Recent advances in magnetic resonance imaging of prostate cancer

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Abstract

This concise review attempts to highlight the recent advances in magnetic resonance imaging (MRI) in relation to all the different aspects of prostate cancer (PCa), and outlines future implications of MRI in the diagnosis, treatment, and surveillance of PCa.

Introduction and context

Prostate cancer (PCa) is the most common malignancy in men – around 200,000 new cases were diagnosed in the US in 2009 – and is responsible for the highest rate of malignancy related mortality after lung cancer [1]. Currently, trans-rectal ultrasound-guided biopsy (TRUS-Bx) is the ‘gold standard’ for diagnosis of PCa. However, TRUS-Bx can lead to serious infections and urosepsis, reported in at least 2-4% of patients [2].

Upon diagnosis of PCa, management decisions pose a dilemma for both the patient and physician. Despite the Scandinavian Prostate Cancer Group Study [3,4] and the European Randomized Study of Screening for Prostate Cancer [5] providing evidence of a reduction in disease-specific mortality in screened and treated PCa populations, it is estimated that between 25 and 84% of PCa patients currently being treated will not succumb to their disease should they be left untreated, in other words, they have a clinically insignificant form of the disease [4,6-10].

Therefore, a sensitive and specific enough imaging modality is needed to help discern between patients with insignificant disease and the patients in need of treatment, and it might also alleviate the need for biopsies to be taken for accurate diagnosis, or at least significantly lower the number of biopsy cores needed.

One such modality is magnetic resonance imaging (MRI), which has been used to evaluate prostate anatomy and

prostate diseases since 1982 [11]. MRI is able to provide detailed anatomical images, particularly of soft tissues, at high spatial resolution, and when combined with the ability to provide functional measurements has lead investigators to extensively explore the role of MRI in diagnosis and staging of PCa. Different sequences (the manner in which the magnet creates pulses and interfaces with the data collected) have been manipulated and even combined to give the greatest information (e.g., contrast-enhanced imaging combined with magnetic resonance spectroscopy).

Recent advances

Tumor localization

MRI PCa localization began with the usage of T2-weighted (T2W) imaging to visualize the anatomy and the architecture of the prostate gland. PCa may be seen as an area with low signal intensity; however, several benign conditions, such as prostatitis, intra-prostatic hemorrhage, and scarring, have a similar appearance, therefore this method has a relatively low specificity of 54-82% and a widely varied sensitivity of 46-96% [12-14]. However, in addition to anatomic information, MRI can elucidate physiological properties of tissue through different imaging techniques such as diffusion-weighted MRI (DW-MRI), which measures the diffusion of water molecules in tissue. Due to its increased cellular density, PCa shows restricted diffusion. Dynamic contrast-enhanced MRI (DCE-MRI) is another technique that assesses the microvascular properties of tissue. As PCa has

an abundant microvasculature, tumors usually show an early signal enhancement and washout of signal intensity. Finally, magnetic resonance spectroscopic imaging (MRSI) can be used to measure metabolite levels in the tissue, particularly choline, citrate, creatine, and various polyamines. PCa usually exhibits an increased concentration of choline, a reduction of citrate, and lower levels of polyamines. Creatine is usually unaffected.

Each imaging technique has been tried separately and been shown to improve PCa localization and detection, but much more interesting is the recent usage of the different modalities in combination, such as multiparametric MRI scanning, which has an improved specificity and sensitivity. Recently, Kitajima *et al.* [15] reported a specificity of 95% and sensitivity of 80% using 3 tesla (3T) MRI and multiparametric scanning. These results have been repeated in many similarly designed trials [16,17].

Tumor volume

In addition to resolving the tumor location, assessing the tumor volume might help with decisions related to the management of the tumor. There is a large variability and generally a poor correlation between MRI-measured tumor volumes and pathologic-examination tumor volume using conventional T2W imaging [18,19]. However, combining different imaging techniques has been shown to significantly increase the accuracy of MRI-calculated tumor volume [19,20]. It is now possible to delineate the tumor with accuracy using MRI, providing a 'safety margin' of 5 mm is maintained [21]. (The safety margin is the rim outside the delineated tumor volume needed to be treated in order to avoid leaving viable tumor cells.) Delineating tumors allows for targeted therapies to be implemented.

Tumor aggressiveness

Tumor biology as currently graded by the Gleason score is one of the key prognostic factors of PCa patients [22,23]. In order to achieve accurate grading one must attain a tissue sample by biopsy. Yet even today, despite more cores being taken per biopsy session, there are still often discrepancies between biopsy samples and final histopathology reports [24].

MRSI is a noninvasive diagnostic tool to assess cancer metabolism and elucidate its biological propensities [25-27]. There is enough evidence to suggest that by using MRSI, risk criteria can be assigned for PCa patients even more accurately than with the Gleason grade determined using TRUS-Bx [28,29]. However, larger studies in multiple centres are required to confirm this observation.

MRI guidance for prostate biopsies

TRUS-Bx, which is currently the 'gold standard' for PCa detection, relies on random sampling of the prostate [30], hence the recent trend for a greater number of core biopsies being taken per patient in order to increase the detection of PCa [31-33]. This can be partly avoided, however, by using lesions that appear suspicious on MRI to direct TRUS-Bx. This has been shown to greatly improve PCa detection in patients with prior negative biopsy and suspicion of harbouring malignancy [34-37].

MRI-guided biopsies have also been performed [38-42] but only limited data is available thus far regarding their efficacy and no trial has compared MRI-guided prostate biopsies with TRUS-Bx.

MRI-guided prostatic interventions

MRI has been used to guide and monitor ablations in a variety of tumors [43-47] including in PCa [48]. In fact, MRI has also been utilized to accurately place high-dose-rate brachytherapy rods [49,50].

MRI has the unique capability to measure the temperature distribution in the prostate gland continuously during thermal ablative treatment to enable delivery of adaptive therapy. This continuous monitoring can be used to compensate for changes in blood flow, prostate size, and minor prostate movement. In addition, quantitative knowledge of the amount of heating in surrounding tissues can be used to protect these regions from thermal damage.

Chen *et al.* [51] performed MRI-guided percutaneous interstitial microwave thermoablation of locally recurrent PCa. MRI-derived temperatures were linearly related to the tissue temperatures, measured with an MRI-compatible thermosensor, therefore they concluded that MRI can be used to guide thermoablation. Chopra *et al.* showed that using MRI thermometry while applying trans-urethral MRI-guided high intensity-focused ultrasound (HIFU) allowed for stable temperature measurements, which were achieved with a standard deviation of approximately $\pm 1^{\circ}\text{C}$ [52].

Assessment of treatment effects and recurrent disease

After different treatments have been conducted that aim to destroy the tumor and leave the prostate behind (such as external beam radiation and focal therapy), it is important to accurately assess the ablation size and validate that it encompassed the desired pre-treatment ablation area, as well as to diagnose disease recurrence.

In order to evaluate the ability of MRI to accurately define ablation volume, Djavan *et al.* [53] utilized radiofrequency

energy to create intraprostatic lesions and demonstrated good correlation between MRI-calculated volume and volume calculated using hematoxylin and eosin (H&E) stains. Larson *et al.* [54] found a strong correlation ($r = 0.92$) between MRI volumetric assessment of damage and H&E assessment of damage when using different minimally invasive treatment modalities to create intraprostatic lesions.

Far more recent studies have shown that MRI is a promising imaging biomarker for therapeutic response of PCa to radiotherapy [55] and allows detection of PCa recurrence after external radiation therapy treatment [56,57] or HIFU treatment [58].

Local persistence or progression after radical prostatectomy is a major reason why prostate-specific antigen (PSA) levels may still be elevated after treatment [59,60]. TRUS of the prostatic fossa in association with TRUS-Bx is considered more sensitive than a digital rectal examination for detecting local recurrence, especially if PSA levels are low [61]. However, TRUS is unlikely to detect tumor mass at low PSA levels (<1 ng/ml) and the role of a biopsy remains unclear, specifically, whether there is really a need to take a biopsy in the event of PSA failure.

Accurate identification of local recurrence with pelvic imaging might improve the effectiveness of tumor eradication with radiotherapy, as MRI has been shown to identify residual disease even when low PSA levels have been detected [62,63]. It seems that DCE imaging further improves the ability to detect local recurrence in patients at high risk of post-prostatectomy failure [64,65].

Active surveillance and MRI

To combat potential overtreatment of clinically insignificant cancer, active surveillance has emerged as an alternative management strategy [66]. Patients who are suspected of having insignificant PCa based on physical examination, PSA levels, and TRUS-Bx results (comprising Gleason score, the number of positive cores, and the percentage of core infiltrated by tumour) are actively monitored. Should the suspicion arise that the disease is progressing or 'active' (as opposed to insignificant disease) based on PSA (rise or kinetics), rectal examination, and repeat biopsies, the patient would undergo curative whole gland treatment. This scheme offers curative treatment to patients we believe warrant it while avoiding inflicting unwarranted side effects on patients who do not need treatment (due to an insignificant disease) [66].

van As *et al.* [67] analysed the apparent diffusion coefficient (ADC) generated from DW-MRI with respect to repeat biopsy findings and time to radical treatment in

86 patients in a prospective study of active surveillance. They demonstrated that a low ADC is associated with adverse histology on repeat biopsy and shorter time to deferred radical treatment. Tumor ADC was highly and significantly correlated with maximum core involvement, percentage of positive cores, and the ratio of free/total PSA. Tumor ADC was also significantly correlated with initial PSA level, but not with PSA velocity.

In a recent retrospective study, Fradet *et al.* [68] demonstrated that patients with lesion findings suggestive of PCa on MRI were at a higher risk for Gleason score upgrading on a subsequent prostate biopsy.

Implications for clinical practice

MRI is fast becoming a multipurpose imaging modality and might soon change the way we think and treat PCa. It is quite plausible that, in the near future, patients who are suspected of harbouring PCa due to elevated serum markers (PSA, PCA3 [prostate cancer antigen 3], or others) will undergo an MRI scan and, according to the results, will either be told all is well or go on an active surveillance protocol, undergo an MRI-guided focal ablation, or go through radical treatment. It stands to reason that the follow-up regimen will consist of biomarker detection and MRI scans; however, currently, the role of MRI is still limited and not well defined by clinical guidelines.

The authors use this imaging tool mostly in patients who have had a previous negative biopsy and are suspected of harbouring PCa, and in prospective studies of patients who are candidates for an active surveillance protocol.

Abbreviations

ADC, apparent diffusion coefficient; DCE-MRI, dynamic contrast-enhanced MRI; DW-MRI, diffusion-weighted MRI; H&E, hematoxylin and eosin; HIFU, high intensity-focused ultrasound; MRI, magnetic resonance imaging; MRSI, magnetic resonance spectroscopic imaging; PCa, prostate cancer; PSA, prostate-specific antigen; T2W, T2-weighted; TRUS-Bx, trans-rectal ultrasound-guided biopsy.

Competing interests

The authors declare that they have no competing interests.

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