An Updated Model for Predicting Side-specific Extraprostatic Extension in the Era of MRI-targeted biopsy

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ABSTRACT

Purpose: Accurate prediction of extraprostatic extension (EPE) is pivotal for surgical planning. Herein, we aimed to provide an updated model for predicting EPE among patients diagnosed with MRI-targeted biopsy.

Materials and methods: We analyzed a multi-institutional dataset of men with clinically localized prostate cancer diagnosed by MRI-targeted biopsy and subsequently underwent prostatectomy. To develop a side-specific predictive model, we considered the prostatic lobes separately. A multivariable logistic regression analysis was fitted to predict side-specific EPE. The decision curve analysis was used to evaluate the net clinical benefit. Finally, a regression tree was employed to identify three risk categories to assist urologists in selecting candidates for nerve-sparing, incremental nerve sparing and non-nerve-sparing surgery

Results: Overall, data from 3,169 hemi-prostates were considered, after the exclusion of prostatic lobes with no biopsy-documented tumor. EPE was present on final pathology in 1,094 (34%) cases. Among these, MRI was able to predict EPE correctly in 568 (52%) cases. A model including PSA, maximum diameter of the index lesion, presence of EPE on MRI, ISUP grade, and percentage of positive cores in the ipsilateral hemi-prostate achieved an AUC of 81% after internal validation. Overall, 566, 577, and 2,026 observations fell in the low-, intermediate- and high-risk groups. The rate of EPE across the groups was: 5.1%, 14.9%, 48% for the low-, intermediate- and high-risk group, respectively.

Conclusion: In this study we present an update of the first side-specific MRI-based nomogram for the prediction of extraprostatic extension together with updated risk categories to help clinicians in deciding on the best approach to nerve-preservation.

1. Introduction

The optimal surgical approach for prostate cancer (PCa) is a clinical challenge, as balancing the risk of tumor's extra-prostatic extension (EPE) against the one of positive surgical margins (PSMs) is not an easy task[1]. In fact, the presence of PSMs on the prostatectomy specimen can impact post-surgical outcomes, such as urinary continence and erectile function [2,3], biochemical and clinical recurrence[4], and, ultimately, healthcare costs, related to adjuvant radiation therapy and/or systemic thearapies[5,6]. Thanks to the introduction of mpMRI in the PCa diagnostic pathway, a greater level of knowledge on the location and extent of clinically significant cancer has been achieved[7]. This can allow surgeons to better tailor surgery to each individual. Yet, the accuracy of MRI is sometimes limited in EPE identification. Prior studies have demonstrated that the combination of clinical and MRI data outperform either clinical data or MRI alone in identifying EPE[8-10].

In 2018, we proposed the first side-specific model based on MRI for EPE prediction[8]. Other models were published after, yet, to the best of our knowledge, none relies solely on data from patients diagnosed with MRI-targeted biopsy[8-10]. For this reason, we aimed to provide an updated model for predicting EPE in a contemporary cohort, as MRI-targeted biopsy represents the standard of care for prostate cancer diagnosis and this results in better tumor characterization.

2. Patients and methods

2.1. Study population

We identified 2,076 individuals from a multi-institutional database. Data for the study was provided by 19 tertiary referral centers. The study was endorsed by the Young Academic Urologists working group on PCa of the EAU.

All patients underwent mpMRI prior to biopsy. Patients with a sole midline lesion were not eligible for the study. Imaging was performed and reported according to the Prostate Imaging Reporting and Data System (PI-RADS) recommendations[11]. All men underwent systematic plus targeted biopsy of PI-RADS ≥3 lesion(s) as well as radical prostatectomy between 2016 and 2021 at each tertiary center. All patients had clinically node-negative disease either on conventional imaging or PSMA PET. The study was approved by the local ethical committees.

2.2. Multiparametric MRI and biopsy technique

All patients underwent a 1.5- or 3-T MRI before prostate biopsy with or without an endorectal coil in compliance with the European Society of Urogenital Radiology guidelines[12]. In all centers, the imaging protocol consisted of multiplanar T2-weighted images, diffusion-weighted imaging, dynamic contrast-enhanced MRI, and T1-weighted images with fat suppression. Overall, imaging protocol did not change substantially over the study period. Images were read and reported according to the PI-RADS guidelines by high-volume, dedicated radiologists[11,12]. The PI-RADS v.2 has been used since 2016[11]. In general, radiologists were not blinded to the PSA values and other clinical characteristics while reporting the scans.

All lesions with a PI-RADS score of ≥3 on MRI were subject to targeted biopsy. A minimum of two targeted cores per lesion were obtained. Biopsies were performed by experienced urologists with the use of real-time transrectal ultrasound guidance with or without software-based MR/ultrasound fusion. All systematic cores were taken at the time of fusion biopsy outside the MRI-targeted area(s) according to standard protocols.

2.3. Outcomes and Covariates

The study outcome was the presence of EPE, defined as a breach of the pseudocapsule and direct extension of the prostatic carcinoma into the peri- prostatic tissue in at least one specific area on final pathology.

For analyses purposes, we considered the two lobes of the prostate separately, as previously described[8-10,13,14]. Because of our side-specific approach, biopsies that were negative on one side of the prostate were not considered for the analysis on ipsilateral EPE.

Imaging variables were considered as side-specific and comprised, for each side: highest PI-RADS score, greater lesion's diameter with the highest PI-RADS, EPE, and SVI. Regarding highest side-specific biopsy ISUP, we evaluated ISUP on both targeted and systematic biopsy.

EPE reporting (coded as side-specific) was left to the discretion of the reporting radiologists and was based on any of the following criteria: presence of neurovascular bundle thickening, abutment, bulge, loss of or irregular prostatic capsule, capsular enhancement or measurable extraprostatic disease detected at high-volume T2-weighted images. SVI (coded as side specific) was defined as: low signal intensity of T2-weighted images and/or abnormal contrast enhancement within or along the seminal vesicle, obliteration of the angle between the prostatic base and the SV, and presence of tumor extension from the prostate to the seminal vesicle.

68   Biopsy data were also side specific. This entailed for each side: ISUP, total positive

69   core length in mm, and percentage of positive cores.

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71   *2.4 Statistical analyses*

72   To investigate differences among prostatic lobes with EPE and those without, we

73   used the Kruskal-Wallis test and X^2, respectively. In an effort to evaluate when to perform

74   nerve sparing surgery, a binary multivariable logistic regression model was fit to predict

75   ipsilateral EPE. We evaluated the role of PSA, index lesions, greater diameter, EPE on MRI,

76   highest ISUP grade and percentage of positive cores in the hemi-prostate considered. Since

77   the database encompassed data from different centers, we included center clustering in the

78   logistic regression using a generalized estimating model through the *cluster* function in

79   Stata®. Internal validation was performed with the leave-one-out cross validation. The

80   predicted probability of EPE, after internal validation, was used to calculate the area under

81   the receiver operator curve (AUC), and to assess net benefit associated with its use applying

82   a decision curve analysis (DCA).

83   Ultimately, we relied on the regression tree to identify the optimal cutoffs for

84   performing nerve preservation. The regression tree was fed with the predicted probability of

85   EPE on final pathology and set to identify three categories. The number of categories was

86   selected *a priori* in an effort to aid clinicians in selecting individuals for nerve sparing

87   preservation in toto, incremental nerve sparing or non-nerve sparing.

88   Statistical analyses were performed on Stata 14 (Stata-CorpLP, College Station, TX,

89   USA). All tests were two-sided, with a significance level set at *p*<0.05.

90

3. Results

3.1 Population characteristics

Overall, 2,076 patients were considered. Median (IQR) patients' age was 66 (62-70). We relied on a total of 3,169 hemi-prostates, after the exclusion of prostatic lobes with no biopsy-documented tumor. Overall, EPE was present on final pathology in 1,094 (34%) prostate lobes. Preoperative PSA, highest PIRADS score, EPE and SVI on MRI, index lesion's greatest diameter, ISUP grade and percentage of positive cores differed significantly between the groups with and without EPE (all $P \leq 0.001$), **Table 1**. Among prostate lobes with EPE on final pathology, MRI was suspected for EPE in 568 (52%) cases.

3.2 EPE prediction

Table 2 displays the multivariable binary logistic regression analysis predicting EPE. A model including PSA, maximum diameter of the index lesion, presence of EPE on MRI, ISUP grade, and percentage of positive cores in the ipsilateral hemi-prostate achieved an AUC of 81% (95% CI:79-83%). The coefficients of the logit function are provided in **Supplemental Table 1**. The benefit derived from applying the model in clinical practice according to the DCA method is shown in **Figure 1**. The nomogram-derived probability of EPE showed greater net clinical benefit relative to the hypothetical scenarios of always performing nerve preservation or never and outperformed relying on presence or absence of EPE on MRI alone.

The regression tree was set *a priori* to identify three categories in order to guide clinicians on when to perform nerve preservation as, in toto, incremental or non-nerve-sparing. The resulting analysis is displayed in **Figure 2**. Overall, 566, 577, and 2,026 observations fell in the low-, intermediate- and high-risk groups. The rate of EPE across the groups was: 5.1%, 14.9%, 48% for the low-, intermediate- and high-risk group, respectively.

4. Discussion

Tailoring the best surgical approach to patients in terms of nerve preservation represents a great challenge, as it requires surgeons to balance the risk of EPE vs the benefits of neurovascular bundle preservation. As oncological outcomes have to be prioritized, inaccurate EPE risk prediction might determine the occurrence of PSM(s). In this study we aimed to update a side-specific nomogram that was introduced first in 2018[8]. The original patient population included individuals who were diagnosed with both systematic and targeted biopsy[7]. Here, we propose an update that reflects the current standard of care in terms of diagnostic pathway, *e.g.* by relying on data from patients diagnosed with systematic and targeted biopsy. To do so, we relied on a multi-institutional database and considered the two prostatic lobes separately. While we acknowledge this being a simplification of tumor's behavior, from a practical standpoint, what matters is how to approach the posterolateral dissection of the prostate and the right and left neurovascular bundles. We did not consider prostatic lobes with no biopsy-documented tumor. Our rationale for this decision was that the prediction of side-specific EPE cannot be independent from the absence of tumor. In clinical practice, a negative biopsy does not typically result in further evaluation for EPE; therefore, a nomogram-derived probability of a negative biopsy is not of clinical utility.

To the best of our knowledge this is the largest study on side-specific EPE prediction that relies only on patients diagnosed with MRI-targeted biopsy and this represents one the main strength of our study. In fact, by having a large sample size like ours, the inherent variability attributable to the multi-institutional nature of the data is likely diluted.

With this article we also propose an update to a practical algorithm for selecting candidates for nerve-sparing surgery, first described by Srivastava et al.[15] and then updated in 2019[16]. We used the regression tree to identify practical risk categories to assist surgeons in choosing candidates for either full nerve preservation, incremental or non-nerve sparing[17].

143   Based on the risk of EPE across the risk categories that we identified, we would suggest

144   performing nerve sparing surgery in prostatic lobes in the low risk category, incremental

145   nerve sparing in the intermediate risk category, and non-nerve sparing in the high risk one.

146   A few other side-specific models have been described in addition to the Martini-2018[8].

147   One is the Soeterik-2020, which, like our earlier nomogram, relied on data from systematic

148   and targeted biopsy[9]. Another study on this domain is the Nyarangi-Dix nomogram[10].

149   Notably, this study incorporated data on capsule contact by the lesion, yet this variable was

150   not recorded in our multi-institutional database.

151   It should be noted that in case of unilateral high-risk disease, defined as the presence

152   of PSA≥20 ng/ml and/or unilateral EPE on mpMRI and/or unilateral Grade group (GG) ≥4,

153   approximately 1 patient out of 10 might have contralateral EPE even in absence of lesions

154   on that side[18]. This should be taken into account when planning surgery. In fact, high-risk

155   disease tends to be multifocal and we tried to address this issue in one of our earlier studies.

156   Our study provides surgeons with a readily available tool to select candidates for

157   nerve preservation (either in toto or incremental) or non-nerve preservation. An alternative

158   to preoperative risk stratification is approaching virtually all patients with a nerve-sparing

159   strategy and perform frozen sections at the posterolateral aspects of the prostate. However,

160   many studies on frozen sections did not report on whether functional outcomes are improved

161   by this approach or not[19-20]. In general, appropriate risk stratification can result in good

162   functional outcomes. On this matter, longer operating time, in case of use of frozen section,

163   and, subsequently, costs should be factored in.

164   Diamand et al. recently evaluated the performance of 16 models in a cohort of 737

165   patients diagnosed with MRI-targeted and systematic biopsy[19]. Overall, they relied on a total

166   of 1,474 prostatic lobes with 389 (26%) of them without tumor on biopsy[19]. The authors

167   found that the models by described by Pak[20], Patel[21], Martini-2018[8], and Soeterik-2020[9]

168   stood out from the others in terms of performance, with the highest AUCs. However, the

169 confidence intervals of the AUCs were overlapping. Given that similar models rely overall

170 on similar parameters, it is hard to identify one that is superior over the others, especially on

171 external validation. One of the main advantages of our proposed update is the fact that the

172 study population, in terms of prostatic lobes, is large, and this, potentially, could result in

173 narrow confidence intervals on future external validations. Notably, while Diamand et al.

174 relied on the largest case load for external validation, the authors considered also prostate

175 lobes without cancer on biopsy and some models, including ours, were built without

176 considering prostate lobes where biopsies were negative for cancer[19]. This could potentially

177 affect any external validation in this domain.

178   At present, our study lacks external validation. We also acknowledge the lack of data

179 on correlation between biopsy findings and side-specific pathological ISUP. Patients with a

180 pure midline lesion where a dominant lobe could not be identified were not considered

181 eligible for the study, yet those patients represent a minority[22,23]. Another limitation is the

182 lack of information about lesion location at a zonal level, which might sometimes behave

183 differently[24]. Additionally, the multi-institutional nature of our data might harbor a certain

184 degree of unaccounted heterogeneity, especially concerning MRI acquisition, reporting, and

185 biopsy. Although all centers were tertiary referral centers, this heterogeneity might influence

186 the results and compromise their generalizability to low-volume centers.

187

188 **5. Conclusions**

189   In this study we present an update of the first side-specific MRI-based nomogram for

190 the prediction of extraprostatic extension. Moreover, we present updated risk categories to

191 help clinicians on how to approach nerve-preservation. Our findings are based on a

192 contemporary cohort where all patients were diagnosed with MRI-targeted biopsy. Our

193 model warrants external validation.

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269 **Figure legends**

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271 **Figure 1.** Decision curve analysis demonstrating the net benefit associated with the use of

272 the model-derived probability and presence or absence of EPE on MRI for selecting

273 individuals for nerve-sparing surgery versus the two hypothetical scenarios of always or

274 never performing nerve preservation.

275

276 **Figure 2.** Distribution of the risk of extraprostatic extension across the three risk groups

277 identified by the regression tree.