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External Validation of a Multiparametric Magnetic Resonance Imaging–based Nomogram for the Prediction of Extracapsular Extension and Seminal Vesicle Invasion in Prostate Cancer Patients Undergoing Radical Prostatectomy

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Abstract

The nomogram reported by Gandaglia et al (The key combined value of multiparametric magnetic resonance imaging, and magnetic resonance imaging-targeted and concomitant systematic biopsies for the prediction of adverse pathological features in prostate cancer patients undergoing radical prostatectomy. Eur Urol 2020;77:733–41) predicting extracapsular extension (ECE) or seminal vesicle invasion (SVI) has been developed using multiparametric magnetic resonance imaging (MRI) parameters and MRI-targeted biopsy. We aimed to validate this nomogram externally by analyzing 566 patients harboring prostate cancer diagnosed on MRI-targeted biopsy followed by radical prostatectomy. At final pathology, 37% and 12% patients had ECE and SVI, respectively. Performance of the nomogram, in comparison with the Memorial Sloan Kettering Cancer Center (MSKCC) model and Partin tables, was evaluated using discrimination, calibration, and decision curve analysis. Regarding ECE prediction, the nomogram showed higher discrimination (71.8% vs 69.8%, $p = 0.3$ and 71.8% vs 61.3%, $p < 0.001$), and similar miscalibration and net benefit for probability threshold above 30% when compared with MSKCC model and Partin tables, respectively. Performance of the nomogram with regard to SVI was comparable in terms of discrimination (68.5% vs 70.4% vs 67.8%, $p \geq 0.6$), presenting a slight overestimation on calibration plots and a net benefit for probability threshold above 7.5%. This is the first multicentric study that externally validates a nomogram predicting ECE and SVI in patients diagnosed with MRI-targeted biopsy. Its

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performance was less optimistic than expected, and implementation of MRI in this setting was not associated with a clear improvement in patient selection and clinical usefulness when compared with available models. We proposed an updated version of the nomogram predicting ECE using the recalibration method, which leads to an improvement in its performance and needs to be validated in another external set.
Patient summary: We validate a prediction tool based on multiparametric magnetic resonance imaging (MRI) parameters and MRI-targeted biopsy predicting extracapsular extension and seminal vesicle invasion at radical prostatectomy. An improvement of patient selection was not clearly demonstrated when compared with available models based on clinical parameters, and implementation of MRI in this setting still needs to be clarified.

Extracapsular extension (ECE) and seminal vesicle invasion (SVI) are known to be important risk factors for adverse oncologic outcome after radical prostatectomy and play an important role when planning a surgical treatment (ie, avoiding surgical margin in case of preservation of the neurovascular bundle or seminal vesicle tips) and evaluating the need for adjuvant treatment [1–3]. Several prediction tools, such as the Memorial Sloan Kettering Cancer Center (MSKCC) model and Partin tables, have been developed using cohorts of patients diagnosed by systematic biopsies [4]. Recently, Gandaglia et al [5] proposed novel nomograms using multiparametric magnetic resonance imaging (MRI) parameters and International Society of Urological Pathology (ISUP) grade group on MRI-targeted biopsy, showing a better net clinical benefit than previous models. We herein present external validation of this nomogram, and compared it with the MSKCC model and Partin tables using contemporary series of patients harboring prostate cancer (PCa) diagnosed on MRI-targeted biopsy and operated across multiple European institutions.

After obtaining institutional review board's approval, data of 708 patients undergoing radical prostatectomy for localized PCa across European centers (Belgium, France, Switzerland, and Italy) were retrospectively analyzed between March 2012 and September 2019. All prebiopsy magnetic resonance images, consisting of T1- and T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast enhancement, were read by dedicated uroradiologists following the European Society of Urogenital Radiology guidelines. The Prostate Imaging-Reporting and Data System (PI-RADS) version 2 protocol was used to define suspicious lesions (ie, PI-RADS score $\geq$3) [6]. MRI scans performed before 2016 were initially described using PI-RADS version 1 score (n = 94, 17% of cohort) and were then retrospectively reclassified according to PI-RADS version 2 score by local dedicated uroradiologists [7]. MRI/ultrasound elastic fusion targeted and systematic biopsies using the KOELIS system (KOELIS, La Tronche, France) were then performed. We excluded patients with incomplete data regarding biopsy, MRI, or pathologic results (n = 142). External validation followed the TRIPOD recommendations [8]. Previously published regression coefficients for each parameter were used to calculate the individual risk of ECE and SVI (Supplementary Table 1). Performance of the nomogram was evaluated in terms of discrimination and calibration. Discrimination was quantified using the area under the receiver operating characteristic curve (AUC). The extent of over- and underestimation was graphically described using calibration plots. Decision curve analysis (DCA) was used to evaluate the net benefit of the model. Comparisons with the MSKCC model and Partin tables were based on discrimination, calibration, and DCA [4,9]. A two-sided p value of $<$0.05 defined statistical significance. All statistical analyses were performed with STATA 14.1 (StataCorp, College Station, TX, USA).

Overall, 566 patients were included in the final analysis and general characteristics of the validation set are represented in Table 1. The median (interquartile range) preoperative prostate-specific antigen (PSA) was 7.7 ng/mL (5.7–11). Overall, ECE and SVI at MRI analysis were described in 79 (14%) and 16 patients (2.8%), respectively. The median diameter of the index lesion was 13 mm (10–17). The median numbers of biopsy cores taken were 12 (10–12) and 4 (3–6) for systematic and targeted biopsies, respectively. ECE and SVI at final pathology were present in 37% and 12% of patients, respectively.

The nomogram achieved the highest AUC for ECE prediction, although a significant threshold was not reached when compared with the MSKCC model (71.8%, 95% confidence interval or CI [67.3–76.2], vs 69.8%, 95% CI [65.4–74.2], p = 0.3), as opposed to Partin tables, which had significantly lower discrimination (71.8%, 95% CI [67.3–76.2], vs 61.3%, 95% CI [56.6–66], $p < 0.001$). SVI prediction remained similar to the MSKCC model and Partin tables (68.5%, 95% CI [61.1–75.9] vs 70.4%, 95% CI [63.5–77.3] vs 67.8%, 95% CI [61.2–74.4], $p \geq 0.6$). Miscalibration of the nomogram predicting ECE, characterized by systematic overestimation of the predicted risk, is shown in Figure 1A. Regarding SVI, close predicted and observed risks were noted with a tendency toward slight overestimation for predicted probabilities above 10% (Fig. 1B). The calibration plots of the MSKCC model and Partin tables predicting ECE and SVI are presented in Supplementary Figure 1. DCA demonstrated a slight improvement of the net benefit for the ECE and SVI predictions for probability thresholds above 30% and 7.5%, respectively, in comparison with the MSKCC model and Partin tables (Fig. 1C and D).

The aim of the present study was to validate a nomogram externally based on MRI and MRI-targeted biopsy, which were recently introduced in the PCa diagnosis pathway in order to improve patient selection and significant cancer detection [1,10]. Our results validate this nomogram despite

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Table 1 – Descriptive perioperative characteristics of the development set published by Gandaglia et al [5] and external validation set.

Variable	Development set (Gandaglia et al [5]) *n* = 614	External validation set *n* = 566
Age at surgery (yr), median (IQR)	65 (60–69)	65 (61–70)
Preoperative PSA (ng/mL), median (IQR)	7.8 (5.5–11)	7.7 (5.7–11)
Clinical stage at DRE, *n* (%)		
T1	438 (71)	317 (56)
T2	176 (29)	218 (38)
T3	0 (0)	6 (1)
PI-RADS score of index lesion, *n* (%)		
3	130 (21)	48 (9)
4	310 (50)	258 (46)
5	174 (28)	248 (44)
Maximum lesion diameter of index lesion at MRI (mm), median (IQR)	11 (9–15)	13 (10–17)
ECE at MRI, *n* (%)	100 (16)	79 (14)
SVI at MRI, *n* (%)	27 (4.4)	16 (2.8)
ISUP grade group (overall), *n* (%)		
1	56 (9.1)	70 (12)
2	318 (52)	253 (45)
3	131 (21)	135 (24)
4	75 (12)	78 (14)
5	34 (5.5)	30 (5)
Number of cores taken, median (IQR)	15 (13–18)	15 (14–17)
Number of positive cores, median (IQR)	5 (3–8)	6 (3–8)
ISUP grade group on targeted biopsy, *n* (%)		
Negative	0 (0)	60 (11)
1	80 (13)	92 (16)
2	311 (51)	194 (34)
3	124 (20)	126 (22)
4	68 (11)	69 (12)
5	31 (5)	25 (4)
Number of cores taken at targeted biopsy, median (IQR)	4 (2–5)	4 (3–6)
Number of positive cores at targeted biopsy, median (IQR)	2 (2–3)	3 (1–4)
ISUP grade group on systematic biopsy, *n* (%)		
Negative	101 (16)	62 (11)
1	140 (23)	130 (23)
2	237 (39)	201 (36)
3	74 (12)	95 (17)
4	35 (5.7)	62 (11)
5	27 (4.4)	14 (2.5)
Number of cores taken at systematic biopsy, median (IQR)	11 (9–13)	12 (10–12)
Number of positive cores at systematic biopsy, median (IQR)	2 (1–5)	3 (1–5)
Surgical technique, *n* (%)		
Open	109 (18)	73 (13)
Laparoscopic	0 (0)	64 (11)
Robotic	505 (82)	429 (76)
ISUP grade group at final pathology, *n* (%)		
1	21 (3.4)	26 (4.6)
2	299 (49)	250 (44)
3	217 (35)	199 (35)
4	24 (3.9)	47 (8.3)
5	53 (8.6)	44 (7.8)
ECE at final pathology, *n* (%)	333 (54)	209 (37)
SVI at final pathology, *n* (%)	88 (14)	68 (12)
Positive surgical margin, *n* (%)	143 (23.3)	159 (28)
Lymph node status, *n* (%)		
N0	555 (90.4)	463 (82)
Nx	0 (0)	61 (11)
N1	59 (9.6)	52 (9.2)

DRE = digital rectal examination; ECE = extracapsular extension; IQR = interquartile range; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; SVI = seminal vesicle invasion.

a less optimistic prediction performance than the internal validation study, which was associated with higher discrimination (73% vs 72% for ECE and 81% vs 69% for SVI), better calibration, and net benefit at DCA.

This performance may induce us to think that MRI does not add significant information to improve current prediction models. Indeed, the sensitivity of MRI to predict ECE and SVI is known to be limited, and this was confirmed in the internal (30% and 31%, respectively) as well as external validation studies (38% and 28%, respectively) [5,11]. However, several recent studies have already demonstrated an extra value of including MRI in multivariable prediction

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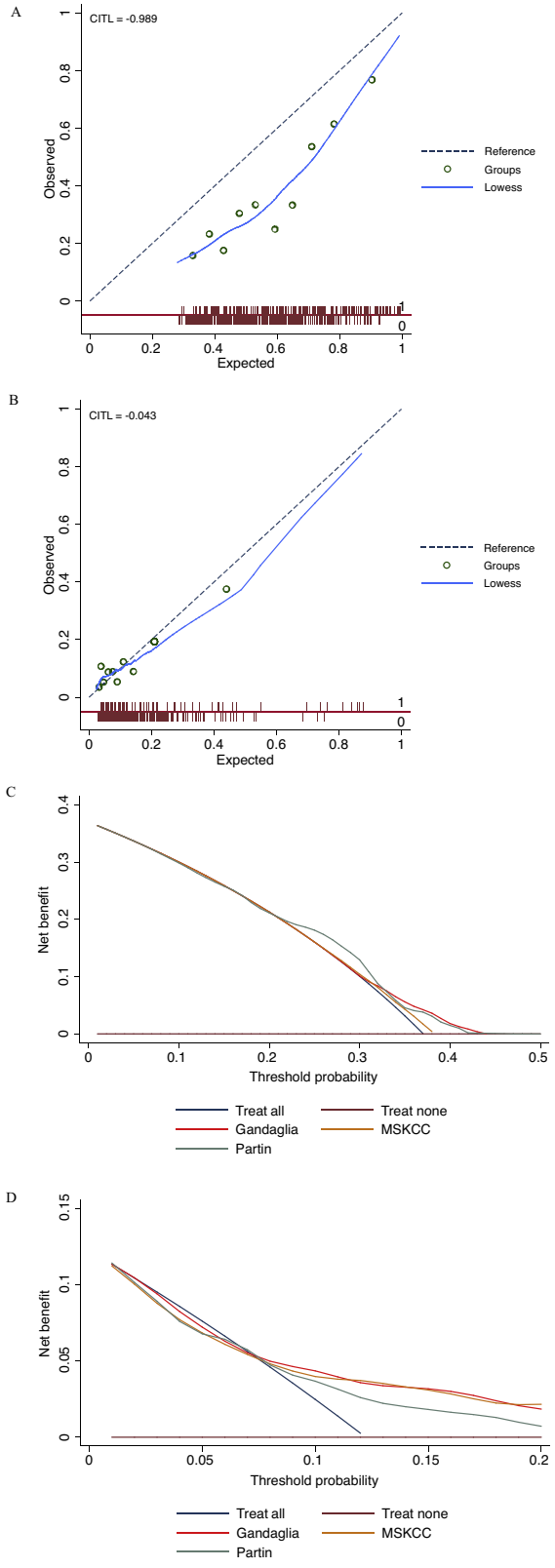

Fig. 1 – Calibration plots of predicted (ie, expected) versus observed probabilities of (A) ECE and (B) SVI using nomogram described by Gandaglia et al [5]. Decision curve analysis showing the net benefit associated with the use of the nomogram described by Gandaglia et al [5], MSKCC model, and Partin tables predicting (C) ECE and (D) SVI. CITL - = calibration in the-large; ECE = extracapsular extension; MSKCC = Memorial Sloan Kettering Cancer Center; SVI = seminal vesicle invasion.

tools such as the Cancer of the Prostate Risk Assessment score, Partin tables, or MSKCC model, with improvement of their performance [12–15]. In confirmation, the present study showed that the nomogram described by Gandaglia et al [5] using MRI as a staging method, in combination with several clinical-biochemical parameters, allowed slight improvement in discrimination, especially for ECE prediction, and net benefit for both ECE and SVI predictions. Of note, the interpretation of MRI is highly dependent on the radiologist's experience. In the present study, we included patients recruited and treated in academic centers with dedicated uroradiologists with a probable reduction of this potential bias [16].

Although the nomogram described by Gandaglia et al [5] predicting ECE exhibited good accuracy and net benefit, a systematic miscalibration characterized by a predicted risk permanently higher than the observed risk was noted. One of the hypothesized explanations can be the difference across the internal and external validation sets. However, preoperative characteristics seemed to be relatively similar in terms of PSA values, distribution of biopsy ISUP grade groups, diameter of the index lesions, and clinical staging using MRI. Moreover, we calculated a percentage of positive systematic biopsies of 17%, while we were unable to compute such a value for the original set of Gandaglia et al [5]. On final pathologic specimen evaluation, proportion of pathologic ECE was much lower in our study (37% vs 54%), while that of SVI was rather similar (12% vs 14%). This lower proportion of pathologic ECE could be explained by one of the two mains reasons: (1) a preoperative parameter influencing ECE prediction was not taken into account in the nomogram or (2) the interpretation of MRI was misleading knowing its low sensitivity. Indeed, either the risk of ECE described on MRI was falsely low compared with the observed risk in the internal validation cohort or the risk on MRI was falsely elevated in our set of patients, or rather, the truth lies between these two extremes. Finally, another explanation could be the definition of the ISUP grade group, which is still a matter of debate, while its interpretation remains challenging, with an elevated risk of discordance across pathologists according to their expertise [17].

In order to fit the novel nomogram proposed by Gandaglia et al [5] to our set of patients, it seemed interesting to perform an update of the prediction tool in order to improve its performance. Concerning the nomogram predicting ECE, the problem of calibration in the large (ie, difference between the mean observed and predicted outcomes, which should to be close to 0 in case of perfect calibration) associated with the permanent overestimation of the predicted risk induced us to propose a simple adjustment of the intercept of the logistic regression formula ("recalibration") [18,19]. We calculated a correction factor, which was added to the intercept, considering the predicted and observed risks (Supplementary Fig. 2). When applied in the validation set, we observed a performance improvement, although discrimination remains similar as there was no change in ranking of the predictor. The updated nomogram presented almost perfect calibration

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and a better net benefit starting from a probability threshold of >20% (Supplementary Figs. 3 and 4).

ECE, SVI, and positive surgical margins are well-documented risk factors for biochemical recurrence [20,21]. Borawski et al [22] have demonstrated that non–organ-confined disease is associated with an increased risk of positive surgical margins in comparison with organ-confined disease (31% vs 2.5%). Moreover, the association between a nerve-sparing procedure and positive surgical margins has long been controverted [20]. Yet, a recent large prospective trial study by Soeterik et al [23] clarified and confirmed such an association: on multivariate analysis, nerve sparing conferred a significant increase in the odds of having an ipsilateral positive margin (odds ratio = 1.42, 95% confidence interval [1.14–1.82]). Finally, a randomized phase 2 trial did not demonstrate a true benefit of preserving the tip of the seminal vesicles in urinary and sexual functional results [24]. As such, it seems clinically relevant to know the risk of facing non–organ-confined disease before surgery, in order to plan correctly the intervention and minimize the risk of positive surgical margins. Nonetheless, available prediction tools showed low utility of decision curves for low probability thresholds below 20% for ECE and 7.5% for SVI [5]. A cutoff has not yet been proposed, as it depends on the surgeon's experience, localization of the tumor, surgical approach, and accepted risk of positive margin by the surgeon and the patient. On this point, further studies will be needed to find a response to this practical question.

We acknowledge that the retrospective nature of the present analysis introduced a potential selection bias. Although all centers adhered to the guidelines and terminologies used in current practice, the absence of central reviewing leads to consequent heterogeneity in MRI reporting and biopsy analysis due to the implication of multiple physicians with different ranges of expertise. Furthermore, although this reflects current real-life clinical practice, MRI and pathologic specimen analysis were not read blindly to the clinical characteristics of the patients and disease. Moreover, patients included at the beginning of the recruitment period were described according to a previous reporting system (ie, PI-RADS version 1 score) and were then retrospectively reclassified. Nonetheless, differences between PI-RADS versions 1 and 2 are still debated [25,26]. Targeted biopsies were all performed using the KOELIS system, reducing subjectivity and variability compared with the cognitive approach, and data were analyzed by dedicated uroradiologists and uropathologists. Finally, the sample size and the number of events, particularly SVI at final pathology, were relatively small and can have an impact on the detection of change in performance in the validation set. The updated model should also be validated externally before its generalization.

In conclusion, we report external validation of the nomogram predicting the risk of ECE and SVI in patients operated by radical prostatectomy and diagnosed by MRI-targeted and systematic biopsies. We demonstrated a less optimistic performance characterized by good discrimination, disappointing calibration regarding ECE prediction, and a small net benefit. Implementation of MRI in this setting still needs to be clarified, as it was not associated with a clear improvement in patient selection and clinical usefulness when compared with the MSKCC model and Partin tables, especially for low probability thresholds. An updated nomogram predicting ECE was able to improve its performance and needs to be validated in another external set.

***Author contributions*:** Romain Diamand 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.

Study concept and design: Diamand.
Acquisition of data: Diamand, Ploussard, Roumiguié, Oderda, Benamran, Fiard, Quackels, Assenmacher, Simone, Van Damme, Malavaud, Iselin, Descotes, Roche, Peltier.
Analysis and interpretation of data: Diamand, Albisinni.
Drafting of the manuscript: Diamand.
Critical revision of the manuscript for important intellectual content: Roumeguère, Ploussard, Fiard.
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Appendix A. Supplementary data

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