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Unraveling Prostate Cancer Genomics, Pathology, and Magnetic Resonance Imaging Visibility

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Magnetic resonance imaging (MRI) has been increasingly adopted as a tool to aid prostate cancer diagnosis and treatment decisions. Data supporting the use of MRI are based almost exclusively on biopsy findings. No long-term studies to date have demonstrated improved long-term oncologic outcomes with MRI utilization. In this context, genomic characterization of MRI-visible and -invisible lesions may provide valuable prognostic insight: if we know of genomic alterations that are associated with clinical outcomes and if MRI visibility correlates with those alterations, then MRI visibility could provide prognostic information beyond traditional parameters such as clinical stage and pathologic biopsy findings. Ultimately, such analyses can inform critical questions, including whether MRI-invisible tumors are biologically less aggressive than MRI-visible tumors. The answers to these questions have wide-ranging implications in terms of accurately determining an individual's need for biopsy, selecting patients for less aggressive management such as focal therapy, and interpreting MRI findings in the setting of active surveillance.

In this issue of *European Urology*, Houlahan et al. [1] present an initial foray into this arena. The authors report their findings based on genomic profiling of 20 tumors with a Prostate Imaging Reporting and Data System (PIRADS) score of 5 as compared to 20 lesions not visible on MRI (PIRADS <3). They found that PIRADS 5 tumors harbored specific genomic features associated with aggressiveness: a higher percentage of the genome was altered and there was elevation of SChLAP1, a noncoding RNA previously associated with clinical outcomes and cribriform architecture [2]. They also observed that some small nucleolar RNAs were upregulated, although not ones with a known function in cancer or previously defined prognostic importance. This study highlights the potential utility of combining imaging and genomic data, however it should be considered exploratory in light of the limited cohort size, variables per outcome of interest in multivariable models, and absence of a validation cohort.

The intersection of radiology, pathology, and genomics is a crowded one, and any relationship is probably multidirectional. Moreover, there are many distinct clinical and biological questions that arise from the convergence of these fields. Thus, precise definition of potential study questions that consider numerous confounders remains critical (Fig. 1). Appropriate matching of visible and invisible lesions in light of tumor-specific features remains challenging. The percentage of Gleason pattern 4, cribriform architecture, and pathologic T3 disease can all be more prevalent in MRI-detected lesions [3–5]. Therefore, ensuring that a study design accounts for such baseline differences is crucial to determining the incremental benefit of adding MRI visibility to genomic risk assessment.

There is certainly potential for genomic data to add to standard pathologic risk factors and better guide our understanding of MRI-invisible lesions. Taking into account the limits of genomics as a prognostic marker and the absence of clear clinical data, one could envision a scenario in which an understanding of the relationship between MRI visibility and some measure of genomic risk could help to guide decision-making for a borderline patient. We know from multiple studies that MRI and targeted biopsy alone fail to detect a significant proportion of cancers of Grade

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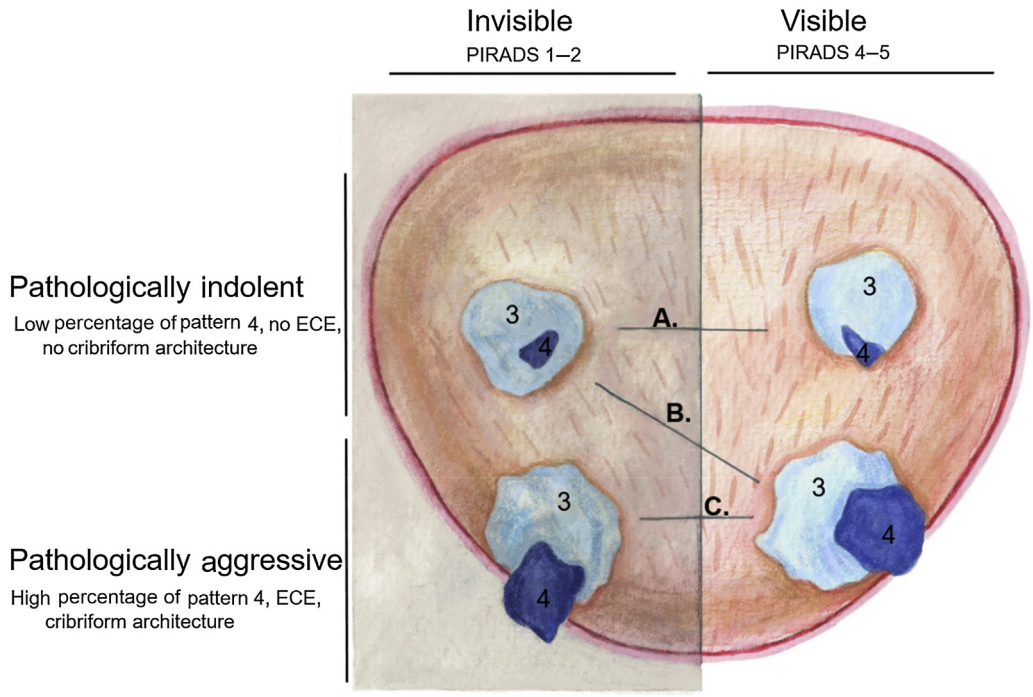

Fig. 1 – Potential comparisons of MRI-invisible and -visible tumors informed by genomic profiling. (A) Matched less pathologically aggressive tumors. Comparison can provide insight into the clinical significance of MRI-invisible lesions. (B) Less pathologically aggressive MRI-invisible tumor compared to more pathologically aggressive MRI-visible tumors as in the report by Houlahan et al. [1]. (C) Matched pathologically aggressive tumors. Comparison can inform the biology underlying MRI visibility or lack thereof. MRI = magnetic resonance imaging; ECE = extracapsular extension; PIRADS = Prostate Imaging Data and Reporting System.

Group 2 (GG2) or higher [5–9]. If we were to find that samples that are pathologically matched do indeed differ in genomic features associated with risk, such as the percentage of the genome altered, this would suggest that a higher threshold for biopsy in patients without MRI-visible lesions might be appropriate, even though we know that some GG2 cancers are missed.

As MRI is still generally not used as a triage test before biopsy, a surplus of biopsy and prostatectomy specimens from men with negative MRI findings are available. Molecular profiling of these specimens compared to specimens matched closely for biopsy pathology (independent of MRI visibility) could provide insight into their associated "genomic risk" relative to cancers with known historical clinical benchmarks. Since PIRADS incorporates cancer size and evidence of extraprostatic extension in the definition of visibility, use of a group enriched for PIRADS 5 tumors as a comparator is problematic, particularly if the goal is to inform a treatment decision in such a borderline patient.

As a field, we have adopted MRI technology without definitive evidence of improved clinical outcomes. We cannot decide that it is not important to diagnose and treat PIRADS <3 cancers without a really good justification for doing so. While overall MRI visibility is associated with aggressive cancers, this may simply be the result of PIRADS taking into account tumor size and evidence of extraprostatic extension, as well as the preferential detection of Gleason pattern 4 and cribriform architecture. Furthermore, it is important to consider the relative aggressiveness of cancers detected only by systematic biopsy or only by targeted biopsy, and visibility may not inform this comparison.

There remains no evidence that the absence of visibility on MRI means that a pathologically matched cancer is not as genomically or clinically aggressive. At present, the preponderance of evidence suggests a benefit from continuing to perform systematic biopsy in patients without MRI-visible lesions. It would be dangerous to assume that an MRI-invisible, histologically matched cancer is any less aggressive than a visible one.

Conflicts of interest: The authors have nothing to disclose.

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