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Multiparametric magnetic resonance imaging and active surveillance: How to better select insignificant prostate cancer?

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Objectives: To evaluate the role of multiparametric magnetic resonance imaging in improving the predictive accuracy of the Prostate Cancer Research International: Active Surveillance and Epstein criteria for active surveillance in prostate cancer.
Methods: A retrospective study was carried out with 126 prostate cancer patients treated with robot-assisted radical prostatectomy, but eligible for active surveillance according to the Prostate Cancer Research International: Active Surveillance criteria; 63 patients were also eligible according to the Epstein criteria. All patients underwent preoperative multiparametric magnetic resonance imaging, after at least 6 weeks from biopsy. The images from the multiparametric magnetic resonance imaging were assessed, and diagrams showing prostate sextants were used to designate regions of abnormalities within the prostate. Findings in the prostate were assigned to one of five categories according the Prostate Imaging-Reporting and Data System guidelines (v1.0), and considered positive for prostate cancer if the final Prostate Imaging-Reporting and Data System guidelines were >3 and negative if ≤3. Multivariate logistic regression analysis was carried out to evaluate the gain in accuracy of the Prostate Cancer Research International: Active Surveillance and Epstein criteria when added to multiparametric magnetic resonance imaging. Decision curve analysis was carried out to identify the net benefit of each model.
Results: The inclusion of multiparametric magnetic resonance imaging to the Epstein criteria and the Prostate Cancer Research International: Active Surveillance multivariate model significantly increased their accuracy in predicting pathologically-confirmed insignificant prostate cancer by 7% and 5%, respectively. At the decision curve analysis evaluation, the model including the Prostate Cancer Research International: Active Surveillance criteria and multiparametric magnetic resonance imaging improved the clinical risk prediction over the other models.
Conclusions: The present findings suggest that multiparametric magnetic resonance imaging is able to increase the predictive accuracy of Prostate Cancer Research International: Active Surveillance and Epstein criteria to identify prostate cancer patients eligible for active surveillance.
Key words: active surveillance, multiparametric magnetic resonance imaging, prognostic accuracy, prostate cancer, radical prostatectomy.

Introduction

Several studies considering RP specimens as the reference standard showed that mpMRI has an excellent sensitivity for larger and more aggressive (GS ≥7) PCa.[1–3] Therefore, mpMRI allows better identification of patients with clinically significant disease and, consequently, has the potential to rule out patients with insignificant disease from active treatment when mpMRI is negative.[4]
In this context, several studies showed the primary importance of DWI during mpMRI. The ADC resulting from DWI provides information on tumor aggressiveness. Recently, it has been documented that ADC values are inversely correlated with GS in PCa, and might be helpful in differentiation of low-, intermediate- and high-risk cancer.[5] Furthermore, ADC candidates for AS, as well as for predicting PCa progression during the monitoring of these patients.[6]
The actual AS criteria are not perfect, misclassifying some patients that are selected with apparent low-risk disease and

then harboring unfavorable disease.[7] In contrast, we must not forget that current AS criteria might be too strict. In this context, GS 3 + 4 patients, with a very small volume of a secondary Gleason 4 and a PSA <10 ng/mL, have been shown to have a disease comparable with GS 3 + 3 patients.[8,9] Van der Bergh et al. recently published a systematic review of 30 studies regarding all new clinical tools (mpMRI, serum biomarkers [_2proPSA and the Prostate Health Index] and urinary markers [PCa antigen 3 gene]) for a better selection and monitoring in patients submitted to AS.[10] The authors concluded that the use of high-quality mpMRI was promising because of the very high negative predictive value with respect to significant PCa, and a favorable mpMRI might obviate the need for repeat biopsy during AS.

Keeping this in mind, we tested the hypothesis that mpMRI could improve the two most frequently used criteria for AS, the PRIAS and Epstein criteria, in a cohort of patients that underwent RP, but were eligible for AS, using RP specimens as the reference standard.

Methods

Study population

A study was carried out among 126 patients with low-risk PCa who underwent robot-assisted RP at a surgical high-volume center (San Luigi Hospital, University of Turin, Orbassano, Turin, Italy) from January 2012 to February 2015.

Such patients, according to common clinical practice at this center, were evaluated with mpMRI before surgery, used for local staging and carried out after 6–8 weeks from 12-core systematic transrectal biopsy in order to minimize postbiopsy artifacts. mpMRI was carried out at two centers with expertise in mpMRI, San Luigi Hospital, Orbassano (Turin), University of Turin and Institute for Cancer Research and Treatment of Candiolo (Turin). All patients were eligible for AS according to the PRIAS criteria (clinical stage T1c or T2 disease, PSA level of ≤10 ng/mL, GS ≤6, PSA-D of <0.20 ng/mL/cc and one or two positive biopsy cores). Among these patients, 63 (50%) were also eligible for AS according to the Epstein criteria (clinical stage T1c, PSA level ≤10 ng/mL, GS ≤6, PSA-D ≤0.15 ng/mL, one or two positive biopsy cores and percentage of core involvement ≤50%). In particular, the patients had been proposed for AS, only based on clinical and biopsy data, but they finally had refused, opting for surgery.

All clinical, mpMRI and final histopathological features were retrospectively analyzed.

mpMRI

Patients preoperatively underwent a mpMRI with a 1.5-Tesla scanner (Signa Excite HD; GE Healthcare, Milwaukee, WI, USA) using a four-channel phase array coil combined with an endorectal coil (Medrad, Warrendale, PA, USA) or with a 1.5 Tesla scanner (Achieva HD; Philips Healthcare, Best, The Netherlands) using a five-channel phase array coil combined with an endorectal coil (Medrad). Studies were carried out with: (i) T2-weighted images in the axial, coronal and sagittal planes to evaluate the prostate and seminal vesicle anatomy; (ii) T1 fast spin echo axial images to identify areas of intraprostatic hemorrhage, and to evaluate the pelvic lymph nodes and bones; and (iii) DWI and DCE images in order to obtain biological and functional information. DWI was carried out using axial echo planar imaging sequences at different b-values: 0–100–1000–2000 s/mm^2. The sequences parameters satisfied the recommendations from a European consensus meeting on MRI imaging for the detection, localization

and characterization of PCa.[11]
All images were sent to two workstations and post-processed (Functool v. 9.4.05a; GE Healthcare; and Intellispace Portal v. 6.0.3.12200; Philips Healthcare). Two experienced uroradiologists analyzed the mpMRI findings identifying all the suspicious ROIs. The uroradiologists were blinded to the pathologist biopsy reports. Diagnostic features for malignancy have been reported in Appendix S1.
Each ROI was assessed, and diagrams showing the prostate sextants were used to designate regions of abnormalities within the prostate. In addition, each ROI was scored on a scale ranging from 1 to 5, with higher scores indicative of higher suspicion of cancer, according to the PI-RADS (v1.0) guidelines, developed by the European Society of Urogenital Radiology in order to standardize the evaluation and reporting of prostate mpMRI.[12]
In particular, a 0–5 score was assigned to each of the three MRI sequences for single ROI (T2-weighted, DWI and DCE), and a single final PI-RADS score was obtained. Overall, we dichotomized the variable, and the mpMRI finding was considered positive if the final PI-RADS was >3, and negative if ≤3. In case of multiple ROIs, we considered only the index lesion, considered as the lesion with the highest PIRADS score.

Pathology evaluation

RP specimens were evaluated using serially 3-mm sectioned whole-mount specimens according to the Stanford protocol,[13] and primary and secondary GS were assigned by an experienced uropathologist, blinded to the mpMRI results, according to the 2005 consensus conference of the International Society of Urological Pathology definitions.[14]
For study purposes, all tumor foci were identified. Specifically, we evaluated the index tumor, defined as the tumor with the highest GS. When multiple tumors had the same grade, the largest tumor focus was considered as the index tumor (we considered approximately a lesion of 1 cm corresponding to a spherical volume of 0.5 mL). In addition, we evaluated the cumulative tumor volume using computerized planimetry accounting for all tumor foci.[15]

Study end-points

Based on the high NPV in ruling out a significant PCa, the primary end-point of the study was to determine the using the European Randomized Screening for Prostate Cancer definition (organ-confined Gleason 3 + 3 tumors, with no Gleason grade 4 or 5, index tumor volume ≤1.3 cm^3 and a total tumor volume of ≤2.5 cm^3).[16] In addition, we evaluated the gain in predictive accuracy obtained with the addition of mpMRI to the PRIAS criteria or Epstein criteria. In accordance with other authors, we used this criteria because we consider the Epstein definition of insignificant PCa too restrictive regarding the PCa volume threshold of 0.5 cm^3 for the index tumor.[17] Indeed, despite a 5% increase in the risk of underestimation of significant PCa, a larger proportion of men would have the chance to follow an AS program.

Statistical analysis

The qualitative data were tested using the v^2-test or Fisher's exact test as appropriate, and the continuous variables were tested by Mann–Whitney U-test or Student's t-test according to their distribution (according to Kolmogorov–Smirnov test) and presented as median (IQR) or mean (_SD), respectively. Univariate and multivariate logistic regression analyses were carried out to identify variables potentially predictive of PCIPCa.

Predictive accuracy of the models was assessed in terms of the AUC value. A total of 1000 bootstrap resamples were used for all accuracy estimates and to reduce overfit bias. AUC were compared by the Mantel–Haenszel test.

We carried out DCA to evaluate the potential clinical usefulness of identifying PCIPCa based on the models including mpMRI.[18]

We estimated NB for prediction models by summing the benefits (true positive PCIPCa) and subtracting the harms (false positive PCIPCa). The threshold probability of each model was estimated. We used a threshold probability between 0% and 80%. The interpretation of DCA is straightforward; a model with the highest NB at a particular threshold should be chosen over alternative models. For all statistical comparisons, significance was considered as $P < 0.05$. Standard statistical software was used (SPSS v.18.0; IBM Corp, Armonk, NY, USA; and R version 2.15.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

At the final histopathological examination, we observed a reclassification in 57 patients (45.2%). A total of 126 dominant lesions were identified, 87 with volume ≤1.3 mL and 39 with volume >1.3 mL. A total of 89 patients had GS ≤6, whereas 37 GS ≥7. We also identified five extracapsular extensions (Table 1).

Overall, mpMRI showed 94 ROIs in 69 positive mpMRI patients. The sensitivity of mpMRI (PI-RADS >3) was 73.7%, the specificity (PI-RADS ≤3) was 60.8%. The PPV for significant PCa was 60.8%, the NPV for ruling out significant PCa and identifying insignificant PCa was 73.7% (Table 1).

At multivariate analysis and after 1000 bootstrapping resampling, the inclusion of mpMRI to the Epstein multivariate model, including total PSA, density PSA, number of positive cores (1 vs 2) and percentage of core involvement, adjusted for age, significantly increased its accuracy in predicting PCIPCa of 7%. Similarly, the inclusion of mpMRI to the PRIAS multivariate model, including total PSA, density PSA, clinical stage (T1 vs T2) and number of positive cores (2 vs 1), adjusted for age, significantly increased its accuracy in predicting PCIPCa of 5% (Table 2; Fig. 1).

At the DCA evaluation, for patients with a threshold >60% of probability of pathologically favorable PCa, the model including PRIAS and mpMRI improved the clinical risk prediction over the other models (Fig. 2).

Discussion

AS is a valid tool to mitigate the risk of overtreatment of low-risk PCa. Recently, Klots et al. confirmed the feasibility of AS in a large cohort study with a long-term follow up.[19] However, during the first 2 years of AS, approximately 20–30% of patients shift toward definitive treatment because of a reclassification into higher-grade tumors.[20] For this reason, there is a need to better identify the tumors bound to progress over time.

In a cohort of patients eligible for AS according to the PRIAS criteria who underwent RP, using RP specimens as the reference standard, our group showed that mpMRI performed better than serum (Prostate Health Index) and urinary (PCa antigen 3) markers in predicting the pathological outcomes, better discriminating between insignificant and significant PCa.[7] Consequently, in the present study, we evaluated the possibility of adding mpMRI to the PRIAS and Epstein

criteria to improve its predictive accuracy and preoperative definition of insignificant PCa. In the present study cohort, we observed a PPV for high-risk PCa of 60.8%, and a NPV for ruling out significant PCa of 73.7%. At multivariate analysis, we showed that mpMRI is able to increase the predictive accuracy of Epstein and PRIAS multivariate models of 7% and 5%, respectively ($P < 0.01$). In addition, we carried out DCA for the predictive models previously developed. Only the model with PRIAS criteria + mpMRI resulted in a greater NB than other models at a threshold of probabilities >60%. Therefore, the present results would recommend the use of mpMRI in addition to actual AS criteria and, according to the results of DCA, the best model to select low-risk PCa patients eligible for AS is represented by PRIAS criteria and mpMRI. In this context, according to a recent study, PRIAS criteria showed the highest ability in identifying patients with insignificant PCa compared with all the other available criteria.[21]

However, in contrast, we must not forget that PPV of mpMRI for predict significant PCa was relatively low at 60.8%. Consequently, approximately 40% of patients with positive mpMRI and who fulfilled the PRIAS criteria showed insignificant PCa. Therefore, we can speculate that if all patients fulfilled the PRIAS criteria, but with positive mpMRI were treated with immediate radical treatments, at least 40% of patients would be overtreated. For this reason, we must always carry out a pathological evaluation by prostate biopsy in order to identify appropriate candidates for AS or during AS follow up.

In a recent systematic review, although characterized by remarkable heterogeneity, Schoots et al. analyzing 10 studies with patients eligible for AS, but who underwent RP with preoperatively MRI, showed that the likelihood of a preoperative positive MRI was 73%, and upgrading occurred in 43% of patients with positive MRI (vs 27% of patients with negative MRI), whereas no difference occurred in terms of upstaging between the two groups.[22] In addition, they analyzed data from seven studies with patients eligible for AS undergoing a confirmatory mpMRI and a subsequent systematic random biopsy or MRI-guided targeted biopsy. The authors showed that MRI was positive in two-thirds of men: in this group, biopsy reclassification occurred in 39% (vs 17% in patients with negative MRI). Focusing on the group with positive MRI and MRIguided targeted biopsy only, biopsy reclassification occurred in 47% of cases. Finally, analyzing two studies with patients on AS follow up that underwent repeated MRI, the authors reported a strong correlation between positive MRI and upgrading during follow up and the possibility of avoiding biopsy in men with stable PSA and negative MRI.

In another recent systematic review and meta-analysis of studies with patients eligible for AS submitted to MRI, Guo et al. showed that mpMRI had a moderate diagnostic accuracy in disease reclassification among AS candidates.[23] In particular, they showed a high NPV and specificity for biopsy reclassification, suggesting that negative prostate mpMRI might support remaining under an AS protocol. In contrast, the PPV and sensitivity were relatively low, but, in the case of lesions of >10 mm in volume, the presence of a suspicious mpMRI might suggest an increased risk of disease progression.

Most recently, Diaz et al. confirmed that mpMRI associated with MRI/transrectal ultrasound fusion biopsy substantially increased the number of pathological progressions detected that would not have been detected by standard biopsy alone.[24] In addition, stable findings on mpMRI were strongly associated with GS stability in patients under AS.

This could potentially reduce the number of unnecessary biopsies during AS follow up.

We agree with Giannarini et al. that mpMRI has yet many problems to solve before being accepted for routine clinical practice on a large scale.[25] However, the present study helps to validate the clinical utility of mpMRI in a setting of patients under AS using RP specimens as the reference standard, that represents the best method for a clinical validation. Unfortunately, we did not carry out a matching between each mpMRI ROI with the corresponding locations on wholemount pathology, because we only considered the MRI findings as dichotomized MRI variable (patients with MRI positive or negative) and the index tumor with cumulative tumor volume on histological findings. Our future challenge will be to revalue each ROI on MRI findings and each tumor lesion on RP specimens in order to evaluate the grade concordance in terms of size and grade. Another problem related to MRI is the detection of TZ tumors. In the present study, we did not consider as suspicious all the lesions with PI-RADS 3, especially those located in the TZ that are, in most cases, secondary to inflammation or adenomatous nodules. Only poorly-defined nodules that distorted the normal architecture and had concordant anomalies on DWI and DCE were considered suspicious for malignancy, and were classified as PIRADS 4 or 5. Several studies have showed that mpMRI did not improve the accuracy of detection and localization of TZ cancers compared with T2-weighted sequences alone for its low specificity.[26]

The present study was limited by the relatively small number of cases examined. Further studies with a larger population should be carried out to confirm our findings. The inclusion of two expert uroradiologists who interpreted the mpMRI could generate an interobserver variability in interpreting imaging findings. However, the radiologists had the same level of expertise (more than 2 years of experience and more than 200 prostate mpMRI examined). PI-RADS v1.0 and not the more recent v2.0 was used, potentially affecting the diagnostic accuracy, especially for the anterior ROI. However, a recent meta-analysis on the use of PI-RADS v1.0 for PCa detection with mpMRI showed a good diagnostic accuracy with a sensitivity of 0.78 and a specificity of 0.79.[27]

Finally, the present study did not include any discussion regarding costs. However, we believe that the higher cost of mpMRI could be mitigated over time because of the economic effect generated by a better risk assessment with a more accurate identification of patients eligible to AS, reducing the overtreatment of indolent tumors, and reducing unnecessary biopsies during follow up.

In conclusion, mpMRI might play an important role in the selection of low-risk PCa patients eligible for AS. In particular, using RP specimens as the standard reference, we showed that mpMRI is able to significantly increase the predictive accuracy of the PRIAS and Epstein criteria. However, robust data from prospective studies are required before adoption of mpMRI on a large scale for this purpose.

Conflict of interest

None declared.

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