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Seminar article

Use of mpMRI in active surveillance for localized prostate cancer

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Abstract

Introduction: In an effort to limit prostate cancer (PCa) overdiagnosis and overtreatment, which have occurred in response to widespread prostate specific antigen testing, numerous strategies aimed at improved risk stratification of patients with PCa have evolved. Multiparametric magnetic resonance imaging (MRI) is being used in concert with prostate specific antigen testing and prostate biopsies to improve sensitivity and specificity of these tests. There are limited data on how multiparametric MRI can be incorporated into active surveillance (AS) protocols.

Evidence acquisition: A PubMed literature search of available English language publications on PCa, AS, and MRI was conducted. Appropriate articles were selected and included for review. Bibliographies were also used to expand our search.

Evidence synthesis: Data from 41 studies were reviewed. AS inclusion criteria and protocols varied among studies, as did indications for use of MRI. Technological improvements are briefly highlighted. Studies are broadly categorized and discussed according to the role of MRI in patient selection, disease staging, and monitoring in AS protocols.

Conclusions: Although improvements in MRI technology have been useful for biopsy guidance and in the diagnosis and staging of PCa, this literature search demonstrates that more prospective research is needed, specifically regarding how this promising technology can be incorporated into AS protocols.

Keywords: Prostate cancer; Active surveillance; Multiparametric MRI; Fusion biopsy; Management

Introduction

In 2015, an estimated 220,800 new cases of prostate cancer (PCa) would be diagnosed in the United States, accounting for approximately 25% of all newly diagnosed cancers in men [1]. With the widespread adoption of prostate specific antigen (PSA) testing in the late 1980s, overall rates of PCa have increased due to disease detection in men with asymptomatic disease [2]. Most of these incident cases are localized to the prostate, and many of the identified cancers are indolent. Detection of indolent cancers, termed overdetection, puts men at risk for treatment and treatment-related side effects without likelihood of benefit. Overdetection and overtreatment are the main harms of screening and can be mitigated by observing, rather than treating, low-risk cancers. Early in the PSA era, most men elected aggressive treatment of low-risk disease (radical prostatectomy [RP] or radiotherapy), whereas today more men with low risk, localized disease are adopting conservative management with active surveillance (AS) [3,4].

Surveillance programs aim to reduce PCa overtreatment and thus limit the well-established side effects of surgery and radiation. This strategy allows for cure if treatment becomes warranted, without compromising disease specific mortality [5]. Numerous AS protocols exist and patients are followed with serial PSA tests, digital rectal examinations (DRE), and periodic transrectal ultrasound-guided (TRUS) biopsy.

The aim of AS is to spare men from the side effects of treatment without undue exposure to the risk of cancer progression. Unfortunately, the available tools (PSA, DRE, and biopsy Gleason score) are imperfect surrogates for disease burden and inadequate predictors of disease progression. Indeed, 20% to25% of patients who meet criteria for surveillance but select surgery have adverse pathologic features at final pathology, limiting enthusiasm for this approach [6–10]. Thus, one of the challenges of AS is choice of appropriate candidates—that is, to identify

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indolent cancers with greater certainty. The other major challenge is to design a monitoring protocol that minimizes the burden on patients and the health care system, while retaining the ability to detect disease progression events while the patient remains within the window of curability [11]. Even in recent years, up to half of men eligible for surveillance choose treatment, and up to a third of those who choose AS eventually go on to have treatment, often in the absence of disease progression [3,4,12]. Thus, improving the certainty of our criteria for AS enrollment, the surveillance protocol itself, and triggers for treatment could lead to more favorable quality-of-life and oncologic outcomes for men with low-risk PCa.

Novel biomarkers and imaging with magnetic resonance imaging (MRI) may have roles in improving the detection of high-grade and potentially progressive disease (increasing sensitivity) and decreasing the detection of low-grade and indolent disease (increasing specificity) to facilitate uptake of AS and improve AS "retention" (i.e., remaining on AS in the absence of disease progression). In this article, we focus on emerging evidence for multiparametric MRI (mpMRI) as a tool for selecting patients for AS and for guiding their subsequent management. mpMRI has increasingly gained attention for its superior potential in diagnosing and risk stratifying patients with PCa [13,14]. Specifically, mpMRI has demonstrated success at accurately identifying clinically significant PCa (i.e., large tumors $\geq$ Gleason 7) [15], improving the sensitivity and specificity of PSA testing, whereas MRI ultrasound (MRI-US) fusion has been useful for effectively targeting prostate biopsies [16,17]. These properties make mpMRI an attractive solution to some of the challenges in selecting patients for AS and monitoring them.

Materials and methods

We conducted a comprehensive literature search of available English language publications to identify studies pertaining to MRI for AS in patients with PCa. The following search terms were used: PCa, AS, and MRI. We searched the PubMed database for abstracts, which were then reviewed to determine eligibility. If it was not clear that the article was suitable for inclusion based on the abstract alone, the entire article was reviewed. We then used the bibliographies of these sources for additional relevant articles to broaden our search.

Evidence synthesis

The rationale for mpMRI in AS

The American Urological Association, National Comprehensive Cancer Network, and the European Association of Urology [18–20] recommend AS as a treatment strategy for selected patients. With this strategy, tumors are indirectly monitored using surrogates of disease burden, like PSA and TRUS biopsy. Although numerous AS protocols exist [13,21–29] problems of overdiagnosis and overtreatment persist. Indeed, 30% [4] to 60% [3] of candidates for AS choose active treatment and up to 1/3 [6,30] of men come off surveillance in the absence of progression. On the other hand, up to 42% of the cases of men who are eligible for AS based on TRUS biopsy are upgraded at RP [7,10,31] demonstrating the limitations of current risk stratification. More accurate disease detection and modes of direct tumor monitoring are needed.

All published protocols rely on TRUS biopsy for tissue diagnosis. Although the number of biopsies recommended over the years has increased, with many centers routinely sampling 12 or more cores, there are significant limitations with this approach. First of all, TRUS biopsies represent a random sampling of a standard template that is not based on known areas of concern within the prostate. This can lead to sampling error and can potentially miss clinically significant PCas. Furthermore, it is well established that TRUS biopsies undersample of the anterior, apical, and anterolateral prostate gland [32–35]. This blind sampling and the concern for underestimating cancer burden increase uncertainty regarding the appropriateness of AS for individuals. In addition, this uncertainty can prompt additional testing, such as confirmatory biopsy, which exposes patients to the harms of additional biopsies, including discomfort and infection.

With more frequent diagnosis of indolent PCas and inherent difficulty in determining optimal treatment strategies, novel tests are needed for improved disease detection, more accurate staging, enhanced patient selection for AS, and better disease monitoring. MRI has emerged as a potential tool for overcoming some of the existent limitations.

Improved MRI technology and equipment; superior lesion targeting

MRI technology has improved markedly over the past several decades and now includes functional sequences, like diffusion-weighted imaging and dynamic contrast enhancement MRI, which lead to better tumor characterization [36,37]. Additionally, MRI magnet strength has increased from 1.5 to 3.0 T improving image resolution, perhaps obviating the need for endorectal coil, and MRI fusion biopsy systems have been developed.

mpMRI encompasses several of these components including T2-weighted imaging to discern prostate morphology, diffusion-weighted imaging to assess functional tissue microstructure, and dynamic contrast enhancement MRI to detect vascular changes associated with malignancy [36]. Magnetic resonance spectroscopic imaging is sometimes added, which determines relative concentrations of metabolites (citrate and choline) in prostate tissue. Although this multitude of sequences provides additional valuable information, interpretation of these various sequences in