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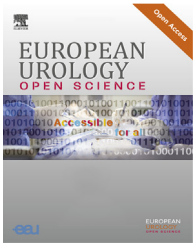

Brief Correspondence

External Validation of a Prediction Model for Side-specific Extraprostatic Extension of Prostate Cancer at Robot-assisted Radical Prostatectomy

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Abstract

The aim of this study was to externally validate a nomogram for side-specific extraprostatic extension (EPE) of prostate cancer (PCa) at robot-assisted radical prostatectomy (RARP). A prospectively maintained cohort of 1170 consecutive patients with PCa who underwent RARP at two high-volume RARP centres between 2018 and 2021 was retrospectively evaluated. Biopsies and magnetic resonance imaging (MRI) scans were centrally reviewed. The side-specific probability of EPE was calculated for each prostate side using prostate-specific antigen density, ipsilateral highest biopsy Gleason score, and ipsilateral MRI tumour stage. Model discrimination and calibration were analysed using the area under the receiver operating characteristic curve (AUC), calibration in the large, and calibration curves. The rate of side-specific EPE was 30% among 2254 prostate sides; the mean predicted rate was also 30%. The discriminatory value of the model was good, with an AUC of 80.4% (interquartile range 78.4–82.3%). The predicted probabilities matched the observed probabilities well (intercept −0.02, slope 1.053). There was slight underestimation of the observed probabilities from 70% upwards. In conclusion, an easy-to-use nomogram for side-specific EPE at RARP was externally validated and can be applied to virtually all PCa patients.

Patient summary: A prediction model used to decide whether to spare the neurovascular bundles during removal of the prostate can be applied to virtually all prostate cancer patients.

The goal of robot-assisted radical prostatectomy (RARP) is to remove the prostate and prostate cancer (PCa) completely, while preserving continence and erectile function. Preserving the neurovascular bundles (NVBs) is associated with better functional outcomes, but is also associated with more positive surgical margins (PSMs), especially for patients with extraprostatic extension (EPE) [1–3]. Magnetic resonance imaging (MRI) alone is not accurate enough to exclude EPE. Therefore, several nomograms have been developed to predict pathological EPE at the time of RARP. A nomogram with easy-to-use biopsy and MRI variables predicting side-specific EPE was recently developed and externally validated [4]. At the time of model development, MRI-targeted biopsy was not yet recommended by the PCa guidelines. Since MRI has become prominent in the diagnosis of PCa, the current PCa patient population may have dif-

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ferent clinical characteristics, which could potentially affect model performance [5]. The aim of this study was to externally validate the nomogram in a different cohort of PCa patients.

The study was approved by the local institutional review board (registration number IRBd19-248). This is a retrospective evaluation of prospectively obtained data. The prediction model was tested in a cohort of patients with biopsy-proven PCa who underwent RARP between January 2018 and August 2021 in two high-volume RARP centres. Patients in the current cohort underwent ultrasound-guided systematic biopsy, MRI-targeted biopsy, or both. All patients underwent 3-T MRI before RARP. All externally produced MRI scans and all externally obtained biopsy material were centrally reviewed by radiologists and pathologists with experience in PCa differentiation. Patients were excluded if they had received previous hormonal treatment or previous radiation therapy to the prostate.

The following data were collected for all patients: prostate-specific antigen (PSA), prostate volume, PSA density, clinical tumour stage, MRI tumour stage, biopsy type, biopsy International Society of Urological Pathology grade group, percentage of positive cores, D'Amico risk group, and presence or absence of pathological EPE.

The probability of EPE was calculated for each prostate side using the B values from the nomogram [4]. The area under the receiver operating characteristic curve (AUC) was calculated to assess the discriminatory value of the model. Model calibration was analysed using calibration in the large and visual inspection of the calibration curve. All analyses were performed with R v4.0. (R Foundation for Statistical Computing, Vienna, Austria).

The baseline characteristics of the 1170 patients are presented in Table 1. The median PSA and PSA density were 8.5 ng/ml (interquartile range [IQR] 6.0–13) and 0.20 ng/ml/ml (IQR 0.13–0.31), respectively. Systematic, MRI-guided, and systematic + MRI-guided biopsy were performed in 481 (41%), 109 (9.3%), and 580 (50%) patients, respectively. D'Amico low-, intermediate-, and high-risk categories were present in 73 (6.2%), 509 (44%), and 588 (50%) patients, respectively. Unilateral biopsy without a contralateral biopsy was performed in 86 patients; therefore, the side-specific probability of EPE could be calculated for 2254 prostate sides. Pathological EPE was found in 667 (30%) prostate sides.

The model showed good discriminatory value in this population (AUC 80.4%, IQR 78.4–82.3%). The mean predicted probability of EPE was 30%, meaning that the model is calibrated in the large. Figure 1 shows the calibration curve. The predicted rates match the observed rates well, with an intercept of −0.015 and slope of 1.053. There was slight underestimation at predicted probabilities ≥70%.

The current study is the first to externally validate the prediction model for side-specific EPE created by Soeterik et al [4]. The model incorporates easy-to-use variables obtained from daily clinical practice. The patients in this cohort underwent MRI-guided or systematic and MRI-guided biopsy more often than in the development cohort (59% vs 44%). The results in the current study show that the model has good discriminatory value. The AUC is comparable to the values of 78%, 83%, and 81% for the development and validation cohorts in the original study. The model calibration is moderately good. Strong calibration means that the predicted risk corresponds to the observed rate for every possible combination of predictor values; this is a utopian goal and is not achieved in clinical practice [6]. The clinical consequence of EPE underestimation at predicted probability values ≥70% is questionable as nerve-sparing surgery (NSS) would generally be discouraged at these thresholds. Therefore, we conclude that this prediction model can be applied to virtually all patients, as the diagnostic approach for PCa is changing to an MRI-first pathway [5].

Prediction models can support clinicians in decisions on whether to preserve the NVBs. Determining a threshold at which NSS should be discouraged is subject to clinician-specific and patient-specific factors. Different patients may value functional outcomes differently and the threshold for NSS can be set accordingly. Therefore, incorporating results from prediction models should always be part of the shared decision-making process in clinical practice.

Another potential application of this nomogram would be to determine a threshold for which immediate frozen section (IFS) analysis (eg, NeuroSAFE) could be performed [7]. With NeuroSAFE, a secondary resection of the NVB

Table 1 – Baseline characteristics for the 1170 patients and 2254 prostate sides

	Patient level	Side-specific level
Number	1170	2254
Median prostate-specific antigen, ng/ml (IQR)	8.5 (6.0–13)	8.5 (6.0–13)
Median prostate-specific antigen density, ng/ml/ml (IQR)	0.20 (0.13–0.31)	0.20 (0.13–0.31)
Clinical tumour stage, *n* (%)		
cT1c	454 (39)	
cT2ab	315 (27)	
cT2c	263 (23)	
cT3	137 (12)	
MRI tumour stage, *n* (%)		
Benign; mT0	43 (3.7)	538 (24)
mT2ab	359 (30)	352 (16)
mT2c	402 (34)	943 (42)
mT3a	270 (23)	299 (13)
mT3b	96 (8.2)	122 (5.4)
Biopsy type, *n* (%)		
Systematic	481 (41)	
MRI-targeted	109 (9.3)	
Systematic and MRI-targeted	580 (50)	
Median percentage of positive biopsy cores, % (IQR)	43 (28–63)	43 (14–75)
Biopsy International Society of Urological Pathology grade, *n* (%)		
Benign	0	516 (23)
Grade 1	172 (15)	453 (20)
Grade 2	484 (51)	674 (30)
Grade 3	252 (22)	314 (14)
Grade 4	158 (14)	180 (8.0)
Grade 5	104 (8.9)	117 (5.2)
D'Amico risk group, *n* (%)		
Low	73 (6.2)	
Intermediate	509 (44)	
High	588 (50)	
Extraprostatic extension (pT3), *n* (%)	558 (48)	667 (30)

IQR = interquartile range; MRI = magnetic resonance imaging.

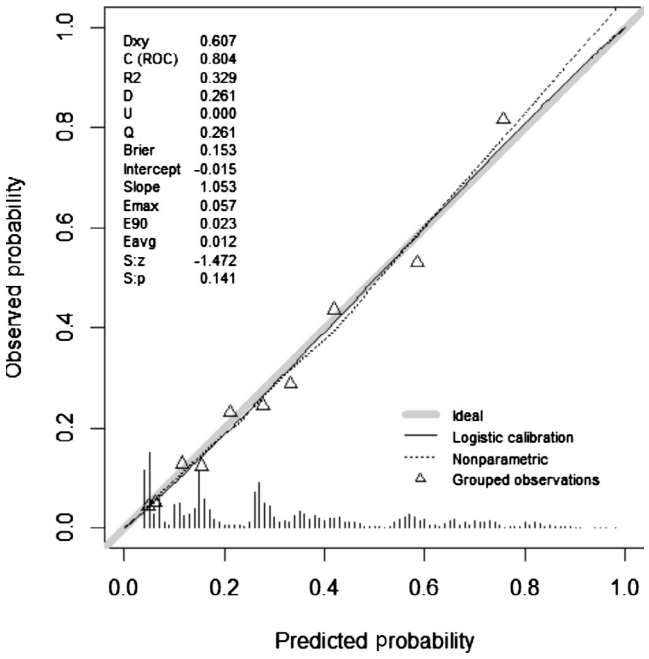

Fig. 1 – Calibration curve for the model. Slight underestimation of the true rate of extraprostatic extension is evident from predicted risk of 70% upwards.

can be performed in cases with a positive IFS result. In our opinion, NeuroSAFE is particularly useful in patients with higher risk of pathological EPE, as it may allow NSS in a group who would otherwise receive more radical treatment. The nomogram could be of aid in selecting these intermediate- to high-risk patients.

Strengths of this study include central review of all external biopsy material and MRI scans by experienced pathologists and radiologists. The side for EPE was not reported for 15 patients. These cases were re-reviewed by a pathologist. Consequently, there were no missing data in this study except for the 86 patients who received MRI-targeted unilateral biopsy without a contralateral biopsy. A limitation of the nomogram is that it predicts side-specific EPE, while a per-lesion prediction or dorsolateral EPE prediction might be more interesting in the decision-making process for NSS. High-risk, ventrally located tumours may still be eligible for NSS, as this location can be avoided when dissecting the NVBs.

In conclusion, the nomogram fits well to a contemporary cohort of prostate cancer patients and adds meaningful clinical information to MRI staging. This nomogram could be a valuable tool to select patients for side-specific nerve-sparing surgery.

Author contributions: Hans Veerman 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: Veerman.
Acquisition of data: Veerman, van der Poel.
Analysis and interpretation of data: Veerman, Heymans.
Drafting of the manuscript: Veerman.
Critical revision of the manuscript for important intellectual content: Heymans, van der Poel.
Statistical analysis: Veerman, Heymans.
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References

[1] Soeterik TFW, van Melick HHE, Dijksman LM, Stomps S, Witjes JA, van Basten JPA. Nerve sparing during robot-assisted radical prostatectomy increases the risk of ipsilateral positive surgical margins. J Urol 2020;204:91–5. https://doi.org/10.1097/JU.0000000000000760.
[2] Ficarra V, Novara G, Ahlering TE, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol 2012;62:418–30. https://doi.org/10.1016/j.eururo.2012.05.046.
[3] Ficarra V, Novara G, Rosen RC, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2012;62:405–17. https://doi.org/10.1016/j.eururo.2012.05.045.
[4] Soeterik TFW, van Melick HHE, Dijksman LM, et al. Development and external validation of a novel nomogram to predict side-specific extraprostatic extension in patients with prostate cancer undergoing radical prostatectomy. Eur Urol Oncol 2020. https://doi.org/10.1016/j.euo.2020.08.008, In press.
[5] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62. https://doi.org/10.1016/j.eururo.2020.09.042.
[6] Van Calster B, Nieboer D, Vergouwe Y, De Cock B, Pencina MJ, Steyerberg EW. A calibration hierarchy for risk models was defined: from utopia to empirical data. J Clin Epidemiol 2016;74:167–76. https://doi.org/10.1016/j.jclinepi.2015.12.005.
[7] Schlomm T, Tennstedt P, Huxhold C, et al. Neurovascular structure-adjacent frozen-section examination (NeuroSAFE) increases nerve-sparing frequency and reduces positive surgical margins in open and robot-assisted laparoscopic radical prostatectomy: experience after 11069 consecutive patients. Eur Urol 2012;62:333–40. https://doi.org/10.1016/j.eururo.2012.04.057.

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