Review Article

Magnetic resonance imaging for prostate cancer clinical application

Bing Li[1,2], Yong Du[1,2], Hanfeng Yang[1,2], Yayong Huang[1,2], Jun Meng[1,2], Dongmei Xiao[1,2]

[1]Sichuan Key Laboratory of Medical Imaging, [2]Department of Radiology, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, China

Corresponding to: Hanfeng Yang, MD. Department of Radiology, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, China. Email: yhf5nc@yahoo.com.

Abstract: As prostate cancer is a biologically heterogeneous disease for which a variety of treatment options are available, the major objective of prostate cancer imaging is to achieve more precise disease characterization. In clinical practice, magnetic resonance imaging (MRI) is one of the imaging tools for the evaluation of prostate cancer, the fusion of MRI or dynamic contrast-enhanced MRI (DCE-MRI) with magnetic resonance spectroscopic imaging (MRSI) is improving the evaluation of cancer location, size, and extent, while providing an indication of tumor aggressiveness. This review summarizes the role of MRI in the application of prostate cancer and describes molecular MRI techniques (including MRSI and DCE-MRI) for aiding prostate cancer management.

Key Words: Prostate cancer; magnetic resonance imaging (MRI); functional MRI; molecular MRI

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Introduction

Despite recent improvements in detection and treatment, prostate cancer continues to be one of the leading causes of cancer-related mortality in men of the Western world (1). Application of magnetic resonance imaging (MRI) of the prostate can aid in many aspects of prostate cancer management, from initial detection to treatment planning and follow-up. MRI allows unique anatomic assessment of prostate with better soft tissue resolution than any other imaging modality (2). Moreover, functional MRI techniques, such as magnetic resonance spectroscopy (MRS), diffusion-weighted MRI (DWI) and dynamic contrast-enhanced MRI (DCE-MRI), will affirmatively play an increasing role in the early detection and characterization of prostate cancer, especially of high-grade tumors (3). This review will describe the current strengths and limitations of conventional MRI and molecular MRI techniques for prostate cancer management.

MRI techniques for prostate cancer evaluation

Conventional MRI

At present, optimal MRI of prostate cancer for detection and local staging requires the use of an endorectal coil in conjunction with a pelvic phased-array coil on a mid- to high-field-strength magnet (4). T2-WI provides high-resolution morphologic imaging of the prostate gland in the three planes, and axial T1-WI is used to detect lymph nodes, post-biopsy hemorrhage, and bone metastasis. On T2-WI, the peripheral zone with high signal intensity is surrounded by a thin rim of low T2 signal, which represents the anatomic or true capsule (1). T1-WI of the prostate has uniform intermediate signal intensity, and hence, the zonal anatomy cannot be clearly identified.

Although prostate cancer exhibits low signal intensity that is easily distinguished in the peripheral zone on T2-WI, low signal intensity in the peripheral zone is nonspecific and may be seen in benign conditions such as

changes from hormone therapy, biopsy-related hemorrhage, prostatitis, and postradiation fibrosis (5). Akin *et al.* (6) in a retrospective study defined the characteristic of a transitional zone tumor which included: a homogenous low signal intensity lesion with irregular margins without a capsule, and invasion of the pseudocapsule, with lenticular, urethral and anterior fibromuscular invasion.

Metabolic and functional MRI techniques

Functional MRI techniques can provide metabolic information, show altered cellularity and contribute to noninvasive characterization of tissue and tumor vascularity, and are being evolved to complement conventional MRI in the detection and staging of prostate cancer. This may improve cancer detection, particularly in patients with previous negative biopsies (7).

MRS

Spectroscopy estimates the relative concentration of different chemical compounds in tissue. Currently, proton (hydrogen) MRS is commercially available for the prostate using a 3D chemical-shift imaging technique (5). MRS provides information about the cellular metabolites within the prostate gland by demonstrating the relative concentrations of key chemical constituents such as choline, citrate, and creatinine (2). The metabolites observed *in vivo* in the prostate gland are choline-containing compounds (3.2 ppm), polyamines (3.1 ppm), creatine (3.0 ppm), and citrate (a doublet of doublets at 2.5-2.8 ppm). Citrate is synthesized, stored and secreted by glandular tissue in the prostate and is abundantly available in glandular benign prostatic hyperplasia and in the normal peripheral zone. In carcinoma, however, the citrate level is significantly reduced, in part due to oxidation of citrate (8). The elevation of the choline peak in prostate cancer is mainly due to higher cell membrane turnover, cell density, and phospholipid metabolism. The ratio of choline to citrate is increased in cancer (9). Currently, the elevation of choline levels or ratio of choline to citrate detected on MRS is an indicator of malignancy (10). Because the resonant peak of creatine is close to that of choline, the ratio of choline plus creatine (Ch + Cr) to citrate (Ci) is typically measured on clinical spectroscopy (11). Higher choline-to-citrate ratios are associated with more aggressive tumors. The polyamines peak is significantly lower in prostate cancer than in benign prostatic tissue (12). Jung *et al.* (11) reported a standardized evaluation system which uses a scale of 1 (benign) to 5 (malignant) for data interpretation; in their study, specificities of 84.6% and 89.3% were achieved when voxel scores of 4 or 5 were used to identify cancer.

Several studies have shown improved detection, localization, and assessment of the aggressiveness of prostate cancer when prostate MRI is used in conjunction with MRS (13,14). Findings showed that high-resolution MRS and three-dimensional (3D) MRSI can be correlated with histopathologic examination to reveal different prostate tissue types and cancer grades (15,16).

MRS is technically challenging and some of its limitations include a long acquisition time, possible variability in results dependent on post-processing or shimming, and difficulty in obtaining optimal shimming, and therefore expensive procedure. These limitations of MRS might be improved by new technical developments and the use of higher magnetic fields (3.0 T). MRS at 3.0 T provides increased signal-to-noise ratio (SNR) and increased spectral resolution. Moreover, the high specificity of MRS is of benefit to assess low-risk patients who may be candidates for watchful waiting or deferred therapy (17).

DCE-MRI

DCE-MRI is based on repetitive acquisition of sequential images during the passage of a contrast agent within a tissue which interested. The signal enhancement due to the concentration increase of contrast agent can be surveyed over time for each voxel in the tissue (18). Typically, a full dose (0.1 mmol/kg) of gadolinium chelate is injected at 3 mL/s, and serial 3D acquisitions are obtained every 2-5 s through the prostate (3). Data of the tissue perfusion including blood flow, blood volume, and mean transit time, the microvessel permeability, and the extracellular leakage space can be obtained (19).

The semiquantitative methods describing signal intensity changes include: (I) the onset time of the signal intensity curve (t_0 = time from appearance in an artery to the arrival of contrast agent in the tissue of interest); (II) the slope and height of the enhancement curve (time-to-peak); (III) the maximum signal intensity (peak enhancement); and (IV) the wash-in-washout gradient or plateau phase (20). These parameters are limited by the fact that they may not accurately reflect contrast agent concentration in tissues and can be influenced by the MRI scanner settings (19).

Several quantitative post-processing parameters have been developed, such as K^{trans} (= transfer constant or the

permeability surface area, relating the fraction of contrast agent transferred from blood to the interstitial space), V_e [= extravascular extracellular space (EES) or interstitial space] and k_{ep} (= rate constant, representing the efflux from the EES to blood plasma) (3).

It has been well known that prostate cancer has increased vascular permeability and interstitial fluid volume. Prostate cancer exhibits earlier enhancement and higher washout on DCE-MR images and demonstrated an increased vascular permeability K^{trans} and higher k_{ep} (21). Higher-grade tumors tend to have higher-rate constants (22). Smaller and lower-grade lesions may not even show enhancement on DCE-MRI, and several benign conditions such as prostatitis and postbiopsy hemorrhage can mimic tumors on DCE-MRI (23). Accuracies of 70-90% have been reported for DCE-MRI in primary diagnosis of prostate carcinoma, again yielding a 20% improvement compared to morphologic T2-WI alone.

The values of contrast enhancement parameters, such as mean transit time, blood flow, permeability of the surface area, and interstitial volume, are evidently greater in cancerous tissue than in normal tissue (24). Engelbrecht *et al.* (25) and Kim *et al.* (26) showed that the measurements of relative peak enhancement, and wash-in and wash-out rates were useful for prostate cancer detection and localization. In Kim's study, the sensitivity and specificity were greater on parametric imaging of the wash-in rate compared to T2-weighted imaging in the entire prostate (96% and 82% *vs.* 65% and 60%, respectively) and the peripheral zone (96% and 97% *vs.* 75% and 53%; $P<0.05$), and in the transitional zone, the sensitivity was greater on parametric imaging (96%) than on T2-weighted imaging (45%; $P=0.016$), but the specificity was similar (51% *vs.* 73%; $P=0.102$) (26).

DWI and diffusion tensor imaging (DTI)

DWI is a promising method of prostate cancer imaging that has recently received attention. It is based on the principle of random molecular motion of water in tissues (27). The degree of restriction to water diffusion in biologic tissue is inversely correlated to tissue cellularity and the integrity of cell membranes. Free motion of water molecules is more restricted in tissues with a high cellular density (19). The displacement of a single water molecule that occurs during a diffusion measurement is estimated to be approximately 8 μm. By comparison, the size of cells in the human body is about 10 μm (28).

Quantitative analysis of DWI can be achieved by calculation of the apparent diffusion coefficient (ADC) (29). The ADC can provide quantitative information on the degree of restriction of water diffusion within tissues, including the contribution from microcapillary perfusion and Brownian diffusion within the extracellular space (30). Therefore, ADC is directly associated with coherent microvessel density and cellularity with microcapillary perfusion contributing to a "fast" diffusion component and extra- and intracellular water movement over a shorter diffusion path length contributing to a "slow" component (31).

The normal prostate gland is abundant in tubular structures, which allows for vast self-diffusion of water molecules within their contents and provides high ADC values. In most cases, the peripheral zone can be easily distinguished from the central gland on DWI, due to it shows relative higher ADC values (19). Movement of water is restricted in tumors, which results in a reduction in the ADC value (32). As a result, prostate cancer in both the peripheral zone and transition zone shows significantly lower ADC values compared to normal prostatic tissue, as well as benign prostatic hyperplasia nodules (33). After the acquisition of DW images, an ADC map, which shows the ADC value of each voxel, can be correlated with T2-weighted images. Prostate cancers are high in signal on raw high-b-field DWI because of reduced diffusion, whereas on ADC maps they are low in signal intensity (23). Recent studies showed that DWI can be used to differentiate benign from malignant prostate tissue, which might make DWI become a potential tool to assess prostate cancer aggressiveness (34,35).

DWI has advantages such as short acquisition time and high contrast resolution between normal and tumors tissue. DWI draws attention to suspicious lesions and this may aid in the radiologist to identify regions of interest for local staging (19). Nevertheless, this technique is limited by poor spatial resolution and the potential risk of image distortion caused by post-biopsy hemorrhage, leading to magnetic field inhomogeneity.

DTI is a new, prospective technique. It has been used to neuroimaging for investigating brain structures. In a similar manner, this technique might be applicable to the estimation of structures of the prostate (36). DTI can offer both ADC and fractional anisotropy (FA) values, which may reflect physiological features and pathological changes at the micron level (37).

Although tensors of the noncancerous prostate generally show a symmetrical and concentric form, they are thought

to demonstrate deformities where prostate cancer, hypertrophy, or hematoma exists (36). Manenti *et al.* (38) observed the opposite effect and found that FA was significantly lower in tumor than in benign tissue. And several studies demonstrated that DTI could be a potential navigator for image-guided biopsy (39) and had perfect sensitivity and nearly perfect specificity in prostate cancer diagnosis when combined with DCE-MRI (40).

MRI for clinical application

Staging

The 2002 TNM Classification for Adenocarcinoma of the Prostate is based on T (primary tumor), N (lymph nodes) and M (metastases) categories (41). Stages T1 is not palpable detected by digital rectal examination (DRE) but is by elevated PSA level. Cancer palpable detected by DRE but confined in the prostatic capsule is considered stage T2. Cancer extending beyond the prostatic capsule is considered T3. This latter group includes extraprostatic tumor extension, periprostatic neurovascular involvement, and seminal vesicle involvement. Tumor extending to other adjacent structures is considered stage T4 (41).

Because of its excellent soft-tissue resolution, MRI provides significant incremental value to standard prostate cancer staging nomograms for predicting extracapsular extension (ECE) and seminal vesicle invasion (SVI) (42). The presence of ECE was one of the most important prognostic factors in patients with prostate cancer and has been associated with treatment failure after radical prostatectomy (43). Features that may help to identify ECE include obliteration of the rectoprostatic angle, and asymmetry of neurovascular bundles (44). Irregular bulging of the prostatic capsule seemed to be the most sensitive indicator of ECE at MRI (45). SVI is associated with an increased incidence of lymph node metastasis and a worse prognosis, even in the absence of lymph node involvement (46). A recent study reported that 3-T DWI used in combination with T2-weighted imaging improved the prediction of SVI in prostate cancer compared with T2-weighted imaging alone (47).

Regional lymph node metastases are strong predictors of progression (48). Metastasis to lymph nodes occurs primarily along the obturator, internal iliac, common iliac, and presacral chains. Although it has been suggested that lymph node metastasis occurs stepwise from the pelvis to the retroperitoneum (49), there have been reports that up to 50% of nodal metastases can be paraaortic without pelvic nodal metastasis, suggesting hematogenous rather than lymphatic spread (50). Techniques using intravenous injection of iron oxide nanoparticles may aid in improving detection of nodal metastases by characterizing lymph node architecture. This technique improved the sensitivity to 91% (51).

Hematogenous metastasis to bone occurs most frequently to the lumbar spine, pelvis, ribs, and femoral heads, visceral metastases are quite rare with prostate cancer (41). MRI is superior to scintigraphy and SPECT in detecting bone metastases in the spine and resolving equivocal scans of the spine, with 39% more deposits identified (44).

There are several limitations associated with local staging of prostate cancer by MRI. For example, hemorrhage can show low signal intensity that is similar to prostate cancer and causes discrepancies between the MRI and histopathology results. Furthermore, the most important thing is that MRI cannot detect microscopic invasion (52). Histological analysis also confirmed that in the capsule outline close to the tumor region where there was no fiber representation (38), therefore suspected for lack of confinement of the disease, there was an extension of the tumor into the periprostatic fat. This finding assumed that in the near future DTI might become capable of providing important information for correct tumor staging.

Aggressiveness

The Gleason grading system is the pathologic reference standard for measuring the aggressiveness of prostate cancer (53). Gleason grades are used for predicting patient outcome, with a higher grade indicating increased tumor aggressiveness and likelihood of disease recurrence (54). Generally, transrectal ultrasound (TRUS)-guided biopsies are performed to confirm the presence of prostate cancer and to determine the Gleason score (GS) of the tumor. However, it has been reported that prostate biopsy GS frequently differs from the radical prostatectomy grade (55,56).

Functional MRI techniques can provide qualitative and quantitative information regarding tumor biology (57). It has been known that the reduction of extracellular space in dense cellular tissue may restrict the movement of water molecules, resulting in decreased ADC values (58). So it is possible that decreased ADC values in the higher GS group were the result of restricted motion of water molecules due to increased tumor cellularity. Multiple studies found that ADC values have been shown to

correlate with tumor staging as well as being a potential marker of tumor aggressiveness (34,59). deSouza *et al.* (31) showed that mean fast and slow ADCs from prostate cancer differed significantly between low-risk (biopsy GS ≤6 and prostate-specific antigen level <10 ng/mL) and high-risk (biopsy GS ≥7 or prostate-specific antigen level ≥10 ng/mL) groups. Tumor volume and the slow diffusion component appear to be discriminators of higher-risk disease. Vargas HA *et al.* (34) also showed that regardless of the b value used, there was a significant difference in the mean ADC between malignant and benign prostate regions. A lower mean ADC was significantly associated with a higher tumor GS [mean ADCs (1.21, 1.10, 0.87, and 0.69)×10^{-3} mm^2/s were associated with GS of 3+3, 3+4, 4+3, and 8 or higher, respectively; P=0.017]. And Itou *et al.* (58) demonstrated that there was a significant inverse correlation between GS and ADC values.

In human prostate cancer samples, the progression of tumors to more aggressive lesions is accompanied by a considerable change in metabolism (60). Preliminary findings of studies (61) of *in vivo* and *in vitro* MRS techniques for assessment of prostate cancer aggressiveness have demonstrated that the ratios of choline + creatine/citrate in lesions correlates with Gleason grade. Kobus T *et al.* (62) showed that MRS offers possibilities for an *in vivo*, noninvasive assessment of prostate cancer aggressiveness. Relative augmentation of choline and reduction of citrate indicate a more aggressive and higher grade tumor. The combination of the different metabolite ratios was used with promising results for discrimination among different aggressiveness classes (62). However, Jambor *et al.* (63) found that ^{1}H-MRS enables detection of localized prostate cancer with comparable and limited accuracy but fails to provide information on cancer aggressiveness.

MR-guided prostate biopsy

Although TRUS-guided biopsy is considered the preferred method for prostate cancer detection (64), this technique is associated with a significant false-negative rate ranging between 20% and 33% (65). Many studies have showed that MRI could increase the sensitivity of biopsies in patients with abnormal PSA and negative biopsy, especially when T2W imaging was associated with at least one functional imaging technique: dynamic MRI or spectroscopy (66,67). It allows suspicious lesions to be identified and guides biopsies at these targeted sites, which provide a valuable tool to direct prostate biopsies.

MR-guided biopsy techniques are becoming more and more available, but there is no current consensus on the optimal technique. Open and closed MRI settings are used in tandem (68). The major advantage of the open MR systems is the improved patient accessibility in comparison to the high-field system (69). Unfortunately, open MR scanners are known for a low SNR related to low field strength (typically 0.5 T). The result is image quality that is too low to adequately localize tumors. To reliably identify the target regions, 1.5 T images must be obtained prior to the biopsy procedure by means of a closed-bore scanner. But MR-guided biopsy under closed high-field MRI presents one major challenges: restricted access (70). Therefore MRI-compatible robots are being deliberately designed to operate in the space and environmental restrictions inside the MRI unit, allowing real-time interventions. A variety of MR-compatible robots have been developed (71,72). Most robots have a manual positioning system, which means that the patient could be removed from the scanner in order to correct the position. Krieger *et al.* (73) developed a MRI-guided transrectal robotic prostate biopsy system that has been used in over 200 biopsies to date at the US National Cancer Institute. Such an instrument would become a worthy clinical tool for biopsies, directly targeting imaged tumor foci and delivering tumor-centered focal therapy.

Real-time MRI-guided brachytherapy

Brachytherapy targeted to the peripheral zone with MRI guidance is a prostate cancer treatment option with potentially fewer complications than other treatments (74). MRI provides more detailed anatomic images of the prostate than does transrectal US and because it has been shown to be the most accurate imaging modality for localization of prostate cancer, MRI-based guidance offers the possibility of more precise targeting, which may be crucial to the success of local therapeutic interventions in the prostate. With precise localization of the implanted radioactive seeds, MRI-based dosimetry would permit a more precise evaluation of the radiation dose to the prostate cancer within the prostate gland (75).

The initial report in 1998 (76) described the experience in nine patients who underwent transperineal MRI-guided prostate brachytherapy in the Signa/SP open-configuration 0.5 T MRI scanner. Susil *et al.* (77) and Menard *et al.* (78) used a 1.5 T closed bore scanner for transperineal MR-guided brachytherapy. They developed a customized needle guiding template attached to a positioning arm for

orienting needles according to the treatment plan. Post-treatment toxicity after MRI-guided prostate brachy-monotherapy was infrequent, brief and rare. Albert *et al.* (79) contributed this to the ability to perform a careful urethral-sparing technique with the MRI-guided approach. Frank *et al.* (75) have developed a novel MRI marker for prostate brachytherapy may be able to replace CT-based dosimetry as the standard-of-care quality assurance evaluation after prostate brachytherapy. This could make clinicians to use MRI to identify the base, the lateral margins, and the apex of the prostate gland.

Newer approaches include using MRS-guided (80) high dose rate brachytherapy will likely lead to an improved ability to deliver higher does to the actual tumor, while reserving more and more normal tissues. This is expected to reduce the toxicity profiles and improve patient outcomes.

Surgery planning

The goal of prostate cancer care is to appropriately select therapies based upon risk assessment through accurate characterization of the location and extent of disease to maximize cancer control while minimizing morbidity related to treatment (81). Key elements for guiding appropriate treatments in the individual include: distinction of organ-confined disease from ECE, a determination of total tumor burden, and a determination of tumor grade, none of which have been satisfactorily accomplished in today's pre-treatment paradigm (82).

Achieving negative surgical margins (SM) serves as a pathologic surrogate for adequacy of complete tumor resection at time of radical prostatectomy (RP). A positive SM has been demonstrated to be associated with biochemical recurrence in 50% of men at 10 years after RP (83). The goal of radical prostatectomy is complete removal of the cancer with negative SM; however, it is difficult to achieve such a result while preserving periprostatic tissues necessary for recovery of normal urinary and sexual function. By displaying the size, location, and extent of prostate cancer, MRI can help the surgeon to prevent positive SM and unnecessary damage to structures essential for normal urinary and sexual function (29).

MRI may help predict intraoperative blood loss because the prominence of the apical periprostatic veins on MRI has been positively associated with blood loss. Assessment of the prominence of the apical periprostatic veins on MRI has been positively associated with intraoperative blood loss and may assist in predicting men at risk for substantial intraoperative hemorrhage (84).

MRI may also be of use in surgical planning by identifying enlarged lymph nodes that may harbor cancer. If lymph node metastases appear likely, MRI may help determine whether systemic therapy should be administered before surgery (29).

Detection of local recurrence after therapy

Recurrence of prostate cancer is suspected due to a rising PSA or because a nodule or induration has been felt on DRE. TRUS-guided sextant biopsy is the current reference standard for the detection of local recurrence of prostate cancer in patients with biochemical failure after external beam radiation therapy, but it is invasive and may fail to depict some tumors because only a small fraction of the gland is sampled (85).

MRI may show local recurrences in the peri-anastomotic and retrovesical regions or at other sites in the pelvis, for example, in retained seminal vesicles or at the lateral or anterior SM. MRI combined with MRS aid in the detection of recurrent or residual cancer after cryosurgery and external beam radiotherapy (86). Several previous studies evaluated the clinical utility of MRI/MRS to predict biochemical recurrence (BCR) of prostate cancer after RP, mainly according to the presence or absence of ECE (87,88). They suggested that the MRI/MRS findings of the extra-prostatic disease were the independent significant predictors of BCR. Nishida *et al.* (89) recent study showed that the combination of T2WI and DWI on performing pretreatment MRI helped predict BCR after RP in clinically localized prostate cancer. The combination of MR-guided biopsy and diagnostic MRI of the prostate was a feasible technique to localize prostate cancer recurrence after brachytherapy.

Conclusions

MRI has shown great promise as a tool for the noninvasive assessment of prostate cancer. Currently available anatomic and molecular MRI techniques, when applied by well-trained imagers, can aid in cancer detection, characterization, and localization before and after treatment. Although functional MRI has still several limitations, it is hoped that advances in 3.0 T MRI as well as advances in molecular imaging will further improve patient care by enabling even better treatment selection, planning, and outcomes.

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