Future Perspectives and Challenges of Prostate MR Imaging

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KEYWORDS

• Prostate • MR imaging • Prostate cancer • Clinically significant cancer • Imaging modalities

KEY POINTS

- MR imaging has become an important part of prostate cancer diagnosis.
- As with any new modality that combines unassailable logic with reasonably good data, it has been rapidly adopted.
- With such rapid growth there are also problems.
- Beyond the carefully controlled environments of academic centers, variations in quality and skill become evident and results in general practice are usually not as impressive.
- However, this very observation provides an impetus to improve the method and make it "bullet proof" and, thus, more widely available and more broadly robust.

INTRODUCTION

Prostate cancer is a major cause of morbidity and mortality worldwide.[1] However, unlike other more aggressive cancers, such as lung and pancreatic cancers, which are almost always aggressive, prostate cancers exhibit a broad range of biology ranging from indolent to highly aggressive. The term "clinically significant" prostate cancer has recently been introduced to distinguish those tumors likely to lead to death from those likely to be indolent and have no impact on survival.[2,3] However, the line of demarcation between these 2 categories of prostate cancer remains unclear and in any given patient can vary.

As a result of this categorization of prostate cancer, management can range from active surveillance to aggressive multimodal radical surgical and radiation therapies. The essential challenge for men diagnosed with prostate cancer is to accurately establish where in this broad spectrum of disease their tumor lies and what its likely trajectory is. This trajectory, which often spans 10 to 20 years, may well overlap and be superseded by the trajectories of other health conditions the patient may have.[4] For instance, in a 75-year-old man with severe cardiovascular disease and hypertension in whom a new intermediate risk prostate cancer is discovered, the former disease is more likely to be a cause of death than the latter; therefore, treatment of the prostate cancer might not be warranted.

It would be comforting if we could foresee exactly what would happen to a patient in the future were their prostate lesions to go undetected or, if detected, untreated. That problem will remain a future challenge for the diagnosis of prostate cancer. However, there is inherent uncertainty over the true aggressiveness of all cancers and new technologies are needed to address this problem. Part of the uncertainty arises simply from sampling issues. For instance, a biopsy may miss a lesion or undersample a lesion.[5] Therefore, more accurate biopsies will ameliorate part of the problem. But the problems go well beyond that. The lesion itself can be interpreted differently

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by different pathologists using standard Gleason scoring.[6–8] Even establishing the correct interpretation, the prediction of patient outcome is not yet satisfactory. Thus, although the concept of tumor aggressiveness is conceptually clear, the reality of establishing it is more difficult. Nonetheless, given the multifocality of prostate cancer and the heterogeneity of tumor type within any given tumor, accurate tissue sampling is a fundamental limitation in establishing the aggressiveness of a cancer.[9]

Over the past 50 years, there have been several major developments in the assessment of prostate cancer. The most important was the development of the Gleason scoring system by Dr Donald Gleason in the 1960s. Dr Gleason established 5 patterns of prostate cancer. He suggested that prostate cancers be scored by adding the 2 major histologic patterns together. Gradually, Gleason patterns 1 and 2 were recognized as benign features with no clinical impact and, therefore, are almost never used in Gleason scoring today. Thus, the original Gleason scoring scale, which encompassed scores between 2 and 10, has been reduced to a scale of 6 to 10 in current usage. A Gleason score of 6 represents pattern 3 + 3, whereas a Gleason score of 7 can represent either a 3 + 4 or a 4 + 3 tumor.[10] The amount of pattern 4 in a specimen is associated with likelihood of recurrence after treatment, which serves as an imperfect surrogate of aggressiveness. The vast majority of Gleason 6 and some Gleason 3 + 4 tumors are low grade and are rarely associated with disease-specific mortality. Thus, except for large-volume, low-grade prostate cancers, most patients with Gleason 6 tumors are recommended to follow active surveillance.[11–13] Intermediate risk cancers are those containing some degree of Gleason pattern 4, and the higher the 4 component, generally the worse the outcome. This is a large group of patients and encompasses the full range of biologic aggressiveness. Many men with these Gleason 7 disease (3 + 4, 4 + 3) are probably overtreated. However, aside from Gleason scoring there is no generally accepted good prognostic biomarker for these cancers. Multiple revisions of the Gleason scoring system have tended to increase the Gleason 3 + 4 category at the expense of Gleason 6 tumors. However, this has the undesirable effect of causing more cancers to be treated because of the increased risk associated with pattern 4. Cancers with higher Gleason scores (Gleason score of $\geq$8) are considered high risk and have a reasonable expectation of aggressiveness and mortality if untreated. The most recent innovation in pathologic assessment involving the Gleason scoring system is the International Society of Urogenital Pathology's (ISUP) system, which is a 1 to 5 score (whereby Gleason 3 + 3 is the equivalent of a ISUP 1, Gleason 3 + 4 equivalent of ISUP2, and so forth) that has largely been a rebranding of the existing system.[2,14] Thus, Gleason or its equivalent ISUP score, despite multiple limitations, remains the preeminent method of assessing the aggressiveness of prostate cancer. Numerous methods of assessing genomics of tumors ranging from whole genome sequencing to select subsets of genes have been introduced to help characterize the aggressiveness of prostate cancers. However, none of these has proven superior to the others and only a minority of patients undergo this test. Moreover, the interpretation of the scores of these gene tests is entirely subjective. Thus, better methods of characterizing prostate cancer aggressiveness are needed.

The second big innovation in prostate cancer management was the introduction of the prostate-specific antigen (PSA) serum test, which was introduced in the late 1980s.[15,16] The introduction of PSA as a serum test led to an explosion of diagnoses of prostate cancer. Initially, PSA testing was very popular and led to popular screening campaigns. Unfortunately, because PSA is secreted by normal hyperplastic and malignant tissue, it tends to have many false-positive results, especially in men with benign prostatic hyperplasia or inflammation. When a patient has an elevated PSA level they are commonly recommended to have a random biopsy (also known as the systematic biopsy or a 12-core biopsy). The combination of PSA and random biopsy led to a rapid increase in the diagnosis of prostate cancer, but mostly low-risk, indolent cancers. Because Gleason 6 disease was not understood to be as indolent in the 1990s as it is understood today, these patients were often treated with radical surgery or radiation with resultant loss in quality-of-life indices. A series of trials from the United States and Europe in the 2000s explored the value of PSA. They generally showed a mild decrease in mortality in subjects undergoing PSA screening, but this was only achieved at the cost of significant decreases in quality of life. Cumulatively, these studies seemed to indicate that the minimal mortality benefit was canceled out by the decline in quality of life.[17,18] Even before the decision of the US Preventive Services Task Force (USPSTF) in 2012 to recommend against screening with PSA, there was a growing disenchantment with PSA screening. In 2012, when the USPSTF discouraged the use of PSA by assigning a letter grade of "D," there was a further decrease in screening.[19] However, reports began emerging