 (79.2)	95.6	34.7	79.2	53.3
9	108 (48.6)	95 (56.2)	13 (24.5)	114 (51.4)	74 (43.8)	40 (75.5)	96.3	35.1	75.5	56.2
10	112 (50.5)	99 (58.6)	13 (24.5)	110 (49.5)	70 (41.4)	40 (75.5)	95.0	36.4	75.5	58.6
15	133 (59.9)	118 (69.8)	15 (28.3)	89 (40.1)	51 (30.2)	38 (71.7)	93.7	42.7	71.7	69.8
20	154 (69.4)	134 (79.3)	20 (37.7)	68 (30.6)	35 (20.7)	33 (62.3)	93.3	48.5	62.3	79.3
25	170 (76.6)	145 (85.8)	25 (47.2)	51 (23.0)	24 (14.2)	27 (50.9)	92.5	52.9	51.9	85.8
30	179 (80.6)	152 (89.9)	27 (50.9)	43 (19.4)	17 (10.1)	26 (49.1)	91.6	60.5	49.1	89.9

Several cut-offs and their ability of discrimination between patients with (n = 53) or without (n = 169) histologically confirmed lymph node invasion were systematically examined. LNI - lymph node invasion; ePLND - extended pelvic lymph node dissection; NPV - negative predictive value; PPV - positive predictive value; **TPR - sensitivity; TNR - specificity**; TN+FN - patients in whom ePLND is not recommended according to the cut-off (below cut-off); TN - patients below cut-off without histologic LNI; FN - patients below cut-off with histologic LNI; TP+FP - patients in whom ePLND is recommended according to the cut-off (above cut-off); FP - patients above cut-off without histologic LNI; TP - patients above cut-off with histologic LNI.

5. Discussion

According to the latest EAU guidelines, the ePLND template is recommended whenever PLND is required [8–10,26]. There are different LNI predictive nomograms [11,27–30]. In our study, we performed an external validation of the Briganti nomogram for the Polish cohort [23]. So far, it has not been checked and formalized for the Polish center's needs. Our main goal was to optimize the local cohort nomogram in patients after radical prostatectomy. We tested different cut-off values that could be used to define with highest accuracy, patients in whom ePLND should be executed. The latest reports indicate the need to change the cut-off value for performing ePLND at RP from 5% to 7%, resulting from the nomogram [17].

Performed analyses showed some critical findings. Firstly, patients undergoing ePLND in different clinical centers may show very different clinical stages and pathological neoplastic changes. Two components are particularly noticeable compared to the primary medium where the Briganti nomogram was developed [23]. In our clinic, the frequency of LNI 23,9% comparing to only 8.3% in original series, which shows that some centers operate on patients at a higher stage of advancement than others. This fact may significantly affect the effectiveness of the prediction tools used, as in some centers, less aggressive tumors are removed. Secondly, we recorded a higher degree of malignancy in the Gleason primary and secondary patterns than in the Briganti's group. In conclusion, our data clearly show that similar cohorts of men with prostate cancer may differ in terms of tumor characteristics, which means that external, cohort-specific validation is required before using a prognostic tool in routine clinical practice.

After testing as part of our external validation on an independent cohort, the nomogram's predicted accuracy was 73.4%, which is preferably compared to the 87.6% obtained by Briganti's internal validation team. The similar overall accuracy of the internal and external validation results indicates that, despite significant discrepancies in biopsy advancement and LNI operations frequency, this nomogram can adjust to these differences with a slight loss of accuracy. It follows that the nomogram's overall accuracy can be

expected to remain similar, even if the target population differs from the original cohort. However, differences indicate that the initially optimal cut-off value will not be ideal for other cohorts.

We analyzed many different potential cut-off values, comparing them with the results obtained by Briganti's team, to determine the best one for our cohort. In the original series, a threshold of 5% was adopted. In studied group, the value that separates patients in whom ePLND should be performed from patients in whom ePLND should be omitted is 7%. This value is the optimal compromise between the number of avoided ePLNDs (42.8% of all patients) compared to the number of missed LNI patients. (18.9% of all LNI patients) [31]. Alternatively, using the proposed initially 5% cut-off, we would have to perform ePLND on a much larger number of men (66,3% vs. 57,2%), and only a small number of patients with LNI would benefit from it (false negative 17% vs. 19%). Despite our choice of a cut-off value of 7%, different sites may choose a different cut-off point that is optimal for their cohort. If the acceptable compromise between the number of ePLNDs performed and the missed LNIs is considered too high, a lower cut-off should be chosen. Conversely, a higher cut-off value may be considered when dealing with a population of patients with better prognostic characteristics and a less malignant course.

The study's overall accuracy is one of the few critical benchmarks in the predictive tool. Calibration or correlation between predicted and observed indicators, represents another key volatility. In particular, the first one shows the operation of the prognostic tool for a specific risk group in the studied population. In a key range of values, it can assess in detail the relationship between the observed LNI risk and that predicted using the nomogram. This range is 0-10%, and within its range, there should be a cut-off point at which ePLND will not be performed. More than 10% of specialists, based on patient's clinical picture, would be inclined to perform this procedure. Therefore, the nomogram's proper calibration is the most essential for this key cut-off range. It includes the gray area of the uncertainty of the need to perform the ePLND. It is noteworthy that the nomogram's calibration was not perfect and revealed an overestimation in terms of the predicted LNI probability. It was insignificant, which indicates the predictive stability of LNI occurrence using this nomogram. This discovery requires meticulous consideration, indicating the appropriate cut-off value. Therefore, it is important to remember and carefully analyze the potential source of a possible error and exercise caution when making final clinical decisions.

Despite its value, our study is not without limitations. First of all, the population compared to external validation in the current study was smaller than in the development cohort of the updated LNI nomogram, which consisted of patients treated in one Polish institution. As mentioned earlier, it would be optimal to externally validate the predictive model in an inter-institutional, possibly international, cohort to obtain even more generalized data. Previous studies, relying on multi-agency data, have found significant differences in accuracy between the different external validation cohorts [32]. However, there may also be problems with data from many institutions, especially in predicting LNI in patients undergoing ePLND. While there is a general perception that ePLND should be performed with each PLND, the quality or scope of such PLND may vary [10].

Additionally, due to the scientific development on PLND over the years, the calendar year of the operation performed may affect the number of lymph nodes collected [33]. Moreover, different institutions may use different surgical approaches (open prostatectomy vs. laparoscopic prostatectomy), which may also influence the results [34,35]. Even though all surgeons used the same template for ePLND, differences between surgeons in lymph node removal efficiency and lymph node detection rate due to different surgical techniques or surgeon's experience may have influenced the results [36].

There may also be differences with the templates that were used in ePLND. Mattei and colleagues carefully examined the prostate's primary lymphatic landing site and found that with classical ePLND only 63% of the lymph nodes will be removed [37]. The extent of classical ePLND by removing the lymph nodes along the common iliac arteries to the intersection of the ureter would increase the percentage of removed lymph nodes to 75%. Consequently, external validation in a different cohort may have led to different accuracy estimates. Another limitation is that patients were somehow pre-selected for ePLND before RP due to the previous nomogram. However, even if patients have been pre-selected, the updated nomogram's performance can still be tested within the current patient cohort. Finally, our study's retrospective nature is another limitation that may have impacted the results.

6. Conclusions

In conclusion, the external validation of the Briganti nomogram on the Polish cohort shows good accuracy and precise calibration. The cut-off value of the data calculated by the nomogram was optimized to 7%, which gave better results than the proposed treshold of 5%. Additional external validation studies should be performed and the predictive value adjusted to the local cohort.

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Institutional Review Board Statement: This retrospective study was conducted in agreement with the declaration of Helsinki of 1975, revised in 2013 and approved by the Ethics Committee of Wrocław Medical University (KB/217/20). Regional Health authorities deleted from the database available for analysis any subject identifiers, aiming at maintaining data anonymity and confidentiality. Thus, none of the patients could be identified, either in this study or in the entire extracted database.

Informed Consent Statement: Due to retrospective nature of this study and maintaining data anonymity and confidentiality, patient consent was waived.

Data Availability Statement: The datasets analyzed are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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