Multiparametric magnetic resonance imaging of prostate cancer

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Abstract

In India, prostate cancer has an incidence rate of 3.9 per 100,000 men and is responsible for 9% of cancer-related mortality. It is the only malignancy that is diagnosed with an apparently blind technique, i.e., transrectal sextant biopsy. With increasing numbers of high-Tesla magnetic resonance imaging (MRI) equipment being installed in India, the radiologist needs to be cognizant about endorectal MRI and multiparametric imaging for prostate cancer. In this review article, we aim to highlight the utility of multiparametric MRI in prostate cancer. It plays a crucial role, mainly in initial staging, restaging, and post-treatment follow-up.

Key words: Diffusion-weighted imaging; dynamic contrast-enhanced-magnetic resonance imaging; magnetic resonance imaging; prostate cancer

Introduction

Prostate cancer is the most commonly diagnosed malignancy in men, with almost one-quarter of males diagnosed with malignancy having cancer of the prostate. The age-adjusted incidence rate in the United States is 156 per 100,000 men per year. In India prostate cancer has an incidence rate of 3.9 per 100,000 men and is responsible for 9% of all cancer-related mortality. It is the only malignancy that is diagnosed with an apparently blind technique, i.e., transrectal sextant biopsy. Magnetic resonance imaging (MRI) plays a crucial role mainly in the initial staging, restaging, and post-treatment follow-up of cases of prostate cancer. The superior soft tissue resolution, multiplanar imaging capability, and technical refinements have established MRI as the most accurate modality for the detection and staging of prostate cancer. The goal of this review is to provide a comprehensive update on advanced MRI techniques for improving the detection, staging, and post-treatment follow-up of patients with prostate cancer.

MRI Anatomy of Normal Prostate Gland and The Technique of Endorectal Magnetic Resonance Imaging

Anatomically, the prostate gland is divided into four parts: The peripheral zone, the transitional zone, the central zone, and the anterior nonglandular fibromuscular stroma. The peripheral zone comprises 70-80% of the glandular tissue, and 70% of prostate cancers arise in this zone. The remaining 30% of cancers occur in the transition zone. On T2-weighted (T2W) images, the central and transitional zones cannot be distinguished and are collectively called the central gland, which is separated from the peripheral zone by a thin pseudocapsule. On T2W images the peripheral zone shows high signal intensity, which is either equal to or more than that of the fat in the vicinity. The high signal intensity is attributed to the fluid-filled ductal and acinar components, with age-related increase in the signal intensity. Compared with the peripheral zone, the central gland displays a low or heterogenous T2 signal intensity since it contains fewer glandular structures and smooth muscles. The central gland may appear heterogeneous due to the presence of nodules and cysts [Figure 3]. The true capsule, seen as a
low-intensity rim, is best appreciated on the posterior and posterolateral aspects of the gland [Figure 4]. This capsule is an important imaging landmark in prostate cancer as extracapsular extension (ECE) can upstage the tumor to T3. Neurovascular bundles can usually be seen on axial images at 5 and 7 o’clock positions [Figure 4]. The penetrating branches of the neurovascular bundles to the apex and base of the gland serve as important pathways for extension of the tumor outside the capsule.[17] The seminal vesicles [Figure 5] are seen as elongated fluid-filled structures with thin septae and are seen as low signal intensity on T1-weighted (T1W) images and high signal intensity on T2W images. The vas deferens is seen as a tubular structure medial to the seminal vesicles and displays low T1 and T2 signal intensity.[12] The seminal vesicles and the vas are better appreciated on coronal and axial images.

The European Consensus Meeting divided the prostate into a minimum of 16 – and optimally 27 – regions of interest [Figure 6] and suggested that a score of 1-5 to be assigned for each region, with a score of “1” denoting that clinically significant disease was highly unlikely to be present and a score of “5” denoting that clinically significant
disease was highly likely to be present. Clinically significant disease was defined as a lesion with volume ≥0.5 cm³ and/or Gleason score of ≥4 + 3.[13] The consensus on imaging, interpretation, scoring, and reporting is shown in Index 1.

The current standard of practice for performance of prostate MRI at 1.5-T uses the balloon endorectal surface coil (ER-MRI) combined with pelvic phased-array coils, which yields high-resolution images with improved signal-to-noise ratio (SNR) and good spatial and spectral resolution.[14] For MRI of prostate with endorectal coil, the patient is first placed in the left lateral decubitus position. After digital rectal examination, an endorectal balloon with a coil mounted inside is inserted into the rectum. The balloon is then inflated with 80 cc of air, which helps to homogenize the magnetic field by reducing the susceptibility differences between the balloon and the prostate. The patient is then placed in the supine position with pelvic phased-array coils. The position of the endorectal coil is first checked on scout images and repositioned if necessary, as appropriate placement of the coil is essential for optimum image quality. At our institute, a standard protocol is followed.[Index 2] Spectroscopy is not routinely performed.

**Imaging Characteristics of Prostate Cancer on Conventional Magnetic Resonance Imaging**

**Organ-confined prostate cancer**

On T2W imaging, peripheral zone cancer foci are seen as rounded or ill-defined low-signal-intensity lesions [Figure 7]. This appearance is, however, mimicked by several other entities such as prostatitis, hemorrhage, benign hyperplasia, atrophy, and treatment-related changes.[14] It is advisable that the radiologist correlate the imaging findings with the timing and inference of prostate biopsy, serum prostate-specific antigen (PSA) level, the Gleason score, and the clinical findings on digital rectal examination. T1W images allow distinction between the post-biopsy hemorrhage [Figure 8], which appears hyperintense on T1W images, and the cancer foci. To allow precise diagnosis and avoid false negative interpretation because of overlying hemorrhage, prostate MRI is usually performed 6-8 weeks after the endorectal biopsy.[15] The transitional zone tumors appear as low-signal-intensity lesions on T2W images and show a lenticular shape, with ill-defined margins and absence of an appreciable capsule[16] [Figure 9]. Localization of tumor in the central gland is very difficult in the setting of stromal hyperplasia because of the background heterogeneity.[6] However, features such as well-defined margins, visible capsule, and round shape favor a diagnosis of benign prostatic hyperplasia (BPH) nodules. The anterior fibro muscular stroma can be invaded by transitional zone tumors. BPH nodules, on the other hand, may displace but do not invade the fibromuscular stroma[16] [Figure 10].

**Extracapsular extension**

The diagnosis of ECE upstages the tumor to T3, thereby changing the management plan and prognosis. Therefore, ECE is best detected by high-resolution multiplanar T2W images. The MRI features suggestive of ECE – and the misleading signs – are described in Table 1.[9,17-21]

![Figure 5: T2-weighted axial and coronal images show normal appearance of seminal vesicles](image1)

![Figure 6: The European Consensus Guidelines division of the prostate gland into the minimal 16 – and optimal 27 – regions of interest](image2)

![Figure 7: T2-weighted axial images show hypointense tumor focus (arrow) in the left basal peripheral zone. Organ-confined cancer was confirmed on surgical histopathology](image3)
Staging
Staging of the prostate cancer is based on local, nodal, and distant extent of disease and is essential for risk stratification and assessment of prognosis. The salient points from the American Joint Committee on Cancer staging manual (7th edition; 2010) are summarized below. The diagnostic groups based on staging and PSA and Gleason score are mentioned in Table 2.

Primary tumor
Clinical:
- $T_0$: Primary tumor cannot be assessed
- $T_0'$: No evidence of primary tumor
- $T_1$: Clinically inapparent tumor, neither palpable nor visible by imaging

Table 1: Extracapsular extension and misleading signs

| MRI features of ECE [Figure 11A and B] |
|----------------------------------------|
| Visualization of extension of hypointense tumor in hyperintense periprostatic adipose tissue or adjacent structures like rectum/bladder |
| Secondary features |
| Asymmetric neurovascular bundles |
| Encasement of neurovascular bundles by the tumor |
| Irregular margin of the gland |
| Capsular obscuration |
| Broad tumor contact with the capsular surface |
| Obliteration of retroprostatic angle |
| Seminal vesicle invasion is seen as extension of hypointense tumor into hyperintense seminal vesicles |
| Misleading signs |
| Irregular bulging in nonpalpable tumors |
| Thickened walls and asymmetric widening of seminal vesicles (can be seen in benign conditions like senile amyloidosis) |

ECE: Extracapsular extension

Table 2: Anatomic stage/diagnostic groups

| Group | T     | N     | M     | PSA  | Gleason |
|-------|-------|-------|-------|------|---------|
| I     | $T_{1a-c}$ | $N_0$ | $M_0$ | <10  | ≤6      |
|       | $T_{2a}$   | $N_0$ | $M_0$ | <10  | ≤6      |
|       | $T_{1-2a}$ | $N_0$ | $M_0$ | X    | X       |
| IIA   | $T_{1a-c}$ | $N_0$ | $M_0$ | <20  | 7       |
|       | $T_{2a}$   | $N_0$ | $M_0$ | ≥10<20 | ≤6    |
|       | $T_{2a}$   | $N_0$ | $M_0$ | ≥10<20 | ≤6    |
|       | $T_{2b}$   | $N_0$ | $M_0$ | <20  | 7       |
|       | $T_{2b}$   | $N_0$ | $M_0$ | X    | X       |
| IIIB  | $T_{2c}$   | $N_0$ | $M_0$ | Any  | Any     |
| III   | $T_{1-2}$  | $N_0$ | $M_0$ | ≥20  | Any     |
|       | $T_{1-2}$  | $N_0$ | $M_0$ | Any  | ≥8      |
|       | $T_{1-2b}$ | $N_0$ | $M_0$ | Any  | Any     |
| IV    | $T_3$     | $N_0$ | $M_0$ | Any  | Any     |
|       | Any T     | $N_1$ | $M_0$ | Any  | Any     |
|       | Any T     | Any N | $M_0$ | Any  | Any     |

PSA: Prostate-specific antigen, T: Primary tumor, N: Regional lymph nodes, M: Distant metastasis

Figure 8: Postbiopsy hemorrhage. T1-weighted images show hyperintense focus (arrow) in the left peripheral zone, consistent with postbiopsy hemorrhage

Figure 9: Organ-confined transitional zone tumor. (A) Axial T2-weighted image shows dark signal in the left tumor focus; (B) the tumor shows restricted diffusion and low ADC (arrow); (C) dynamic contrast-enhanced magnetic resonance imaging with quantitative color-coded map of reverse flow of contrast medium (Kep) shows elevated values within the tumor focus (arrow)
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- **T$_{1a}$**: Tumor incidental; histologic finding in $\leq$5% of tissue resected
- **T$_{1b}$**: Tumor incidental; histologic finding in $>$5% of tissue resected
- **T$_{1c}$**: Tumor identified by needle biopsy (e.g., because of elevated PSA)
- **T$_2$**: Tumor confined within prostate
- **T$_{2a}$**: Tumor involves one-half of one lobe or less
- **T$_{2b}$**: Tumor involves more than one-half of one lobe but not both lobes
- **T$_2c$**: Tumor involves both lobes
- **T$_3$**: Tumor extends through the prostate capsule
- **T$_{3a}$**: ECE (unilateral or bilateral)
- **T$_3b$**: Tumor invades seminal vesicle(s)
- **T$_4$**: Tumor is fixed or invades adjacent structures other than seminal vesicles, e.g., external sphincter, rectum, bladder, levator muscles, and/or pelvic wall [Figure 12].

**Regional lymph nodes**

- **N$_0$**: Regional lymph nodes (N) not assessed
- **N$_1$**: No regional lymph node metastasis
- **N$_i$**: Metastasis in regional lymph node(s).

**Distant metastasis**

- **M$_0$**: No distant metastasis (M)
- **M$_1$**: Distant metastasis
- **M$_{1a}$**: Nonregional lymph node(s)
- **M$_{1b}$**: Bone(s) [Figure 13]
- **M$_{1c}$**: Other site(s), with or without bone disease.

**Detection of metastatic disease**

The likelihood of detecting metastasis is higher when the tumor is T$_2$ or higher, serum PSA level is $>$20 ng/ml, and Gleason score is $\geq$7. Prostate cancer can metastasize by either the lymphatic or the hematogenous route. The lymph nodal groups that are often involved are obturator, internal iliac, common iliac, and presacral [Figure 14]. The site of the involved lymph node is an important parameter as it affects the staging; pelvic nodal disease is considered as N$_i$, and common iliac or retroperitoneal nodal disease is considered as M$_1$. Disease progression and survival is affected by the number of lymph nodes involved. If more than five lymph nodes are involved, recurrence-free 10-year survival is

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**Figure 10**: T2-weighted image shows benign prostatic hyperplasia nodule in the transitional zone. Note the displacement of the fibromuscular stroma (arrow)

**Figure 11 (A)**: Signs of extracapsular extension (ECE) on T2-weighted magnetic resonance imaging: (a) Irregular margin of the peripheral zone (arrow); (b) involvement of neurovascular bundles (arrow); (c) obliteration of rectoprostatic angle (arrow)

**Figure 11 (B)**: Signs of ECE–seminal vesicle involvement noted on coronal and axial images

**Figure 12**: T$_4$ stage disease. Axial T2-weighted image shows involvement of rectal wall (arrow)
49%, as compared with 70% in patients with 1-2 lymph nodes.\textsuperscript{[23]} Hematogenous metastasis is seen most commonly in lumbar vertebrae, pelvic bones, ribs, and proximal ends of the femora. Visceral metastases are rare compared with bony metastases.\textsuperscript{[22,24]}

To improve the diagnostic accuracy, advanced MRI techniques like diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI), MR spectroscopy, and lymphotropic superparamagnetic nanoparticle–enhanced MRI (LSN–MRI) are being increasingly used.

**Diffusion-Weighted Imaging**

DWI exploits the property of constant Brownian motion of the water molecules in tissue.\textsuperscript{[25]} This property is affected by increased cellularity, tissue organization, extracellular space, and integrity of cell membranes.\textsuperscript{[23]} Prostate cancer foci are composed of tightly packed cellular elements with reduced extracellular space, which can be visualized on DWI images as areas of restricted diffusion (high signal intensity), with corresponding low signal intensity on Apparent Diffusion Coefficient (ADC) maps [Figure 15].\textsuperscript{[27]}

With the advent of parallel imaging, high field-strength magnets, and endorectal coils, it is now possible to obtain DWI with improved SNR. At our institution, DWI is a part of our routine prostate cancer imaging protocol. Diffusion in normal prostatic tissue is variable. The ADC map shows significantly higher signal (less restricted diffusion) in the peripheral zone due to the high proportion of glandular tissue.\textsuperscript{[28]} The ADC and DWI are affected by age as well.\textsuperscript{[29]} Haider \textit{et al}. demonstrated that the combination of a combined T2W images and DWI performed better than the former alone in the detection of peripheral zone tumors that were >4 mm and had Gleason score of ≥6.\textsuperscript{[30]} High lesion conspicuity on DWI is especially important for guiding second biopsy in patients with high clinical suspicion for tumor but negative first biopsy.\textsuperscript{[31]} Furthermore, Kim \textit{et al}. demonstrated that DWI combined with T2W images have better diagnostic performance than the latter alone in predicting invasion of seminal vesicles.\textsuperscript{[32]} DWI, however, only distinguishes cancer foci if the tumor/volume ratio is 50% or more.\textsuperscript{[33]} DWI can also be used for detection of recurrent tumor as shown in a recent study by Kim \textit{et al}. The sensitivity and specificity reported by them were 25% and 57%, respectively, for T2W images alone compared to 62% and 91%, respectively, for combined T2WI and DWI. The mean ADC noted of recurrent tumor was 0.98 × 10\textsuperscript{-3} mm\textsuperscript{2}/s and that of normal tissue was 1.60 × 10\textsuperscript{-3} mm\textsuperscript{2}/s.\textsuperscript{[34]} Despite its advantages, DWI has drawbacks such as nonstandardized protocols, image distortion, susceptibility artifacts, and decreased specificity because of considerable overlap between malignant and benign conditions; for example, BPH and prostatitis have altered cellular density and interstitial pressure and thereby can mimic cancer on DWI.\textsuperscript{[26,35]}

**Dynamic Contrast-Enhanced Magnetic Resonance Imaging**

The basic principle of DCE-MRI is related to tumor angiogenesis. Any tumor > 2 mm inevitably shows
angiogenesis.[34] Prostate cancer cells by expressing (VEGF) vascular endothelial growth factor are no exception.[37] There is discrepancy between the interstitial space of cancer tissue and normal tissue.[31] Due to large interstitial spaces, there is difference in the concentration of intravenous contrast material between intravascular and extravascular spaces, which accentuates contrast transfer through vascular walls and thus results in the unique enhancement pattern of strong early enhancement and rapid washout.[38,39] DCE-MRI provides quantitative parameters reflecting the permeability and flow characteristics of vessels within the lesion.[14] The enhancement curves generated from DCE-MRI are fit to a pharmacokinetic model like Toft’s. This generates the following quantitative parameters:

1. $K_{\text{trans}}$: Transendothelial transport of contrast from vessel lumen to tumor interstitium, i.e., permeability
2. $V_e$: Fractional volume of extravascular extracellular space
3. $K_{\text{ep}}$: Reverse transport parameter of contrast medium back to the vascular space.

In prostatic cancer foci, these values are significantly higher than that of normal tissue [Figure 16].

At our institute, for DCE-MRI, 20 cc gadolinium is injected at a rate of 3 cc per second and serial T1W 3D images are obtained every 2-5 s through the entire prostate.

A recent study by Jackson et al. showed that the sensitivity and specificity of DCE-MRI (50% and 85%, respectively) is higher than that of T2W imaging (21% and 81%, respectively). Because of the increased microvessel density, DCE can help distinguish carcinomatous foci from BPH nodules.[40] Yoshizako et al. demonstrated that DCE-MRI can be used as a complementary tool along with DWI and T2W images, with the combination yielding a specificity of 93.8% and positive predictive value 94.7%.[44] For the detection of recurrent prostatic carcinomas after electron beam radiation therapy (EBRT), DCE-MRI has a better sensitivity and positive and negative predictive values (72%, 46%, and 95%, respectively) than T2W imaging alone.[45] In patients post radical prostatectomy, the sensitivity and specificity has been shown to be 84.1% and 89.3%, respectively.[46]

**MR Spectroscopy**

MR spectroscopy provides information about the biochemical and metabolic status of the tissue. MR spectroscopy evaluates the gland in three dimensions with voxel size of 0.24-0.34 cm$^3$ using chemical shift imaging (CSI) and point-resolved spectroscopy (PRESS). The metabolic data is superimposed on the MR images to identify and localize the cancer.[31] The normal prostatic tissue is citrate rich, with low choline and creatine levels in the peripheral zone. In the central and transitional zones, the citrate levels are lower than in the peripheral zones.[48] The fibromuscular stroma and periurethral tissues have even lower levels of citrate. Instead of the normal high citrate metabolism, cancer cells utilize citrate oxidizing metabolism.[38,49] High turnover of phospholipids raises the choline level and thus increases the choline/citrate ratio. This can be used to detect malignancy in the peripheral zone. Creatine, on the other hand, is a marker of cellular energy storage and the levels are not significantly different between healthy and cancerous prostatic tissue. The creatine peak may be indistinguishable from the choline peak because of the close proximity between the two. The mean normal choline + creatine/citrate ratio is 0.22 ± 0.0013 at 1.5-T.[50] Peripheral zone voxels with choline and creatine ratio to citrate that are >3 SD (standard deviations) above average is considered as highly suggestive of cancer [Figure 17].[40] The exact ratio is affected by factors such as magnet strength and settings. The 5-point scale devised by Jung et al. is reasonably accurate, with excellent interobserver agreement, in distinguishing benign from malignant tissue. According to this scale: 1 = probably benign; 2 = possibly benign; 3 = equivocal; 4 = possibly malignant; and 5 = probably malignant.[50] The spectra can be affected by postbiopsy hemorrhage, which can degrade it, and also by prostatitis and BPH, which can mimic carcinoma.[15,51,52] Coupled with MRI, MR spectroscopy is shown to have sensitivity and...
specificity of 95% and 91%, respectively, for intraprostatic tumor localization. MR spectroscopy can also depict metabolic atrophy post treatment, which can be used for distinguishing post-treatment changes from recurrence.

Lymphotrophic Superparamagnetic Nanoparticle–Enhanced Magnetic Resonance Imaging

Lymphotrophic superparamagnetic nanoparticle–enhanced magnetic resonance imaging (LSN-MRI) was developed recently and has been validated by multiple clinical trials. Reticuloendothelial cells in lymph nodes show uptake of these nanoparticles typically 48 hours post intravenous injection [Figure 18]. In nodal spread of malignancies, the reticuloendothelial cells are replaced by tumor cells, which fail to show normal uptake of iron thereby increasing specificity of nodal involvement by tumor irrespective of size criterion which is known for false negative results.

For characterizing lymph nodes in prostatic cancer the highest sensitivity reported was by Harisinghani et al., who reported sensitivity of 100% (with specificity of 96%) with metastatic nodes outside the classical field of lymph node dissection in 11%. In another study by Heesakkers et al., the positive predictive value was 69% and negative predictive value was 96%. LSN-MRI is thus a noninvasive functional imaging tool that has potential for improving preoperative staging.

Summary

There have been remarkable technical advances in multiparametric MRI and its role in detecting, localizing, and staging prostate cancer, as well as in evaluating local recurrence after treatment. However, consistency in conducting er-MRI and its interpretation is the key to the widespread use of this multiparametric imaging tool. A multipronged approach and the combined use of these techniques can improve diagnostic performance, provided the radiologist understands the advantages and limitations of each technique.

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Areas of consensus on imaging interpretation, scoring, and reporting:

1. Areas of positive consensus
   - When scoring the prostate for the presence or absence of cancer for T2W, diffusion-weighted, contrast-enhanced, and MR spectroscopy sequences, the range of scores should be 1-5 for each imaging type.
   - Both individual lesions and areas of the prostate should be separately scored for probability of malignancy.
   - The maximum diameter of the largest abnormal lesion should be recorded.
   - The following should be scored for involvement, with an individual scoring range of 1-5:
     - ECE
     - Seminal vesicles (extra-and intraprostatic)
     - Distal sphincter
     - Rectal wall
     - Neurovascular bundles
     - Bladder neck.
   - As a minimum requirement, the prostate should be divided into 16 regions of interest (apical, mid, and base quadrants) and, as an optimum requirement, into 27 regions of interest.
   - The ADC value should be stated for any suspicious lesion detected.
Dynamic contrast-enhanced should be scored according to the morphological enhancement pattern.

The following clinical information is important for reporting the imaging and should be included:
- PSA level
- Digital rectal examination findings
- Time scale since prostate biopsies, and results of previous biopsies
- Results of previous MRI scans
- History of previous prostate treatment or intervention (e.g., transurethral resection of prostate, prostate radiotherapy)
- History of medical treatment (e.g., 5-α-reductase inhibitors, hormones).

As a minimum requirement, each MRI should be assessed and scored by one radiologist and, as an optimal requirement, scored by two radiologists independently, with discrepancies referred for consensus.

If one of the modalities within the minimum dataset is noninterpretable due to artefact, the denominator of the scoring system should be changed to allow for the lack of score for the affected sequence.

Dedicated software for imaging interpretation should be developed for this purpose, with the ability to display, co-register, segment, fuse, and analyze every tool in an integrated single workspace.

The final report should be presented electronically, in both number and picture form, and should include relevant images.

Areas lacking consensus
- Areas of the prostate should be scored separately rather than by individual lesions.
- The overall score for probability of tumor given by the radiologist should be influenced by other clinical results (e.g., PSA level).
- The overall score should be based purely on imaging appearances.
- A separate radiologist’s “hunch” score should be given that represents the radiologist’s personal hunch on the likelihood of malignancy, regardless of the objective radiologic score.
- The final score should be given as individual scores, a sum of the individual scores, or as a radiologist’s overall opinion score.
- T-staging should be a formal part of the final report.

Index 2

1. Protocol: 1.5- or 3.0-T MRI technique
   - T1W axial sequence
   - T2W axial sequence
   - T2W coronal sequence
   - T2W sagittal sequence
2. DWI and ADC maps
3. Postcontrast DCE sequences

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