Modernizing the Diagnostic and Decision-Making Pathway for Prostate Cancer

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Abstract

PSA has led to a drastic increase in the detection of prostate cancer, rendering this biomarker the gateway for the diagnostic pathway of prostatic neoplasms. However, the increase in incidence has not been mirrored by a similar reduction in mortality. Widespread PSA testing has facilitated the overdiagnosis and overtreatment of indolent disease. To reduce this phenomenon and avoid negative repercussions on the quality of life of men undergoing unnecessary therapies, the diagnostic pathway of prostate cancer needs to be improved. Multiparametric MRI (mp-MRI) can enhance the sensitivity and specificity of PSA, as well as the shortcomings of random biopsy sampling. This novel imaging technique has been proven to identify larger and more aggressive cancer foci, which should be targeted for treatment. New technological developments now allow for fusion of mp-MRI images with real-time ultrasound, opening the way to lesion-targeted biopsies. Furthermore, mp-MRI and targeted biopsies can also improve active surveillance protocols and permit more conservative focal therapy strategies. By implementing targeted biopsies, the diagnostic pathway will focus on clinically significant disease, consequently reducing overdiagnosis and overtreatment. Before this novel protocol becomes the new gold standard, mp-MRI acquisition and interpretation need to be standardized and targeted-biopsy strategies need to be further validated prior to abandoning random-sampling ones. Several multidisciplinary consortiums are already working on the standardization of prostate MRI, and there are ongoing prospective trials on targeted biopsies and MRI. Soon, imaging of prostatic lesions and selected biopsies will modify the diagnostic evaluation of prostate cancer, reducing overtreatment and therapy-derived complications that negatively affect quality of life.

The first revolution in prostate cancer diagnosis and management was heralded by the introduction of PSA testing in the late 1980s. PSA-triggered biopsies led to a historic peak

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in the incidence of and subsequent pro-found downward stage migration for prostate cancer (1 and 2). However, over the ensuing two decades, the increase in diagnostic lead time introduced by PSA testing was not matched by a commensurate decrease in overall mortality (1–4). It became clear that there was also a dramatic increase in the detection of indolent disease, and the patients in whom it was found did not benefit from radical therapy, especially in those with a limited life expectancy (3, 5, 6). Treating these men not only did not improve longevity but often may have decreased their quality of life.

Despite a growing recognition regarding their limitations, PSA and PSA-triggered random biopsies remain the main gateway to the diagnosis of prostate cancer. Even if active surveillance is implemented to reduce overtreatment, there are data that very few low-risk patients opt for such a strategy or continue on it for fear of missing the "window of cure" (7). Therefore, the challenge that prostate cancer specialists face is not simply to detect all cancers, but to identify those patients with clinically significant cancers that would benefit from treatment.

The first step to reduce overtreatment is to decrease overdiagnosis of indolent disease, and this can be achieved by improving the current diagnostic strategy. Several authors have proposed the adoption of risk calculators to select patients for biopsy (8, 9). However, even if accurate and constructed with sound methodology, these risk calculators are unlikely to change long-standing clinical behavior, just as other nomograms in other aspects of prostate cancer treatment have been similarly ineffective. In addition to improving patient selection, attention should also be directed at how biopsies are performed.

Furthermore, the conventional random transrectal ultrasound (TRUS)-guided prostate biopsy procedure is inherently prone to sampling bias (10, 11). Entry into and exit from active surveillance protocols is also strongly dependent on biopsy findings, and even among this highly selected population, up to 40% of patients unsus-pectingly harbor more significant disease due to limitations in the accuracy of random biopsies. At present, the only means to sample the prostate gland that approximates that of surgical pathology is through extensive template mapping biopsies (TMB), or "saturation biopsies," whereby 50 to 80 biopsy cores are harvested using a transperineal grid. Apart from being costly and invasive, TMB usually requires anesthesia. Considering that prostate cancer is still the second most lethal solid neoplasm among men and that bone metastases cause debilitating pain, poor quality of life, and lead to an increase of treatment costs (12, 13), we are in need of a novel diagnostic pathway, one that can distinguish life-threatening, aggressive cancers from indolent ones.

We strongly believe that the next revolution in prostate cancer screening and diagnosis will be brought about by the integration of imaging, image-guided biopsy, and image-guided targeted therapies. During the past decade, multiparametric MRI (mp-MRI) of the prostate gland has emerged as a method (14) that not only can detect cancerous lesions but also can characterize their aggressiveness to some extent (14). For instance, diffusion-weighted images (DWI) or dynamic contrast-enhanced (DCE) sequences can often accurately differentiate between low-grade and high-grade cancer, although not to the extent of eliminating the need for a confirmatory biopsy (15). Experienced radiologists can recognize lesions suspicious for cancer using three mp-MRI sequences with a positive predictive value

greater than 95% for lesions approximately 1 cm in dimension (16). In fact, the performance of mp-MRI for detecting cancers 5 mm or larger in diameter and with a Gleason score of 7 or higher (17) exceeds 90% in many studies (14). Because indolent cancer has been pathologically defined as a tumor less than 0.5 cm^3 in volume and without Gleason pattern 4 or 5 (10), mp-MRI meets the requirements of a tool capable of identifying cancers that are potentially life-threatening and therefore necessary to treat, while often missing small or low-grade, clinically insignificant tumors. However, to date, we do not know the minimal spatial resolution of mp-MRI, and thus minuscule volume cancer foci harboring Gleason pattern 4 or 5 might be missed. Even if classic definitions of indolent disease exclude high Gleason patterns, there is evidence that men harboring low-volume Gleason 7 disease have favorable outcomes managed with active surveillance (18–20). Thus, it might be postulated that missing this cancer in the context of a low-grade diagnosis might not do harm, provided that the patient is monitored in time with subsequent studies that might detect possible increase in volumes of an aggressive tumor focus.

Multiparametric MRI provides a basis for image-guided biopsy, instead of random biopsies, diagnosing clinically significant disease, while minimizing the detection of indolent cancers. TRUS-MRI fusion platforms have been developed, allowing the real-time use of previously obtained mp-MRI images to guide TRUS-mp-MRI fusion biopsies in an outpatient setting (21–23). In addition, targeted biopsies have been shown to detect cancer in about 40% of the patients with previous negative biopsies but persistently rising PSA, and about one third of these men harbored aggressive Gleason 8 disease or higher (24, 25).

Thus, mp-MRI could influence the management of prostate cancer in several ways. First, overdiagnosis of prostate cancer could be reduced when using mp-MRI-targeted biopsies. Ideally, a patient's risk of harboring cancer would be assessed with selective PSA testing and other clinical parameters, such as family history, race, age, and prostate volume. Only those patients with a high level of suspicion would undergo mp-MRI. Thereafter, suspicious MRI findings would prompt image-guided, targeted biopsies. These levels of selection would limit the diagnosis of prostate cancer to those at highest risk. In the absence of a well-defined lesion on MRI, the patient could be followed owing to the high negative predictive value of mp-MRI for significant cancer (14). MRI imaging can also be used to follow men on active surveillance protocols. There is evidence that mp-MRI can accurately predict Gleason upgrading in men on active surveillance by demonstrating growth of the index lesion (26). Therefore, men on active surveillance could be followed prospectively with mp-MRI, possibly reducing the number of biopsies. Finally, mp-MRI can be of benefit for the judicious planning and follow-up of therapeutic strategies. As mentioned, the decision about whether a patient undergoes active surveillance, focal therapy, or radical treatment all rely on biopsy findings.

Before MRI-TRUS-targeted biopsies become a new gold standard for diagnosing and characterizing prostate cancer, several steps must occur. First, there must be focused training of radiologists, urologists, and pathologists before they begin interpreting and relying on mp-MRI images and targeted biopsy findings. Indeed, there is a strong correlation between radiologist experience and accuracy of image interpretation (26, 27). Mp-MRI findings can be fused with TRUS images for targeting guidance in potentially any urological clinic that

has access to the hardware and software necessary for TRUS-MRI fusion biopsies and, therefore, radiologists and urologists must learn to speak the same language to aid communication. Second, there should be a consensus on how to interpret MRI findings, as has been done for pathological grading, to ensure standardization and facilitate education. In this context, the START (Standards of Reporting for MRI-Targeted Biopsy Studies) consortium has already released a format to report studies investigating MRI-targeted biopsies (28). Further more, we still need a consensus on which sequences to use and how to implement findings in different sequences to potential biopsy targets Currently four prospective clinical trials have been registered on www.clinicaltrial.gov with the intent of assessing the ability of mp-MRI in improving prostate cancer diagnosis (NCT01864135 and NCT01292291), in avoiding repeat biopsy (NCT01492270), and in better differentiating low from high Gleason grades (NCT01766869). Third, because treatment planning strongly relies on biopsy Gleason score findings, experienced uropathologists will need to be involved in the review of targeted biopsy cores, to ensure correct Gleason score assignment, and avoid undergrading due to lack of experience in prostate cancer (29, 30).

Ultimately, mp-MRI must add value and prove itself economically as well as medically worthy. In the words of Dickenson and colleagues (31): "If a new test, such as mp-MRI, could deliver fewer biopsies, better biopsies, better risk stratification, more appropriate treatment allocation, fewer diagnoses, and fewer men treated overall, we might have a test that could impart significant cost savings over decades." (pg. 282) Future studies of mp-MRI must begin to account for costs in comparison to the current standard methods.

In summary, prostate cancer management has come to a point whereby a modification of the current diagnostic pathway is much needed. There is no doubt that screening reduces mortality when applied to the correct population, but there is a need to define the at-risk population that harbor lethal cancers. The introduction of mp-MRI could greatly reduce the diagnosis of inconsequential tumors while increasing the diagnosis of clinically significant tumors. In this fashion, prostate cancer could be relegated to a chronic, manageable disease whereby men confidently remain on active surveillance, enjoying a high quality of life for as long as possible, until treatment becomes necessary.

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Translational Relevance

Since its introduction into clinical practice, PSA has been the gateway for prostate cancer screening and diagnosis. However, this serum marker has been shown to lack specificity and has a high false-positive rate. Furthermore, current prostate biopsy methods rely on random-sampling strategies, yielding a false-negative rate approaching 40%. To further complicate the situation, PSA screening has led to an increase in the diagnosis of indolent and clinically insignificant disease that often leads to unnecessary treatment, worsening quality of life. In the last decade, advancements in multiparametric MRI (mp-MRI) have opened the doors to prostate imaging. Evidence suggests that the sensitivity of mp-MRI in detecting high grade, clinically significant prostate cancers is greater than 90%. Technological developments nowadays allow the use of mp-MRI findings in conjunction with live ultrasound images to guide prostate biopsies, permitting targeted biopsies of suspicious lesions, potentially reducing the overdiagnosis of indolent tumors and opening the avenue to personalized lesion-targeted therapies.