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EDITORIAL

# Incremental value of magnetic resonance imaging in the advanced management of prostate cancer

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## Abstract

Prostate cancer is a major public health burden throughout the world. The high incidence of prostate cancer, combined with earlier detection and downstaging at the time of diagnosis, and the slow natural progression and biological heterogeneity of the disease, has made its management a complex and controversial issue. There is growing demand for patient-specific therapies that can minimize treatment morbidity while maximizing treatment benefits. There are a number of clinical parameters and clinical nomograms to help with the choice of treatment. Magnetic resonance imaging (MRI) is a technique which makes safer, more individualized therapies possible due to high spatial resolution, superior contrast resolution, multiplanar capability, and a large field of view. Other MRI techniques such as MR spectroscopic imaging, dynamic contrast-enhanced MRI or perfusion MRI, and diffusion-weighted imaging complement MRI by reflecting tissue biochemistry, Brownian motion of water molecules, and capillary wall permeability, respectively. This editorial review highlights the incremental value of MRI in the advanced management of prostate cancer to non-invasively improve cancer staging, biologic potential, treatment planning, therapy response, local recurrence, and to guide target biopsy for clinical suspected cancer with previous negative biopsy. Finally, some future prospects for MRI in prostate cancer management are given.



**Key words:** Prostate neoplasms; Health care costs; Magnetic resonance imaging; Patient care planning; Clinical nomograms

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## INTRODUCTION

Prostate cancer affects men of all races, cultures and ethnic backgrounds and is a major public health burden throughout the world[1-3]. It is the most common non-cutaneous cancer and the second/third leading cause of cancer death in men in the United State and European Community[1,3,4]. Asian/Pacific Islanders have a lower incidence of prostate cancer than either African Americans or Caucasians[5] but the death toll from prostate cancer mortality in East Asia continues to rise[6]. A wide discrepancy exists between the number of men diagnosed and those dying from prostate cancer. Prostate cancer is an age-related disease and the increasing natural life expectation will result in a further increase of both the incidence of and the deaths related to prostate cancer[1,7].

The high incidence of prostate cancer, combined with earlier detection and downstaging at the time of diagnosis, and the slow natural progression and biological heterogeneity of the disease, has made its management a complex and controversial issue. The National Cancer Institute's Surveillance, Epidemiology, and End Results Program reported that from 1996 to 2004, 91% of prostate cancer cases were of a local or regional stage at diagnosis, and patients had a 5-year relative survival rate of 100% from 1996 to 2004[1]. The 100% 5-year relative survival rate for all stages indicates that prostate tumors have a slow growth rate and allow for prolonged survival[8]. However, the downstaging resulting from prostatic serum antigen (PSA) screening has been accompanied by an unfortunate trend of overdetection and overtreatment of biologically indolent (low-grade, clinically insignificant) disease[8-11]. Autopsy studies indicated that the "overdetected" cancers never impacted patient longevity[10]. Primary therapies with curative intent (surgery or radiation) provide excellent long-term cancer control but are accompanied by a risk of treatment-related morbidity. Conversely, the understandable appeal of watchful waiting or active surveillance is balanced by the potential harm of missing a window of curative opportunity for a cancer destined to progress[8]. One challenge physicians and patients face is to differentiate men who have disease destined to progress and cause morbidity/mortality from those who will not require immediate, or possibly even delayed, therapeutic intervention[12-14].

Depending on patient age at diagnosis, the stage and aggressiveness of the tumor, the potential side-effects of the treatment, and patient comorbidity[8,15], the options for treatment may include watchful waiting, androgen ablation (chemical or surgical castration), hormone therapy, radical surgery, and various forms of radiation therapy (brachytherapy, external beam irradiation, beam irradiation)[16,17]. In addition, new focal therapies, such as cryotherapy, high-intensity focused ultrasound and radiofrequency ablation is raising clinical interest[18]. There is growing demand for patient-specific therapies that can minimize treatment morbidity while maximizing treatment benefits[19,20]. An important objective prior to any cancer therapy is to obtain a comprehensive and accurate knowledge of tumor location, size, extent, and biologic potential. Better tools are needed to help physicians and patients decide what type of treatment is most appropriate, or whether any treatment is needed at all.

There are a number of clinical parameters and clinical nomograms to help with the choice of treatment[20-26]. To aid in patient counseling, the National Comprehensive Cancer Network guidelines define low risk as a PSA less than 10 ng/mL, a Gleason score of 6 or lower, and a T stage of T2a or lower; the guidelines define high risk as a PSA of more than 20 ng/mL, a Gleason score of 8 or higher, or T2c; intermediate risk is defined as a PSA of 10 to 20 ng/mL, T2b, or a Gleason score of 7[27]. To replace somewhat arbitrary combinations of individual clinical variables, nomograms have been developed and used to give a prediction of the final pathologic stage, the chances of freedom from disease recurrence and an estimate of biologic potential, and to aid in the choice of treatment[20,24-26,28,29]. The Partin staging nomogram (also called the "Partin tables"), which is based on clinical stage, Gleason score, and serum PSA level, was first published in 1993 and was updated in 1997 and again in 2001 to predict the pathological stage at radical prostatectomy[28-30]. Other nomograms, such as Kattan's nomograms, have been developed to predict stage, recurrence, or biologic potential. The nomograms are graphic representations of a statistical model, with scales for calculating the prognostic weight of a value for each individual variable[26,31]. As an important advance in accurate prediction for clinical medicine, the nomograms allow calculation of the continuous probability of a particular outcome and tend to outperform both expert clinicians and risk grouping. The nomograms are validated predictive instruments widely used for individual patient counseling and important decision-making. Despite the strong predictive ability and the cost-effectiveness of the nomograms, there is room for improved accuracy of prediction, particularly as clinical staging in the nomograms is based only on digital rectal examination and biopsy-determined Gleason grade. Although valuable, biopsy is subject to sampling error. Moreover, the nomograms are limited because they do not incorporate the results of imaging studies that could guide interventions to control local disease. Thus, a technique that noninvasively demonstrates the presence, extent, and biologic potential of prostate cancer could contribute incremental value to clinical nomograms and variables and make a substantial contribution to the decision-making process for individualized treatment[32,33].

Magnetic resonance imaging (MRI) is a technique which makes safer, more individualized therapies possible due to high spatial resolution, superior contrast resolution, multiplanar capability (Figure 1)[34-38]. In the last decade, MRI has improved significantly with technologic refinements and increased reader experience. Newer techniques, such as MR spectroscopic imaging (MRSI) (Figure 2), dynamic contrast-enhanced MRI (DCE-MRI) or perfusion MRI (Figure 3), diffusion-weighted imaging (DWI) (Figure 4), high-field strength MRI scanning (Figures 1 and 5), image post-processing and picture and communication systems (PACS) provide greater resources for improved interpretation of MR images of the prostate by experienced radiologists[39,40]. MRSI identifies prostate cancer by an increased ratio of choline plus polyamines plus creatine to citrate (Figure 2)[41]. As a result of increased energy metabolism, the citrate level is reduced in prostate cancer. Owing to a high phospholipid cell membrane turnover the choline level is elevated in proliferating malignant tissue. DWI measures the Brownian motion of water molecules in biologic tissues where increased cellularity and the integrity of cell

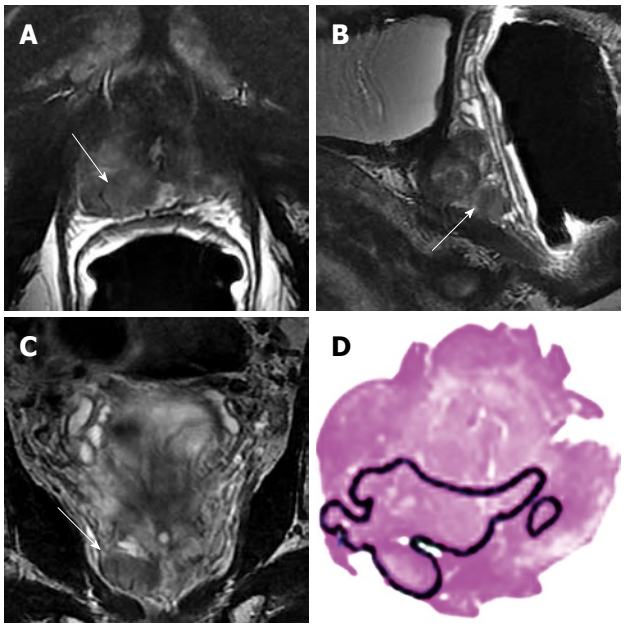


**Figure 1 3T magnetic resonance (MR) images of extracapsular extension (ECE) of prostate cancer in a 65-year-old man with clinical stage T1c prostate nodule and prostate specific antigen (PSA) level of 10.7 ng/mL and Gleason grade 4+4 and PT3a.** Transverse 3 mm-thick MR (6500/175) image (A), sagittal 3 mm-thick MR (7000/165) image (B) and coronal 3 mm-thick MR (7000/170) image (C) show a hypointense tumor (arrows) with extraprostatic extension in the right apex and mid of the prostate; D: Whole-mount serial section of the removed prostate shows tumor and ECE involving the right apex and mid of the prostate.

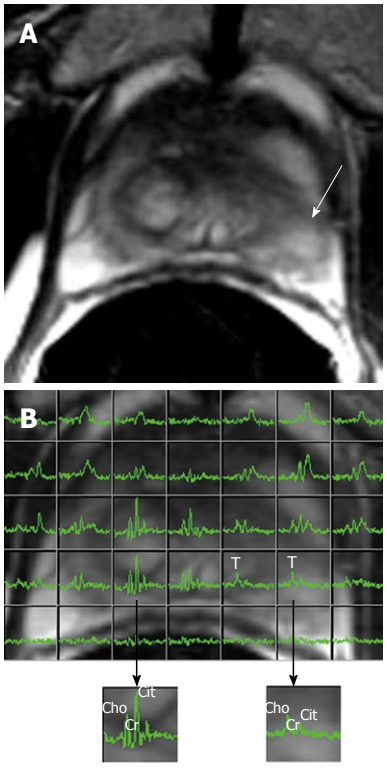


**Figure 2 Prostate cancer in a 65-year-old patient with PSA level of 4.76 ng/mL.** Transverse T2-weighted MR image (WI) (A) and corresponding MR spectroscopic imaging (MRSI) grid (B) superimposed on the anatomic image show the tumor (arrow) on the left apex. MRSI demonstrates reduced citrate and elevated choline in the left peripheral zone tumor (T) and normal spectra in the healthy right peripheral area. Cho: Choline; Cr: Creatine; Cit: Citrate.

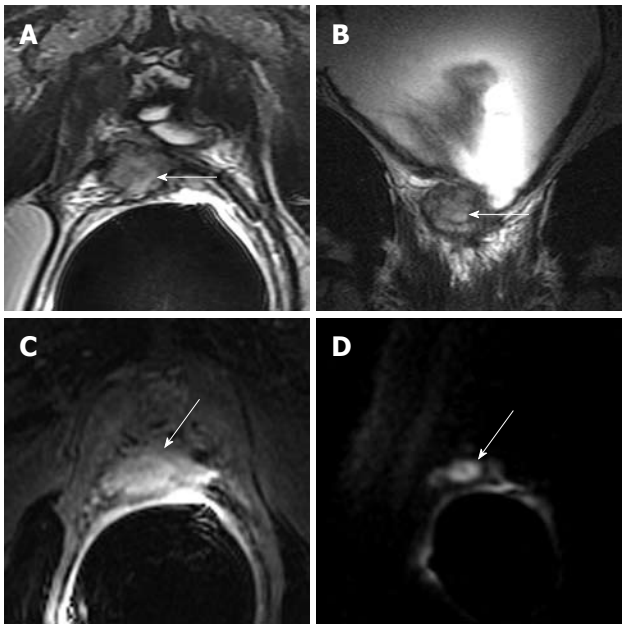


**Figure 3 1.5T MR images of locally recurrent prostate cancer in a 63-year-old man with rising PSA levels after radical prostatectomy.** Transverse 3 mm-thick T2-WI (4000/125) (A) and coronal 3 mm-thick T2-WI (5300/100) (B) show intermediate SI mass (arrows) to the right posterior aspect of the bladder neck at the anastomosis; C: Transverse 3 mm-thick T1-WI (5.5/2.4) shows significant enhancement of the mass (arrow) after intravenous administration of gadolinium; D: Transverse 3 mm-thick diffusion-weighted image (DWI) (3500/93, b-value of 1000 s/mm$^2$) shows intense increased signal (restricted diffusion) throughout the mass (arrow).

membranes restrict water diffusion. The apparent diffusion coefficient (ADC) derived from DWI, has been in use for detection of prostate cancer. DWI demonstrated reduced ADC values and increased fractional anisotropy in prostate cancer. DCE-MRI has been used to visualize tumor perfusion and tumor capillary wall permeability and hydrostatic pressure[42]. Vascular endothelial growth factor has a role in increasing tumor capillary wall permeability. This review addresses the incremental value of MRI in the advanced management of prostate cancer to non-invasively improve cancer staging, biologic potential, treatment planning, therapy response, local recurrence, and to guide target biopsy for clinically suspected cancer with previous negative biopsy, and discusses the future prospects of MRI in prostate cancer management.

## PROSTATE CANCER STAGING

The staging of prostate cancer was based on the TNM (tumor node metastasis) staging. TNM staging of prostate cancer has undergone a number of modifications, the latest ones having been made in 2010 by the American Joint Committee on Cancer. The 2010 revised TNM system, shown in Table 1, is clinically useful and precisely stratifies newly diagnosed cancer[43]. Most importantly, clinicians must distinguish between patients with pathologically organ-confined prostate cancer (OCPC) (pT2), considered good surgical candidates, and those

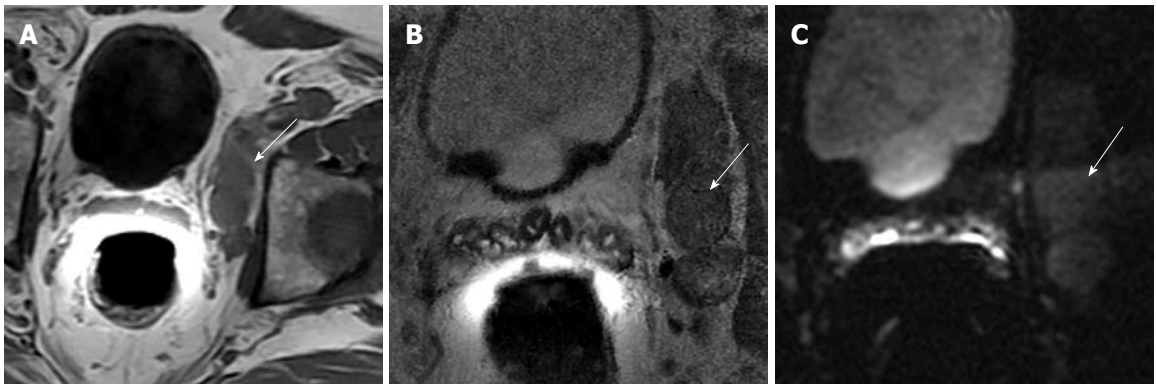


**Figure 4 MR depiction of malignant adenopathy from prostate cancer in a 63-year-old man with Gleason score 4 + 5 and PSA level of 24 ng/mL.** Transverse 5 mm-thick T1-WI (600/8) (A) and transverse 3 mm-thick T2-WI (5450/118) (B) show intermediate SI bulky adenopathy (arrows) with short-axis dimensions of > 10 mm is present in left external iliac and obturator distributions; C: Transverse 3 mm-thick DWI (3500/98, b-value of 1000 s/mm$^2$) show intense, increased signal (restricted diffusion) throughout the mass (arrow).

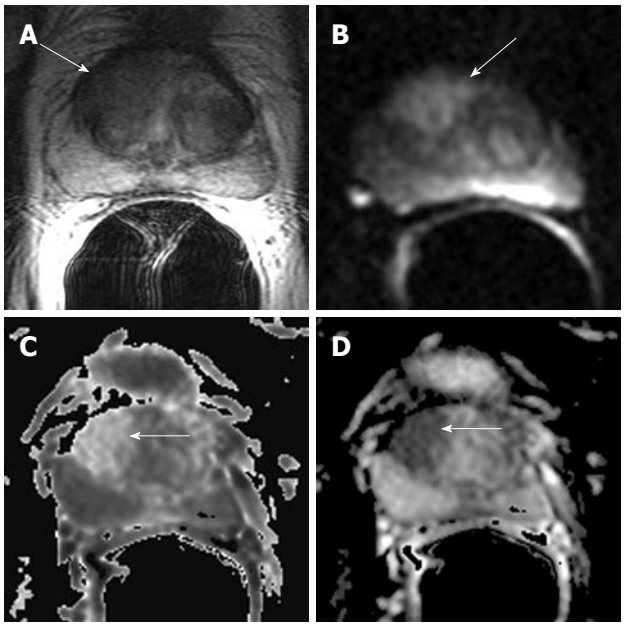


**Figure 5 3T MR images of transitional zone tumor in a 59-year-old man with PSA level of 7.6 ng/mL and Gleason grade 3 + 4 and PT4.** Transverse T2-WI (A) and transverse diffusion image (B) (b-value of 1000 s/mm$^2$), exponential apparent diffusion coefficient (ADC) (C) and ADC obtained (D) show an infiltrating tumor (arrows) in the right transitional zone extending from base to mid-gland with anterior extraprostatic extension.

with non-organ-confined prostate cancer (pT3-4). If cancer extends outside the prostate, the chances of cure are substantially diminished and the surgical or radiation treatment planning must be adapted to ensure complete eradication of the cancer[44,45].

### *Detection of OCPC (pT2)*

A cancer completely confined to the prostate is defined as pT2. Pretreatment knowledge of OCPC is important for treatment selection and planning, regardless of whether the treatment method ultimately chosen is watchful waiting, surgery, or radiation therapy. After radical prostatectomy (RP), patients with OCPC have an excellent prognosis, as more than 90% of them are free from biochemical recurrence at 5 years[24,25]. Since the introduction of the Partin tables in 1997, investigators have repeatedly validated the nomograms' capacity to help predict the pathologic stage of clinically localized prostate cancer[46-48]. In 2001, the nomograms were updated based on a more contemporary cohort of disease features[28]. The accuracy of the Partin tables in predicting OCPC is high, with reports of the area under the receiver operating characteristic (ROC) curve ranging from 0.79 to 0.82[46-48]. MR findings (from endorectal MRI or combined endorectal MRI-MRSI) contribute significant incremental value to clinical staging nomograms in the prediction of OCPC. One study on 612 consecutive patients demonstrated that MR findings contributed significant incremental value ($P \leqslant 0.02$) to the Partin tables in the overall study population. The contribution of MR findings was significant in all risk groups but was greatest in the intermediate- and high-risk groups ($P < 0.01$ for both). Overall, in the prediction of OCPC, the area under the ROC curve for the staging nomograms was 0.80, while the area under the ROC curve for the staging nomograms plus MR findings was 0.88; the difference was significant ($P < 0.01$). In the combined endorectal MRI-MRSI group, the areas under the ROC curves were 0.81 for the staging nomograms and 0.90 for the staging nomograms plus MR findings; the difference was significant ($P < 0.01$). A prospective study of 27 patients reported MRI had significantly higher standardized canonical discriminant function coefficients than the Partin tables in prediction of OCPC.

### *Detection of extracapsular extension (ECE) (pT3a)*

A cancer that extends through the prostatic capsule into the periprostatic adipose tissue is defined as a pT3a tumor[49]. ECE is an important predictor of tumor progression because it is associated with greater risk of a positive surgical margin, recurrence and a decreased chance of long-term cancer control[45,49-52]. Awareness of the presence and likely location of ECE would allow surgeons to plan radical prostatectomy more carefully, with

**Table 1 Tumor node metastasis staging of prostate cancer (American Joint Committee on Cancer, 7th ed. 2010)[43]**

| |
|---|
| Evaluation of the (primary) tumor ('T') |
| Clinical |
| TX: can not evaluate primary tumor |
| T0: no evidence of primary tumor |
| T1: clinically inapparent tumor neither palpable nor visible by imaging |
| T1a: tumor was incidentally found in less than 5% of prostate tissue resected |
| T1b: tumor was incidentally found in more than 5% of prostate tissue resected |
| T1c: tumor was found in a needle biopsy performed because of elevated serum PSA |
| T2: tumor confined within prostate[1] |
| T2a: the tumor is in half or less than half of one of the prostate gland's 2 lobes |
| T2b: the tumor is in more than half of one lobe, but not both |
| T2c: the tumor is in both lobes |
| T3: the tumor has spread through the prostatic capsule (if it is only part-way through, it is still T2) |
| T3a: the tumor has spread through the capsule on one or both sides |
| T3b: the tumor has invaded one or both seminal vesicles |
| T4: the tumor has invaded adjacent structures other than seminal vesicles (e.g. external sphincter, rectum, bladder, levator muscles, and/or pelvic wall) |
| Pathologic (pT)[2] |
| pT2: organ confined |
| pT2a: unilateral, one-half of one side or less |
| pT2b: unilateral, involving more than one-half of side but not both sides |
| pT2c: bilateral disease |
| pT3: extraprostatic extension |
| pT3a: extraprostatic extension or microscopic invasion of bladder neck |
| pT3b: seminal vesicles invasion |
| pT4: Invasion of rectum, levator muscles, and/or pelvic wall |
| Evaluation of the regional lymph nodes ('N') |
| (p)NX: regional lymph nodes were not assessed (sampled) |
| (p)N0: there has been no spread to the regional lymph nodes |
| (p)N1: there has been spread to the regional lymph nodes |
| Evaluation of distant metastasis ('M') |
| M0: there is no distant metastasis |
| M1: there is distant metastasis |
| M1a: the cancer has spread to lymph nodes beyond the regional ones |
| M1b: the cancer has spread to bone |
| M1c: the cancer has spread to other sites (regardless of bone involvement) |

[1]Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c; [2]There is no pathologic T1 classification.

the aim of resecting the cancer completely and minimizing the risk of damaging surrounding tissues important to recovery of sexual function[24,53,54]. On endorectal MRI, the criteria for ECE include a contour deformity with a step-off or angulated margin; an irregular bulge or edge retraction; a breach of the capsule with evidence of direct tumor extension; obliteration of the recto-prostatic angle; and asymmetry of the neurovascular bundles (NVBs) (Figures 5 and 6)[36,55,56]. A decision analysis model suggested that preoperative MRI was cost-effective in patients with a moderate or high risk of ECE[57]. A multivariate analysis of endorectal MRI findings and

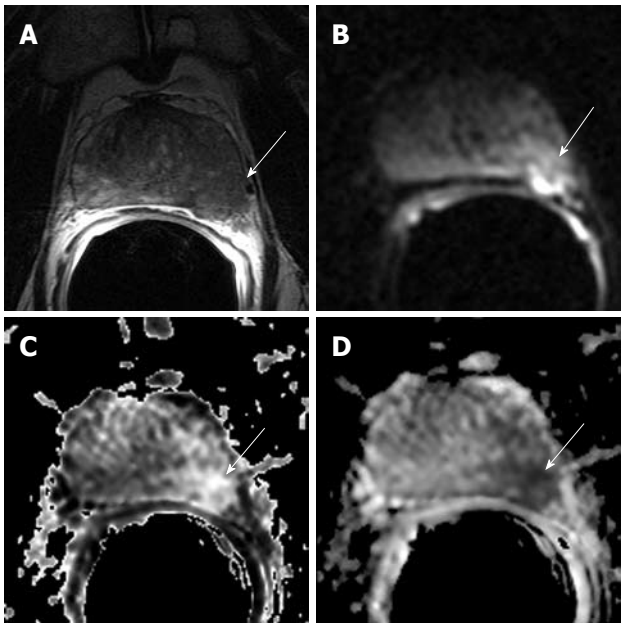


**Figure 6 MR images of established ECE of prostate cancer into the periprostatic fat in a 59-year-old man with PSA level of 21.7 ng/mL and Gleason grade 4 + 4 and PT3a.** Transverse 3 mm-thick MR (5800/108) image (A) and transverse diffusion image (4000/85. b1000) (B), exponential ADC (C) and ADC (D) of the prostate mid-gland reveal an infiltrative peripheral zone tumor (arrows) that extends into the left periprostatic fat.

other preoperative variables (PSA level, clinical stage, Gleason score, percentage of cancer in biopsy cores, and perineural invasion) in a study of 344 patients showed that endorectal MRI findings were significant presurgical predictors of ECE in patients with prostate cancer, and added incremental value to clinical variables[33]. Areas under the ROC curves for 2 models, with and without endorectal MRI findings, were 0.838 and 0.772, respectively ($P = 0.022$). Endorectal MRI findings had a larger AUC than any of the clinical or histologic variables, a high negative predictive value and a high positive predictive value (0.743, 83.8% and 74.5%, respectively).

While transaxial planes of section are essential in the evaluation of ECE, the utility of combining transaxial and coronal plane images using PACS cross-referencing to facilitate the diagnosis of ECE was shown in the study of Wang *et al*[39]. The study investigated 255 consecutive patients who underwent endorectal MRI before radical prostatectomy. In detecting ECE, the 2 radiologists had higher AUCs using cross-referencing (their AUCs increased from 0.66 to 0.87, and from 0.69 to 0.86; $P < 0.001$ for both). The weighted kappa was 0.56 with MRI alone and 0.76 with cross-referencing, indicating fair to good inter-reader agreement. Sensitivity/specificity for ECE with MRI alone and with cross-referencing, respectively, were 44%/85% and 68%/95% for reader 1 and 56%/78% and 74%/95 for reader 2.

The addition of MRSI to MRI has been shown to significantly increase staging accuracy for inexperienced readers and thus reduce interobserver variability[58]. In a study of 344 consecutive patients preprostatectomy

endorectal MRI findings showed that, overall, endorectal MRI findings were significant predictors of ECE and added significant incremental value to clinical variables when the images were interpreted by genitourinary radiologists experienced in MRI of the prostate (AUC 0.854 *vs* 0.760, $P = 0.019$), but not when they were interpreted by general body MRI radiologists (AUC 0.813 *vs* 0.788, $P = 0.31$)[59]. In the genitourinary MRI radiologists' group of patients, the AUC for endorectal MRI findings (0.833) was superior to that of all other predictors tested (0.566-0.701). In the general body MRI radiologists' group of patients, AUC for endorectal MRI findings (0.646) was similar to that of the clinical predictors (0.582-0.793). This suggests that the recent improvement in the performance of MRI can be attributed to increased reader experience as well as to the maturation of MRI technology (e.g. faster imaging sequences, more powerful gradient coils, and post-processing image correction), and better understanding of morphological criteria used to diagnose ECE. A prospective study of 27 patients reported MRI had significantly higher standardized canonical discriminant function coefficients than the Partin tables in prediction of ECE[60].

### Detection of seminal vesicle invasion (SVI) (pT3b)

SVI is defined as the extension of cancer into the muscular layer of the seminal vesicle[49]. SVI is an important predictor of tumor progression because it is associated with increased risks of lymph node metastasis (LNM), recurrence[51,52,61-63]. The criteria for SVI on endorectal MRI include contiguous low-signal-intensity tumor extension from the base of the gland into the seminal vesicles; tumor extension along the ejaculatory duct (non-visualization of the ejaculatory duct); asymmetric decrease in the signal intensity of the seminal vesicles; and decreased conspicuity of the seminal vesicle wall on T2 weighted images[36,64]. Prediction of SVI before treatment may influence treatment selection in favor of radiation therapy instead of surgery. Furthermore, while resection of the seminal vesicles has been a standard component of radical prostatectomy, it has recently been suggested that if SVI can be confidently ruled out, the surgeon may wish to spare the seminal vesicles during radical prostatectomy to prevent long-term loss of urinary continence[65].

A study investigated 573 patients who underwent endorectal MRI before surgery for prostate cancer and had systematic needle biopsy results available for the base of the prostate[66]. The results show that the Kattan nomogram (based on serum PSA, biopsy Gleason grade, clinical staging, and systematic needle biopsy cores from the base of the prostate) plus endorectal MRI (0.87) had a significantly larger AUC than either endorectal MRI alone (0.76) or the Kattan nomogram alone (0.80, $P < 0.05$ for both). These results showed that MRI can add significant incremental value to clinical variables in the prediction of SVI. A study of 283 patients reported the AUC for T2-weighted imaging plus DW imaging (0.897) was significantly larger than that for T2-weighted imaging alone (0.779). T2 images combined with DWI shows significantly more accuracy than T2-weighted imaging alone in the prediction of SVI[67]. A study of 30 patients demonstrated significant improvement in the prediction of SVI for the less experienced readers[68]. DCE MRI may depict extracapsular spread and SVI and NVBs more clearly and improve the staging performance of the less experienced readers[69]. A study of 255 consecutive patients demonstrated the use of PACS cross-referencing, which automatically links axial, coronal and sagittal section planes, to facilitate noninvasive evaluation of SVI[39]. In detecting SVI, the AUCs of 2 radiologists increased with cross-referencing (from 0.62 to 0.87, $P = 0.007$ and from 0.73 to 0.90, $P = 0.056$ for readers 1 and 2, respectively). Sensitivity/specificity for SVI with MRI alone and with cross-referencing, respectively, were 38%/81% and 62%/93% for reader 1 and 62%/84% and 69%/94% for reader 2. PACS cross-referencing is particularly helpful in displaying the junction of the seminal vesicles and the central zone of the prostate. The results showed that PACS cross-referencing significantly improves the detection of prostate cancer SVI by 3D MRI.

### Detection of LNM

The presence of LNM at the time of prostate cancer diagnosis is associated with a high probability of progression after treatment and a poor prognosis[70]. The risk of dying of prostate cancer at 10 years is much higher for patients with positive nodes than for patients with negative nodes[71]. Pretreatment knowledge of prostate cancer LNM is important for patient counseling and appropriate treatment selection and planning. The PSA level recommended by the American Urological Association for identifying patients who are at high risk for developing LMN is 15 ng/mL. There is, however, a wide variation in the cut-off values for PSA reported in the literature[72]. The conventional criterion for detection of metastatic lymph nodes on imaging is a short axis of 8 mm[73]. MRI and computed tomography (CT) have similar efficacy in detecting lymph node metastases, with both modalities having low sensitivity. The low sensitivity of MRI has been attributed mainly to the inability of cross-sectional imaging to detect metastases in normal-sized nodes[73,74]. Promising results have been reported for the use of ultra-small, super-paramagnetic iron oxide particles as an aid to diagnosing LNM by MRI[73]. These particles are taken up by normal nodal tissue but not by metastatic tissue, providing tissue contrast within the lymph node and allowing detection of metastases. The sensitivity of MRI for LNM may be increased through use of these compounds, since they appear to permit detection of metastases in normal-sized nodes[73,75]. A study of 411 consecutive patients[32] showed that MRI was an independent statistically significant predictor of LNM

($P$ = 0.002), with sensitivity and specificity of 27.27% and 98.46%, respectively, and positive predictive value and negative predictive value of 50% and 95.99%, respectively. On multivariate analysis, prediction of lymph node status using the model that included all MRI variables (ECE, SVI, and LNM) along with the Partin nomogram results had a significantly greater AUC than the univariate model that included only MRI LNM findings (AUC = 0.892 *vs* 0.633, respectively, $P < 0.01$). The study data confirmed the high negative predictive value of MRI for LNM and indicated that a combination of endorectal and phased-array MRI with the Partin tables had high accuracy in predicting LNM. As MRI also provides anatomic information that is helpful in treatment planning, these findings suggest that MRI, in conjunction with the Partin tables, may be useful for determining whether further imaging with lymphotropic superparamagnetic nanoparticles is warranted.

## PROSTATE CANCER BIOLOGIC POTENTIAL

Noninvasive assessment of prostate cancer biologic potential for prostate cancer management may provide important diagnostic information and therefore help stratify patients for appropriate treatment. The Gleason scoring system assigns increasing pattern grades as the glands formed by the prostate epithelial cells become more poorly differentiated, the margins of the tumor become more poorly defined, and the degree of stromal invasion increases[76,77]. The Gleason scoring system remains one of the most powerful prognostic predictors of prostate cancer nearly 40 years after its initial description. It is endorsed as the primary grading system for prostate cancer by the World Health Organization, the Armed Forces Institute of Pathology Fascicle on Prostate Cancer, the Association of Directors of Anatomic and Surgical Pathology, and the College of American Pathologists[78].

MRI and MRSI may have a role in the evaluation of tumor aggressiveness, because signal intensity ratios from T2-weighted MRI and biochemical data from MRSI correlate with the Gleason grade of prostate cancer[79-81]. A study of 455 patients demonstrated that the signal intensities of prostate cancer on T2w MRI correlated with Gleason grade obtained from surgical pathology, with lower tumor-to-muscle ratios being associated with higher Gleason grades. A recent study demonstrates that MRI derived parameters (ADC and T2 relaxation time) at 3 Tesla correlate with prostate tumor cellularity[80]. A study of 220 patients demonstrated that both MRI and MRI/MRSI have incremental value in the clinical models predicting the probability of insignificant prostate cancer[41].

## TREATMENT PLANNING

The surgeon's ultimate goal is to excise the cancer completely while preserving the nearby normal structures, thus avoiding positive surgical margins and minimizing the chances of recurrence and allowing recovery of physiological function. Impotence (erectile dysfunction) is one of the possible complications after RP. Impotence after RP is quantitatively related to the resection of the NVBs that closely run along 2 sides of the prostate and control the blood flow to the penis and erections[82]. Because the recovery of erectile function and the avoidance of positive surgical margins are important but competing outcomes, the decision to preserve or resect a NVB during radical prostatectomy should be based on the most accurate information concerning the location and extent of the tumor. As described in a study of 135 patients, information from MRI can assist in pre-surgical planning[53]. The areas under the ROC curves were 0.741 for pre-MRI and 0.832 for post-MRI surgical planning ($P < 0.01$). MRI findings suggested altering the surgical plan in 39% of NVBs. In 36 high-risk patients, MRI findings changed the surgical plan for 78% of NVBs (the change was found to be appropriate in 93% cases). A study of 75 consecutive patients demonstrated MRI findings successfully changed the operative strategy for NVBs in 44% of patients[83]. MRI can help to refine the surgical plan, to maximize the preservation of periprostatic tissues (important for recovery of urinary and sexual function), and to minimize the risk of positive surgical margins.

In the radiation treatment planning of localized prostate cancer, prostate contouring on MR is associated with less inter-observer variation than on CT[84].

## THERAPY RESPONSE

Accurate therapy response assessment is essential for evaluation of either the success or failure of therapy. Early selection of patients who are most likely to benefit from chemotherapy or radiotherapy may prevent unnecessary toxicity in non-responding patients. Early response of prostate carcinoma xenografts to docetaxel chemotherapy is monitored with diffusion MRI. DWI MRI can be used as a biomarker for early detection of prostate cancer xenograft response to docetaxel chemotherapy[85] and is consistent with the therapeutic response in patients with metastatic prostate cancer to bone[86]. In a multivariate analysis of 67 patients, SVI on MRI and MRSI prior to external-beam radiation therapy predicted a worse prognosis[87]. The group demonstrated that the presence and degree of ECE on MRI significantly predicted post-treatment metastatic recurrence[88]. A study of 36 consecutive patients demonstrated a significantly greater area under the ROC curve (Az) for combined T2WI and DWI (Az = 0.879, $P < 0.01$) as compared to T2WI (Az = 0.612). A study demonstrated significant changes in perfusion and extraction coefficient derived from DCE-MRI in monitoring the response to percutaneous intensity-modulated radiotherapy of prostate cancer[89].

## TUMOR RECURRENCE

Accurate identification of the risk of disease recurrence would also be particularly useful in clinical trials to assure comparability of treatment and control groups or to identify appropriate candidates for investigational treatment[31,90]. Patients with a PSA ⩽ 1.5 ng/mL after radical prostatectomy are best treated by salvage radiation therapy. Patients with local recurrence after external beam radiation therapy are good candidates for salvage prostatectomy.

An estimated one third of patients treated with radical prostatectomy later experience biochemical recurrence as defined by increases in PSA levels[91]. The natural history of biochemical recurrence after radical prostatectomy can be long but variable. Early identification, before detectable PSA is measured, of men likely to ultimately experience disease progression would be useful in considering early adjuvant therapy[92-95]. Clinical nomograms predicting freedom from biochemical recurrence 5 and 10 years after RP are in use[31,96]. A study of 610 patients demonstrated MRI was a strong predictor of biochemical recurrence after RP with hazard ratios of 1.76 and 1.81 in the 5- and 10-year models of clinical nomograms, respectively, but did not significantly improve prognostic value to standard clinical nomograms[97]. A study of 88 patients demonstrated a Cox model combining all clinical predictors had a C-index of 0.89; the C-index increased to 0.95 when MRI/MRSI was added[41]. In a study of 82 patients, sensitivity of MRI was 95%, and specificity was 100%. A study of 70 patients at high risk of local recurrence after RP demonstrated that combined MRSI and DCE-MRI showed a high sensitivity and specificity in identifying local prostate cancer recurrence in patients with biochemical progression after RP[98]. A study of 51 patients concluded that MRI combined with DCE-MRI is an accurate method to identify local recurrence after radical prostatectomy[99].

A study concluded that prostate cancer local recurrence after radiation therapy occurs at the site of the primary tumor[100]. In a study of 21 patients with biochemical failure after external beam radiation therapy, 3 or more suspicious voxels in a hemiprostate demonstrated a sensitivity and specificity of 89% and 82%, respectively, for the detection of local recurrence.

## TO GUIDE TARGET BIOPSY FOR CLINICALLY SUSPECTED CANCER IN PATIENTS WITH NEGATIVE BIOPSY

MRI has been proven to improve tumor detection of prostate cancer in patients with persistently elevated PSA levels and repeated negative biopsies, and rule out cancer[101]. In a study of 54 patients with elevated PSA and negative biopsies, MRI had a sensitivity of 83% and a PPV of 50% for detection of prostate cancer. A study of 92 patients concluded that for patients with elevated PSA and 2 previous negative biopsies, a negative MRI can rule out cancer and avoid subsequent biopsies[102]. In a study of 24 patients, the sensitivity, specificity, positive and negative predictive values, and the accuracy of MRSI for prostate cancer detection were 70.6%, 66.7%, 57.1% and 58.3%, 83.3%[103]. In a study of 42 patients the sensitivity, specificity, positive and negative predictive values, and the accuracy of combined MRI/MRSI for prostate cancer detection were 73.3%, 96.3%, 91.6%, 86.6% and 88%, respectively[104].

## FUTURE PROSPECTS

As 3T MR scanners become more available, body imaging at high field strength and improved coil design is becoming the subject of intensive research[105-109]. Theoretically, increasing static magnetic field strength, $B_0$, from 1.5T to 3T will result in a theoretical doubling of the signal-to-noise ratio (SNR). This in turn can be used to achieve greater spatial resolution and/or reduce scanning time. However, chemical shift and susceptibility artifacts also increase linearly with $B_0$. Improvements in coil design include the use of rigid coils with higher signal and the introduction of a susceptibility-matched agent into the rectum to reduce distortions relating to the interface of rectal air and tissue. The following advantages can be expected from imaging of prostate cancer with higher field strength and improved coil design: (1) Increased spatial resolution due to increased SNR may improve the detection of microscopic ECE; (2) Higher field strength provide increased spectral and spatial resolution for MRSI, but new pulse sequences will have to be designed for overcoming field inhomogeneities and citrate J-modulation issues. Significant improvement in metabolite resolution in MRSI with prostate cancer should be expected; (3) Faster scanning may help to reduce image artifacts related to patient motion and rectal peristalsis; (4) DCE-MRI may achieve increased SNR and faster image acquisition, with a significantly better trade-off between temporal and spatial resolution; and (5) With 3T and an endorectal coil, the voxel size can be reduced to 0.13 $mm^3$ as compared to 1.21 $mm^3$ at 1.5T[40]. Further investigation is needed to develop MRI/MRSI/DWI/DCE-MRI criteria on 3T MRI scanners for prostate cancer detection and staging.

The whole body MRI, one of the advances in MR techniques, may be more sensitive than the traditional work-up for identifying bone metastases. In the future of prostate cancer management, MR-guided prostate interventions such as MRI-guided focused ultrasound surgery will result in major changes.

## CONCLUSION

In patients with prostate cancer, there is growing demand for patient-specific therapies that can minimize treatment morbidity while maximizing treatment benefits. MRI non-invasively improves cancer staging,

biologic potential and treatment planning, monitors anti-tumor therapy and local recurrence, and guides target biopsy for clinically suspected cancer with previous negative biopsy. The incorporation of endorectal MR findings into future nomograms for the prediction of prostate cancer stage and freedom from biochemical recurrence is warranted. Advances in technology, such as MRSI, DWI, DCE-MRI, high field strength MRI scanner, and whole body MRI, and in the expertise of radiologists dedicated to the genitourinary field, suggests that MRI can play an increasingly useful role in prostate cancer management.

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