Review Article

Prostate MRI Can Reduce Overdiagnosis and Overtreatment of Prostate Cancer

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Abstract: The contemporary management of prostate cancer (PCa) has been criticized as fostering overdetection and overtreatment of indolent disease. In particular, the historical inability to identify those men with an elevated PSA who truly warrant biopsy, and, for those needing biopsy, to localize aggressive tumors within the prostate, has contributed to suboptimal diagnosis and treatment strategies. This article describes how modern multi-parametric MRI of the prostate addresses such challenges and reduces both overdiagnosis and overtreatment. The central role of diffusion-weighted imaging (DWI) in contributing to MRI's current impact is described. Prostate MRI incorporating DWI achieves higher sensitivity than standard systematic biopsy for intermediate-to-high risk tumor, while having lower sensitivity for low-grade tumors that are unlikely to impact longevity. Particular applications of prostate MRI that are explored include selection of a subset of men with clinical suspicion of PCa to undergo biopsy as well as reliable confirmation of only low-risk disease in active surveillance patients. Various challenges to redefining the standard of care to incorporate solely MRI-targeted cores, without concomitant standard systematic cores, are identified. These include needs for further technical optimization of current systems for performing MRI-targeted biopsies, enhanced education and expertise in prostate MRI among radiologists, greater standardization in prostate MRI reporting across centers, and recognition of the roles of pre-biopsy MRI and MRI-targeted biopsy by payers. Ultimately, it is hoped that the medical community in the United States will embrace prostate MRI and MRI-targeted biopsy, allowing all patients with known or suspected prostate cancer to benefit from this approach.

Key Words: Prostate cancer; prostate MRI; prostate biopsy; diffusion-weighted imaging; overdiagonsis; overtreatment; active surveillance.

The time has come to change the manner by which prostate cancer is diagnosed and treated. Widespread population screening via serum prostate-specific antigen (PSA) testing has received harsh criticism within the media and medical community owing to the risk of overtreatment of indolent disease that is unlikely to result in disease-related morbidity or mortality (1,2). Most recently, the US Preventive Services Task Force has advised against PSA screening of the general population, regardless of age (3). Such criticism is noteworthy in view of a reduction in mortality through PSA screening that even opponents of screening generally acknowledge (4). For instance, the European Randomized Study of Screening for Prostate Cancer, which is the largest reported clinical trial to date of PSA screening, observed a 20% reduction in mortality (5). In addition, the Goteborg randomized screening trial reported a reduction in mortality of almost 50% at 14 years of follow-up, with a benefit from PSA screening that compared favorably to screening programs for other cancers (6). However, critics emphasize the indolent nature of prostate cancer in most cases, such that the cancer would fail to ever harm the patient if never diagnosed or treated, as supported by the frequent incidental detection of prostate cancer in autopsy series (7). This balance of benefit versus harm from treatment is at the crux of the concern regarding overdiagnosis from PSA screening (4). Although a large number of men with indolent disease must be diagnosed with, and treated for, prostate cancer to save one life, this number-needed-to-treat has varied widely among studies, ranging between five and 48 men (5,6,8), indicating the difficulty in quantifying the magnitude of the burden of overdiagnosis. A critical dichotomy in the interpretation of the problem and its solution exists between opponents and proponents of PSA screening. Although both groups recognize the overdetection problem, proponents of testing argue that modification of the screening paradigm offers the ability to reduce overdetection without compromising the observed improvements in survival.

Proponents of screening argue that the underlying problem is not inherently the PSA test itself but rather the next steps

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that occur after a positive result (4,9,10). These problems fundamentally relate to the historical inability to identify men with an elevated PSA level who truly are in need of biopsy, and, for those who do need biopsy, to localize aggressive tumors within the prostate (9). This limitation has led to clearly suboptimal diagnosis and treatment strategies and legitimate claims of overdiagnosis and overtreatment (9). In terms of the diagnostic technique, an abnormal PSA level has typically resulted in a systematic biopsy in which needles sample multiples areas of the prostate in a nontargeted fashion in hopes of identifying any tumor that may be present. This approach commonly identifies indolent tumor and cannot confidently exclude the presence of aggressive tumor and therefore is unable to reliably differentiate patients with low risk from intermediate-to-high-risk prostate cancer. In terms of treatment, prostate cancer has historically been managed via whole-gland therapy (surgery or radiation), in which the entire prostate is treated, even if there is evidence of only a tiny amount of tumor in one small part of the gland. Patients with low-risk disease are unlikely to receive any benefit from such interventions and instead are subject to harm because of the intervention's negative impact on quality of life, including impotence and incontinence, in a considerable fraction of patients. For instance, one study estimated that >90% of prostatectomy patients with no previous problems reported sexual difficulties at 3-year follow-up, whereas >50% had urinary problems (11). Much of the impetus to treat men with low-risk disease has arisen from biopsy's poor localization capability. In men with low-risk disease demonstrated on standard biopsy, >40% demonstrate higher Gleason score and/or locally advanced disease at the time of radical prostatectomy (12).

To address these issues, three closely linked paradigm shifts must occur. First, a means of determining which men with an elevated PSA level will benefit from biopsy is necessary. A multitude of PSA isoforms, serum and urine biomarkers, as well as clinical nomograms have been evaluated for their ability to improve the specificity of PSA (13). Although generally achieving improved specificity, the majority result in reductions in sensitivity without distinction between high- and low-risk disease. Second, a better biopsy is needed. Specifically, the biopsy that is performed after an abnormal PSA must reliably separate low- and intermediate-to-high-risk disease. Third, the diagnosis itself of prostate cancer must be "dissociated" from treatment (10). Rather than routinely offering aggressive therapy to all new diagnoses, such interventions should be primarily provided to patients having intermediate-to-high-risk disease, whereas patients with low-risk disease receive less-invasive treatment options or even no immediate intervention at all. This shift in approach incorporating individualized treatment selection can only be effective if the initial diagnostic pathway is trusted to give an accurate prognostic assessment. Indeed, "active surveillance" (AS) defers immediate intervention for patients with suspected low-risk disease, instead of closely monitoring the patient for any subsequent evidence of higher risk disease, which in turn triggers intervention with curative intent (14). By reducing overtreatment, AS reduces the potential burden resulting from overdiagnosis. Although of growing interest, AS remains heavily underused, representing the selected treatment approach in a minority of patients with low-risk disease (15,16).

In this article, we describe how magnetic resonance (MR) imaging (MRI) can address these challenges and reduce both overdiagnosis and overtreatment for prostate cancer. This aim requires not only high-quality acquisition and interpretation of multiparametric prostate MRI examinations but also implementation of targeted biopsies of MRI-defined lesions. Challenges to the incorporation of MRI and MRI-targeted biopsy into routine clinical practice are also considered.

IMPROVED RISK STRATIFICATION AND TREATMENT SELECTION USING MRI

The accuracy of prostate MRI has improved over the past decade, partly relating to advances in scanner and receiver coil hardware (17). However, it has been the emergence of diffusion-weighted imaging (DWI) as a central component of prostate MRI acquisition and interpretation (18) that has been crucial to MRI's current impact. Apparent diffusion coefficient (ADC) values derived from DWI are significantly associated with tumor Gleason score (19), which is firmly established as the single best available predictor of prostate cancer outcome and currently serves as the primary determinant of a patient's level of risk (20). Furthermore, prostate MRI incorporating DWI achieves high sensitivity for intermediate-to-high-risk tumor (21). Indeed, numerous recent studies report a negative predictive value of modern prostate MRI protocols for clinically significant cancer of >90% (22–26). Systems are currently commercially available to perform targeted biopsies either directly within the bore of the scanner (27) or using real-time MRI/ultrasound fusion (28) as guidance. These systems can be used to target MRI findings suspicious for clinically significant cancer and thereby improve the sensitivity of biopsy for such lesions.

Several centers have reported benefit from performing MRI and MRI-targeted biopsy in patients being considered for AS (26,29,30). Specifically, targeted biopsy has higher sensitivity than systematic biopsy for intermediate-to-high-risk tumor, such that a diagnosis of low-risk disease can be more confidently trusted. This more reliable diagnosis of low-risk tumor assures patients of the appropriateness of their decision regarding AS. For instance, in one study, targeted biopsy using MRI/ultrasound fusion in patients initially qualifying for AS resulted in disqualification of 29% of patients because of detection of higher risk disease, confirming suitability of surveillance in remaining patients (30). Also, in a study of men undergoing both systematic biopsy and MRI-targeted biopsy using MRI/ultrasound fusion, a higher Gleason score was detected in 38.9% of patients using fusion biopsy, whereas 55% of Gleason score ≥8 tumors were missed on standard biopsy, and none were