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Platinum Opinion

Multiparametric Magnetic Resonance Imaging Before Prostate Biopsy: A Chain is Only as Strong as its Weakest Link

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Over the past decade, compelling evidence has shown that multiparametric magnetic resonance imaging (mpMRI) identifies International Society of Urological Pathology (ISUP) grade ≥2 prostate cancer (PCa) with excellent sensitivity [1]. mpMRI is increasingly performed before prostate biopsy so that prostate areas appearing suspicious on mpMRI may be specifically targeted. It has been shown that combining targeted (TBx) and systematic (SBx) biopsy improves the detection of clinically significant PCa (csPCa), at least in patients with persistent suspicion of PCa and prior negative SBx [2]. As a result, the European Association of Urology (EAU) prostate cancer guidelines recommended performing prostate mpMRI before repeat biopsy in 2015.

The 2019 edition of the EAU-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy & Oncology (ESTRO)-European Society of Urogenital Radiology (ESUR)-International Society of Geriatric Oncology (SIOG) prostate cancer guideline now recommends performing mpMRI before a first set of biopsies. Indeed, concordant results from a recent Cochrane meta-analysis and two prospective multicenter trials (MRI-FIRST, 4M) showed that combining TBx and SBx substantially improved the detection of ISUP grade ≥2 cancers in biopsy-naïve patients [1,3,4]. Furthermore, in the PRECISION multicenter randomized controlled trial, TBx detected significantly more ISUP grade ≥2 cancers than SBx [5]. However, many concerns still need to be addressed.

First, it remains unclear whether TBx should be performed alone or in combination with SBx. The "TBx-only" diagnostic pathway (in which patients with positive mpMRI undergo TBx only and patients with negative mpMRI do not undergo biopsy at all) is appealing. On the basis of the PRECISION findings, this strategy would reduce the number of biopsy procedures by 28% and (over) detection of ISUP grade 1 cancers by 59% [5]. However, before relegating SBx to the museum, one must carefully evaluate the added values of TBx and SBx, that is, the percentages of patients with csPCa detected by only one biopsy technique. This can be estimated from the MRI-FIRST and 4M results, since these trials, unlike PRECISION, compared TBx and SBx in the same patients. In MRI-FIRST and 4M, the added value for detecting ISUP grade ≥2 cancers was 7.6% and 7% for TBx, and 5.2% and 5% for SBx for prevalence of 37.5% and 30%, respectively [3,4]. In the Cochrane meta-analysis of 20 head-to-head comparisons, the added value was 6.3% (95% confidence interval [CI] 4.8–8.2%) for TBx and 4.3% (95% CI 2.6–6.9%) for SBx for a prevalence of 27.7% (95% CI 23.7–32.6%) [1]. Such consistency across studies strongly suggests that SBx retains substantial added value for biopsy-naïve patients. For the repeat biopsy setting, however, the Cochrane meta-analysis revealed added value of 9.6% (95% CI 7.7–11.8%) for TBx and 2.3% (95% CI 1.2–4.5%) for SBx for a prevalence of 22.8% (95% CI 20.0–26.2%) [1]. Thus, in the case of repeat biopsy, the marginal added value of SBx argues for the TBx-only approach.

Second, most studies reported that mpMRI had high negative predictive value (NPV) for csPCa [6]. However, this may be misleading since NPV depends on disease prevalence (ie, the a priori risk of disease). Although many physicians are aware that NPV decreases when the a priori risk increases, they usually fail to understand the practical

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consequences [7]. Even in the repeat biopsy setting, in which the "TBx-only" approach is recommended, a patient with high clinical suspicion of PCa and negative mpMRI findings may require SBx. Conversely, even if SBx is recommended for biopsy-naïve patients with negative mpMRI, a patient with low clinical suspicion may safely omit biopsy. This argues for an individualized risk stratification before deciding who can safely omit SBx in the case of negative mpMRI. Risk stratification may be based on prostate-specific antigen density, urine or serum biomarkers, or more advanced risk calculators incorporating mpMRI findings [8–10]. However, robust risk thresholds are still lacking.

Another concern is the (in)accuracy of TBx. A substantial part of the added value of SBx is due to the fact that TBx misses some targets, even with the use of ultrasound/MRI fusion systems [3,11]. Obtaining only one or two biopsy cores from a suspicious area is not sufficient, and saturation biopsy of prostate areas that are suspicious at mpMRI may be necessary [12]. There is an urgent need for assessing both the minimal number of targeted cores to be obtained, depending on lesion size, lesion location, and prostate volume, and the impact of the operator expertise on TBx accuracy.

In addition, more general concerns must be acknowledged. First, guidelines are based on published results that usually come from experienced high-volume centers. These results might not be reproduced by less experienced centers. Better mpMRI reproducibility is needed [12] and will come through continual refinement of scoring systems, quantitative imaging and closer collaboration between urologists and radiologists. Second, prebiopsy mpMRI has only been evaluated in patients whose risk of csPCa was judged high enough to deserve biopsy. Prebiopsy mpMRI must not be used in patients who do not have an indication for prostate biopsy on the basis of their family history and clinical and biochemical data. Owing to its low specificity, mpMRI in such patients with very low risk would result in inflation of false-positive findings and subsequent unnecessary biopsies. Third, the impact on cancer-specific survival of early detection of some csPCa due to TBx or of delayed detection of other csPCa due to omission of SBx is unknown. This question is linked to the highly controversial question of the definition of csPCa, that is, the definition of PCas that need immediate diagnosis and treatment. Since mpMRI sensitivity is higher for the most aggressive cancers, a shift of this definition towards more aggressive cancers will result in an increasingly important role for mpMRI and TBx.

In conclusion, mpMRI and TBx currently play an important role in PCa diagnosis. However, in the whole chain of events leading to this diagnosis, many links require strengthening. In particular, it is crucial to obtain a reliable risk stratification scheme for patients, to improve mpMRI inter-reader reproducibility and specificity, to assess and improve the accuracy of targeting methods for TBx, and to define the cancers that need immediate diagnosis. Only then will the chain be strong enough to facilitate a reliable diagnosis of csPCa.

Conflicts of interest: Olivier Rouvière has received company speaker honoraria from EDAP-TMS, participates in trials by EDAP-TMS and Vermon, and has received research and travel grants from Philips. Nicolas Mottet is a company consultant for Janssen, GE, BMS, Sanofi, and Astellas, has received speaker honoraria from Astellas, Pierre Fabre, Steba, Janssen, and Ferring, and has received fellowships and travel grants from Astellas, IPSEN, Sanofi, Janssen, and Roche. Ivo G. Schoots has nothing to disclose.

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