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External validation of a novel side-specific, multiparametric magnetic resonance imaging-based nomogram for the prediction of extracapsular extension of prostate cancer: preliminary outcomes on a series diagnosed with mpMRI targeted *plus* systematic saturation biopsy

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Aknowledgment to:

Ilaria Bagni,

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Dear Editor, we read with great interest the article from Martini and Coworkers, who developed a novel side-specific, multiparametric magnetic resonance imaging (mpMRI)-based nomogram for the prediction of extracapsular extension (ECE) of prostate cancer (PCa). The knowledge of the presence of ECE would help surgeons tailor the amount of nerve-sparing and improve the tradeoff between functional and oncological outcomes of radical prostatectomy (RP)[1,2]. Several nomograms aimed to predict ECE have been developed, based on clinical and pathological variables from prostate biopsy. However, most of them are not side-specific [1] and only few tools have been externally validated.

With the advent of mpMRI for the detection of clinically significant PCa, several Authors evaluated its role to improve local staging [3,4]. When compared to ultrasound and CT scans, it enhances the visualization of PCa and its relationship to the capsule, provided an adequate spatial resolution with functional sequences. However, mpMRI sensitivity to detect ECE still remains widely variable (35-78%)[1].

The incremental role of mpMRI added to pre-existing models has been explored too - with regards to Partin Tables, CAPRA score and the Memorial Sloan-Kattering nomogram [3,4]– resulting in an improved predictive performance with mpMRI integration.

Martini et al [1] proposed a model for the side-specific prediction of ECE, based on PSA, highest biopsy Gleason Grade Group (GGG), maximum percentage of core and presence of ECE at mpMRI; the nomogram showed a good discrimination at internal validation with an area under the curve(AUC) of 82.1%.

To the purpose to apply the nomogram prospectively, we performed an external validation on a retrospective series of 106 patients with a positive mpMRI submitted to RP, accounting for a total of 137 biopsy-positive prostatic lobes. The retrospective assessment of factors predicting prostate cancer aggressiveness (including radiological, pathological and laboratories variables as well) was approved by the local Ethic Committee (982/2018/OSS/AOUMO).

PCa diagnosis was obtained in all cases with transperineal-biopsies with targeted (2-4 cores) biopsy *plus* systematic saturation biopsy, as previously described [5]. All prostate biopsy and RP were performed at our Institution, thus limiting the risk of biases due to different sampling techniques, devices or operators' learning curve; mpMRI were carried out in two different Radiological Units by radiologists specifically dedicated to MRI reading.

The primary endpoint was to perform an external validation, considering both discrimination (AUC) and external calibration (to evaluate the degree of agreement between model-predicted and observed rates of ECE). As a secondary endpoint, we explored the incremental role of the mpMRI-variable added to conventional clinical-pathological ones comparing between AUCs of two-nested models with the test of Heller[6].

A descriptive analysis of the variables of the validation dataset is reported as follows: the median age was 67 (IQrange:62-71); the median PSA was 7.5ng/ml (5.5-10.3); the median percentage of positive core was 40% (10-70); GGG=1 was found in 91(66.4%) prostatic lobes, GGG=2 in 27(19.7%), GGG=3 in 10(7.3%) and GGG=4-5 in 9 lobes. mpMRI was positive for ECE in 20/137 lobes; ECE at final pathology was detected in 40 lobes.

The AUC at the present external validation was 67.6% (95%CI:57.4%-77.8%). Sensitivity and specificity at the 20% cutoff suggested by Authors were 53.6% (95%CI:33.9%-72.5%) and 77.1% (95%CI:68%-84.6%), respectively. The model showed a poor calibration with tendency towards underestimation (Figure1). As far as the secondary endpoint, the tool without mpMRI-variable showed a 66.5% discrimination (95% CI:56.5%-76.7%) and the difference between the two AUCs was not statistically significant (p=0.113).

Some comments may arise from the current outcomes.

From an epidemiological point of view, it should be remarked that the predictive performance of a model can vary extensively when applied to a population other than the development one, due to geographical, temporal and domain differences [7].

From a clinical point of view, the dichotomized and not-graded mpMRI variable chosen by Authors (loss or irregularity of capsule considered as positive *versus* contact or bulge or abutment as negative for ECE) [1] may have accounted for the variability of the predictive performance in a different dataset.

The present external validation has a main strength: all patients had targeted-biopsies of mpMRI suspicious lesions added to saturation sampling. Since Martini's model is developed on a series with mpMRI either before and after prostate biopsy - with only 17.5% receiving a targeted sampling – we

would have expected an improved predictive performance with biopsy technique - targeted *plus* saturation - at its best.

The noteworthy limit of the current study is the moderate single-centre case series as well as the moderate number of events to be predicted (ECE). The absence of a centralized review of imaging is another limitation, especially if considering the subjective interpretation of the mpMRI covariate chosen by Authors.

Given these limits, Martini et al are to be commended for developing a side-specific imaging-based nomogram; further external validation studies on larger sample size are required to assess the generalizability of this novel tool aiming to predict ECE.

References

1. Martini A, Gupta A, Lewis C et al. Development and internal validation of a side-specific, multiparametric magnetic resonance imaging-based nomogram for the prediction of extracapsular extension of prostate cancer. BJU Int 2018; 1-9
2. Patel V, Sandri M, Grasso AAC et al. A novel tool for predicting extracapsular extension during graded partial nerve sparing in radical prostatectomy. BJU Int 2018; 121:373-382
3. Feng TS, Sharif-Afshar AR, Wu J et al. Multiparametric MRI improves accuracy of clinical nomograms for predicting extracapsular extension of prostate cancer. Urology 2015; 86: 332-337
4. Morlacco A, Sharma V, Viers BR at al. The incremental role of magnetic resonance imaging for prostate cancer staging before radical prostatectomy. Eur Urol 2017; 71: 701-704
5. Martorana E, Pirola G, Scialpi M et al. Lesion volume predicts prostate cancer risk and aggressiveness: validation of its value alone and matched with prostate imaging reporting and data system score. BJU Int 2017; 120: 92-103
6. Heller G., Seshan V.E., Moskowitz CS et al. Inference for the difference in the area under the ROC curve derived from nested binary regression models. *Biostatistics* 2016; 18: 260-274
7. Rocco B, Sighinolfi MC, Sandri M et al. Editorial on: "Development and Internal Validation of a Side Specific, Multiparametric MRI- based Nomogram for the Prediction of Extracapsular Extension of Prostate Cancer" by Martini et al. BJU Int, https://onlinelibrary.wiley.com/doi/10.1111/bju.14503

Figure 1. Discrimination (top panel) and calibration (bottom panel) of the model in the current validation dataset. In the top panel: ROC curve of the Martini's model (black line) and of the multivariate model without mpMRI (gray line).