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Multiparametric magnetic resonance imaging in prostate cancer: present and future

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Abstract

Purpose of review—The purpose of this article is to review the current status of advanced MRI techniques based on anatomic, metabolic and physiologic properties of prostate cancer with a focus on their impact in managing prostate cancer patients.

Recent findings—Prostate cancer can be identified based on reduced T_2 signal intensity on MRI, increased choline and decreased citrate and polyamines on magnetic resonance spectroscopic imaging (MRSI), decreased diffusivity on diffusion tensor imaging (DTI), and increased uptake on dynamic contrast enhanced (DCE) imaging. All can be obtained within a 60-min 3T magnetic resonance exam. Each complementary method has inherent advantages and disadvantages: T_2 MRI has high sensitivity but poor specificity; magnetic resonance spectroscopic imaging has high specificity but poor sensitivity; diffusion tensor imaging has high spatial resolution, is the fastest, but sensitivity/specificity needs to be established; dynamic contrast enhanced imaging has high spatial resolution, but requires a gadolinium based contrast agent injection, and sensitivity/specificity needs to be established.

Summary—The best characterization of prostate cancer in individual patients will most likely result from a multiparametric (MRI/MRSI/DTI/DCE) exam using 3T magnetic resonance scanners but questions remain as to how to analyze and display this large amount of imaging data, and how to optimally combine the data for the most accurate assessment of prostate cancer. Histological correlations or clinical outcomes are required to determine sensitivity/specificity for each method and optimal combinations of these approaches.

Keywords

diffusion tensor imaging; dynamic contrast imaging; magnetic resonance imaging; magnetic resonance spectroscopic imaging; prostate cancer

Introduction

Development of MRI as a clinically useful technique for the assessment of prostate cancer has been a research focus since the mid-1980s [1–5]. Vigorous progress still continues in the still-young science of prostate MRI, and in new, related imaging techniques such as magnetic resonance spectroscopic imaging (MRSI) [6], diffusion tensor imaging (DTI) [7,8], and dynamic contrast enhanced (DCE) imaging [9–15]. A number of recent MRI studies have demonstrated that the detection and characterization of prostate cancer can be improved through the addition of MRSI [16,17,18•,19,20•,21,22•,23–26,27••,28–30,31•,32], DTI [33–38],

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and DCE imaging to an MRI staging exam [39••,40,41••,42–44], and by performing the imaging exam at 3T [45–47]. In this article, the current clinical status of these advanced imaging techniques for the detection and characterization of prostate cancer will be concisely reviewed with an emphasis on the clinical utility of the resulting imaging information.

Combined MRI/magnetic resonance spectroscopic imaging

While MRI traces anatomy, MRSI is used to spatially detect deviations from normal biochemistry that occur in tumor tissue. Specifically, magnetic resonance (MR) anatomic images, especially high spatial resolution combined endorectal coil pelvic phased array MR images, provide an excellent depiction of prostatic anatomy with regions of healthy prostate tissue demonstrating higher signal intensity than prostate cancer (Fig. 1a, red arrows) [1–5]. MRSI provides a noninvasive method of detecting small molecular markers (choline-containing metabolites, polyamines and citrate) within the cytosol and extracellular spaces of the prostate and is performed in conjunction with high-resolution anatomic imaging (MRI) [6]. On MRSI spectra, the resonances for choline, creatine, polyamines and citrate occur at distinct frequencies (Fig. 1b). The areas under these signals are related to the concentration of the respective metabolites, and changes in these concentrations can be used to identify cancer with high specificity [48,49]. Specifically, in spectra taken from regions of prostate cancer (Fig. 1b, red box), citrate and polyamines are significantly reduced or absent, while choline is elevated relative to spectra taken from surrounding healthy peripheral zone tissue. The morphologic and biochemical causes of these metabolic changes are fairly well understood and have been discussed in a review article [6]. There is also a growing amount of published data indicating the metabolic information provided by MRSI combined with the anatomical information provided by MRI can significantly improve the clinical assessment of cancer location and volume within the prostate [48,49–53], extracapsular spread [54,55••], and cancer aggressiveness [56,57]. The presence of tens of thousands of whole-body 1.5T MRI scanners in hospitals worldwide and the availability of commercial MRI/MRSI packages will allow the routine clinical use of these techniques in the near future.

Multiparametric MRI at 3T

Although 1.5T prostate MRI/^{1}H MRSI is now commercially available and is becoming more widely used, the growing availability of 3T MR scanners offers the potential for significant improvements in both spatial and spectral resolution and in speed [46,58,59]. Imaging at 3T can also improve DTI and DCE imaging that can provide additional quantitative functional measures of the prostate at a higher spatial resolution than MRSI [44,46,47,60]. DCE MRI provides valuable information concerning prostate cancer microvascularity and angiogenesis [9–15]. DCE MRI is performed by injecting a small molecular weight MR contrast agent (gadolinium-DTPA) into the patient, and measuring the increase in signal intensity on fast T_1-weighted images of the prostate. The rate of enhancement in the images is reflective of the vascular volume and the permeability of the vessels, while the magnitude of enhancement reflects the extravascular/extracellular leakage space. Studies have demonstrated that DCE MRI can discriminate prostate cancer from surrounding healthy prostate tissues based on a higher and faster rate of contrast enhancement (Fig. 1d) [15,61–64]. Diffusion-weighted imaging is sensitive to the motion of water molecules at microscopic spatial scales within biological tissues [7,8]. Unlike other tumors that demonstrate increased average water diffusivity (<*D*>) compared to surrounding benign tissues, initial studies suggest that prostate cancers demonstrate lower <*D*> values (Fig. 1c) [34,36,65–69].

Detection and localization of cancer within the prostate

In clinical practice, reliable detection and localization of often small regions of prostate cancer is of increasing therapeutic importance due to the emergence of ‘active surveillance’ and focal

ablative therapy such as interstitial brachytherapy, intensity-modulated radiotherapy, high-intensity focused ultrasound, and cryosurgery [70]. MRI alone has demonstrated good sensitivity but poor specificity in detecting cancer in the prostate [44,71,72•]. Recent estimates using T_2-weighted sequences and endorectal coils vary from 60 to 96% [42]. The poor specificity is due to other benign pathologies [inflammation, stromal benign prostatic hyperplasia (BPH)] and therapy also causing a loss of ductal morphology and low T_2 on MRI [73•]. Additionally, infiltrating prostate cancer may not cause a reduction in normal glandular morphology and therefore will not be hypointense on MRI [73•]. Similar to imaging at 1.5T, T_2-weighted image quality, prostate cancer localization and staging is significantly improved at 3T with the use of an endorectal coil as compared with a external phased array coil [74•]. Identifying prostate cancer within the central gland is particularly difficult for MRI due to the overlap of T_2 weighted signal intensity in predominately stromal BPH. In a recent study of 148 prostate cancer patients prior to radical prostatectomy MRI alone detected transition zone prostate cancers with modest accuracy with areas under the reader operator curve (AUC) ranging from 0.73–0.75 [75].

The higher specificity of MRSI to metabolically identify cancer can be used to improve the ability of MRI to identify the location and volume of cancer within the prostate [48–50,76–78]. A study of 53 biopsy proven prostate cancer patients prior to radical prostatectomy and step-section pathologic examination demonstrated a significant improvement in cancer localization to a prostatic sextant (left and right; base, midgland, and apex) using combined MRI/MRSI versus MRI alone [49]. A combined positive result from both MRI and MRSI indicated the presence of tumor with high specificity (91%) while high sensitivity (95%) was attained when either test alone indicated the presence of cancer [49]. The addition of a positive sextant biopsy findings to concordant MRI/MRSI findings further increased the specificity (98%) of cancer localization [48]. More recent studies in early stage prostate cancer patients, however, have indicated that combined 1.5T MRI/MRSI does poorly at detecting and localizing small ($<0.5\ cm^3$) low grade ($\leq 3 + 3$) tumors [57,76,78]. One study [57] demonstrated that overall sensitivity ofMR spectroscopic imaging was 56% for tumor detection, increasing from 44% in lesions with Gleason score of 3 + 3 to 89% in lesions with Gleason score greater than or equal to 4 + 4. The inability to detect small low grade tumors by 1.5T MRSI is primarily due to the partial voluming of surrounding benign tissue in spectroscopic volumes containing cancer due to the relatively coarse spatial resolution of 1.5T MRSI ($0.34\ cm^3$, ~ 7 mm on a side). At 3T, higher spatial resolution of MRSI can be obtained ($0.16\ cm^3$, ~ 5 mm on a side) in the same acquisition time as 1.5T, thereby improving the ability of MRSI to detect small, early stage tumors (Fig. 1b).

DTI and DCE images can be acquired at very high spatial resolution ($0.9 \times 1.8 \times 4$ mm) potentially improving MR detection of small low grade tumors, and within a matter of minutes allowing their addition to a clinically reasonable MRI/MRSI exam. DCE imaging at 1.5T and 3.0T demonstrated similar sensitivities (73 and 73%, respectively) and specificities (81 and 77%, respectively) for identifying cancer within the prostate [10,44]. In another study of 34 prostate cancer patients who received an MRI/MRSI/DCE exam prior to radical prostatectomy, it was demonstrated that reader accuracy in tumor detection was significantly ($P < 0.01$) better for three-dimensional MRSI (AUC 0.80) and DCE (AUC 0.91) than T_2-weighted imaging (AUC 0.68) [41••]. No attempt was made, however, to determine the accuracy when all three techniques were combined. DTI studies at 3T also demonstrated good sensitivity (84%) and specificity (80%) for identifying cancer within the prostate [38], and the overall accuracy (AUC 0.89) was found to be better than that of T_2 imaging (AUC 0.82) [33]. A positive correlation was also found between MRSI and DTI findings for prostate cancer [68]. As demonstrated in Fig. 1, MRI/MRSI/DTI/DCE can be performed in a 1-h 3T MR exam; the most accurate detection and characterization of prostate cancer will most likely arise from combining information from all four techniques.

Tumor volume estimation

The pathologic finding that larger tumors are more likely to be of an advanced stage suggests measurement of prostate cancer tumor volume may provide important information on prognosis that is independent of direct morphologic assessment of extracapsular extension [79]. This has important implications for the potential prognostic role of imaging in prostate cancer, since 'it is beyond the capability of any current imaging study to detect microscopic local tumor extension' [80]. Two recent studies suggest that MRI/MRSI and DCE imaging may noninvasively provide estimates of cancer volume at diagnosis. One study [78] demonstrated that for nodules greater than 0.5 cm^3, tumor volume measurements by MRI, MRSI, and combined MRI and MRSI were all positively correlated with histopathologic volume (Pearson's correlation coefficients of 0.49, 0.59, and 0.55, respectively), but only measurements by MRSI and combined MRI/MRSI reached statistical significance (P <0.05). The addition of MRSI to MRI also increased the overall accuracy of prostate cancer tumor volume measurement, although measurement variability still limited consistent quantitative tumor volume estimation, particularly for small tumors (<0.5 cm^3). Another study [39••] demonstrated that DCE imaging can determine the volume of smaller foci of prostate cancer with greater overall accuracy than MRI/MRSI. Sensitivity, specificity, and positive and negative predictive values for cancer detection by DCE imaging were 77%, 91%, 86% and 85% for foci greater than 0.2 cm^3, and 90%, 88%, 77% and 95% for foci greater than 0.5 cm^3, respectively.

Predicting organ confined prostate cancer

A more accurate prediction of organ confined prostate cancer at the time of diagnosis would allow the determination of whether 'focal therapy' is appropriate for a given patient. At 1.5T MRI, it has been demonstrated that anatomical features on MRI such as bulging of the prostate obliteration of the rectoprostatic angle and asymmetry of the neurovascular bundle can predict extra-capsular extension (ECE), with specificity up to 95% but with low sensitivity (38%) [81]. It was found that tumor volume per lobe estimated by MRSI was significantly (P <0.01) higher in patients with ECE than in patients without ECE [54]. Moreover the addition of an MRSI estimate of tumor volume to high specificity MRI findings for ECE [81] improved the diagnostic accuracy and decreased the inter-observer variability of MRI in the diagnosis of extracapsular extension of prostate cancer [54].

An important advance in the staging of prostate cancer has been the development of multivariable risk prediction instruments such as the Partin tables [82] and nomograms, which combine clinical stage, serum prostate specific antigen (PSA) levels, and grade of biopsies results to predict the pathologic stage of the cancer and likelihood of recurrence after therapy, respectively [83–85]. Two recent studies demonstrated that addition of MRI/MRSI findings could significantly improve the predictive ability of biopsy based staging nomograms. In a study of 24 prostate cancer patients prior to radical prostatectomy the addition of endorectal MRI results contributed significant incremental value to a nomogram for predicting seminal vesicle invasion (SVI). It was found that the nomogram plus endorectal MRI (0.87) had a significantly larger (P <0.05) AUC than either endorectal MRI alone (0.76) or the nomogram alone (0.80) [31•]. In another study of 383 prostate cancer patients prior to radical prostatectomy, 1.5T MRI/MRSI data were added to a nomogram for predicting organ-confined prostate cancer (no ECE or SVI) in order to assess its incremental value. The contribution of MRI/MRSI findings were significant in all patient risk groups but were greatest in the intermediate- and high-risk groups (P <0.01 for both) [55••].

Predicting indolent disease

Due to increased screening using serum PSA and extended-template transrectal ultrasound-guided biopsies, thousands of patients with prostate cancer are being identified at an earlier and potentially more treatable stage [86••]. The risk of overdetection, detecting a cancer which would not become clinically significant during that patient's lifetime if left untreated, however, has been estimated to vary between 15 and 84% [87–89]. Therefore there is an increased interest in active surveillance, but clinical parameters alone are not sufficient to predict a benign disease course. A recent study suggested that the addition of MRI/MRSI data to clinical parameters could improve this prediction. In a study of 220 patients prior to surgery, the addition of MRI (AUC 0.803) and MRI/MRSI (AUC 0.854) to biopsy based nomograms (basic AUC 0.57, comprehensive 0.73) was found to significantly improve the prediction of indolent prostate cancer using a surgical definition of indolent disease (no ECE or SVI and <0.5 cm^3 of cancer with no pattern 4 or 5 cancer) as the standard of reference [86••]. In another study of men who selected active surveillance, serial PSA levels were found to correlate with cancer but not BPH at serial endorectal MRI/MRSI, suggesting that PSA is a useful longitudinal tumor marker in this population [18•]. This study suggests that using a PSA velocity of over 0.75 ng/ml/year would allow the identification of men with progressive disease who would benefit from a follow-up imaging exam.

Conclusion

Commercial MRI/MRSI packages for staging prostate cancer on 1.5T MR scanners are now available and the technology is becoming mature enough to begin assessing its clinical utility in large patient cohort studies using surgical pathology or clinical outcomes as the standard of reference. Recent studies have demonstrated that 1.5T MRI/MRSI has the potential to significantly improve the local evaluation of prostate cancer presence and volume and has been shown to have a significant incremental benefit in the prediction of pathological stage when added to nomograms incorporating nonimaging preoperative risk factors. Combined 1.5T MRI/MRSI also has recognized limitations, including the potential for false positive and false negative results, particularly for small volume (<0.5 cm^3) early stage cancer. Recent studies have shown that accuracy can be improved by performing MRI/MRSI at higher magnetic field strengths (3T) and through the addition of other functional MR techniques, namely DTI and DCE imaging. There are currently no commercially available 3T MRI/MRSI/DTI/DCE staging exams but the ability to accomplish this exam on clinical 3T scanners in a clinical reasonable time has been demonstrated and commercial products should be available within the next couple of years. A challenge to the clinical utility of such a multiparametric exam is having the appropriate tools to analyze and display the large amount of data acquired and how to optimally combine the data to give the most accurate assessment of prostate cancer in individual patients.

Acknowledgments

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 126–127).

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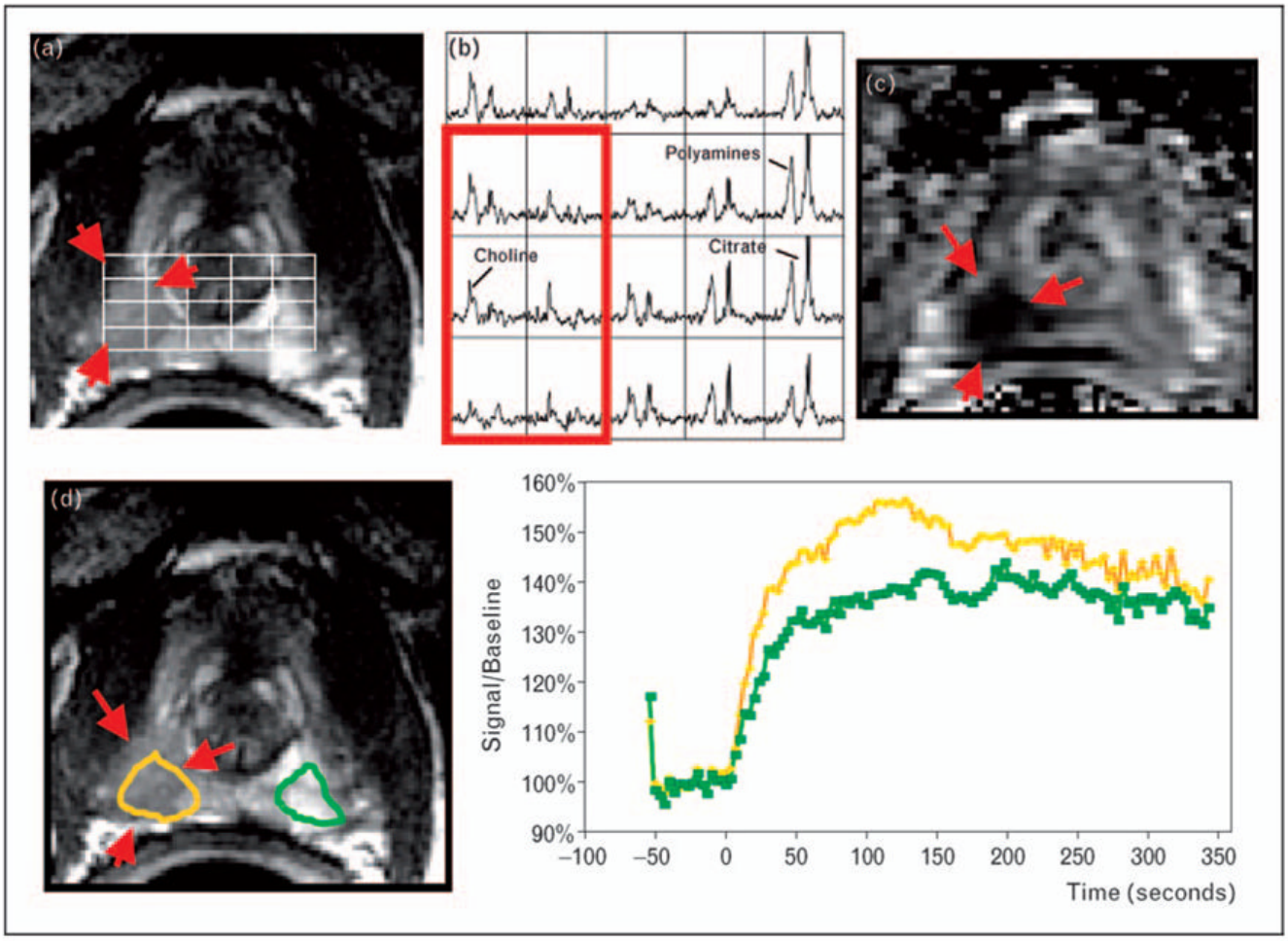

Figure 1.

An example of a multiparametric 3T magnetic resonance exam of a 55-year-old patient with a prostate specific antigen of 8.46 ng/ml and biopsy-proven cancer (left apex, 1/12 cores having 5 mm of G3+3)

(a) T_2 weighted MRI showing a region of low signal intensity lesion (red arrows) in the right apex. (b) Corresponding spectral 0.16cm^3 array showing abnormal spectra (red box) in the same region as the suspicious region of low T_2 signal intensity. (c) A calculated water diffusion image demonstrating a reduction in intensity in the region of prostate cancer. (d) The contrast uptake curves from the region of prostate cancer (yellow) was more dramatic and washed-out faster than healthy prostate peripheral zone (green) tissue on dynamic contrast enhanced MRI. Prostate cancer in the left apex was confirmed at surgery.