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Multiparametric Magnetic Resonance Imaging for Prostate Cancer Detection: What We See and What We Miss

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The Prostate Imaging-Reporting and Data System (PI-RADS) for prostate cancer (PC) diagnosis is the de facto international standard for reporting multiparametric magnetic resonance imaging (mpMRI) of the prostate gland for biopsy-naïve and prior biopsy-negative men at risk of PC [1]. PI-RADS assessment categories provide MRI-derived information on the likelihood of the presence of clinically significant PC (csPC) and indicate targets for tissue sampling [2]. However, there are only a few detailed radiologic-histopathologic correlation studies using PI-RADS v.2 [3–5]. Studies show that smaller, nonindex, cribriform pattern [6] csPC foci are often undetected, and/or their size is underestimated [3]. There is an ongoing need to improve our understanding of the characteristics of detected and undetected PCs via PI-RADS v.2, including sensitivity by size, Gleason grade (GG), pathologic features including subtype and percentage GG 4/5 involvement, lesion location, and index lesion status.

The study by Johnson et al. [7] in this issue of *European Urology* addresses this shortcoming. The authors performed detailed pathologic correlations of PI-RADS assessment categories using whole-mount histopathologic sectioning. The work expands on the group's prior experiences by increasing the number of prostatectomy numbers and lesions evaluated from 122 specimens with 283 unique histologically confirmed PC foci [8] to 588 patients with 1213 unique histologically confirmed PC lesions. The message delivered is that in daily practice, mpMRI successfully detects larger index lesions with higher GG. As noted in their previous study [8], smaller, nonindex lesions are often overlooked, even if they are of high grade, and the size of lesions is systematically underestimated. The only significant new information is that when multiple, smaller lesions are present, they are more likely to go undetected compared to larger solitary lesions. Unfortunately, the authors have not taken the opportunity to detail other histologic factors that render lesions less MRI-visible, including anatomic blind spots (including transition- and central-zone PCs [4]), subcapular spreading lesions, microfocal patterns, histologic subtypes (cribriform pattern [6]), and, importantly, the sensitivity of mpMRI detection by percentage GG 4 involvement in Gleason score (GS) 3 + 4 disease (percentage GG 4/5 and volume of disease are predictors of tumor aggressiveness) [5]. The inability to demonstrate on multivariate analysis that GG affected csPC detection is at variance with a companion publication [9].

Before we consider what the study tells us about the PI-RADS systems, we need to remember that this is a retrospective evaluation of patients undergoing prostatectomy for known PC (csPC [GS $\geq$ 3 + 4] prevalence 88%). PI-RADS is designed to prospectively indicate the likelihood of csPC in treatment-naïve men, including many who do not have PC, with variable prevalence of disease [1]. Furthermore, we should remember that although PI-RADS is a lesion-based analysis method, most of the published literature focuses on patient-level analyses. Thus, statements such as “mpMRI detected 541/1213 pathologic lesions, which represents sensitivity of 45% (95% CI 42–47%) and a PPV of 81% (95% CI 78–84%)” cannot be taken to imply that the same performance would be seen at the patient level. Thus, any lesion-based sensitivity and predictive value data should be treated with caution when

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it comes to absolute numbers. However, we can broadly say that lesions with a higher PI-RADS assessment category are associated with a greater frequency of higher grade and larger tumors, as has been reported previously for pathologic specimens [3–5] and in saturation-biopsy studies [10].

Unfortunately, a detailed sensitivity analysis of the lesions seen and missed by PI-RADS assessment categories was not undertaken in the current study but some details can be found in the companion publication [9]. To understand why lesions were undetected, we should note that multiple factors contribute to MRI nonvisualization, including equipment-related factors (field strength, sequences deployed, sequence parameter values used, reception coil usage, signal-to-noise ratio of images), MRI interpretation criteria and reader experience, anatomic blind spots, and histological definition of csPC, including percentage GG 4 in GS 3 + 4 disease [11]. Besides these, we should also note that that PI-RADS interpretation does not require identification of all possible PC foci on mpMRI scans [1], and in practice only one to two lesions are prospectively identified. Thus, the number and range of lesions identified by mpMRI will often be lower than the more exhaustive attempt to identify every lesion undertaken at histopathology (in this study 1213 histopathologic lesions in 588 men were correlated with 685 mpMRI-delineated regions in 420 men).

What are the study implications for PC care? Clearly, we cannot conclude that PI-RADS is limited for patient diagnosis, as this has been comprehensively established by multiple prospective studies that yielded level 1 evidence [11–13]. Instead, we would contend that the direct implications are for the planning of gland-sparing therapies, where per-lesion as opposed to per-patient sensitivity is of utmost importance. As noted in this study, patients with known csPC are highly likely to have multiple disease foci that are often unseen or undocumented on mpMRI. Therefore, we recommend that patients who are being considered for gland-sparing procedures undergo comprehensive template mapping biopsies to improve confidence in the range and locations of lesions before therapy decisions are made . Furthermore, any patients receiving focal therapy on the basis of mpMRI detection and MRDB alone should undergo appropriate surveillance to find and treat emerging lesions. The duration of such follow-up requires investigation.

Conflicts of interest: The authors have nothing to disclose.

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