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Multiparametric-MRI in diagnosis of prostate cancer

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Abstract

Multiparametric-magnetic resonance imaging (mp-MRI) has shown promising results in diagnosis, localization, risk stratification and staging of clinically significant prostate cancer. It has also opened up opportunities for focal treatment of prostate cancer. Combinations of T2-weighted imaging, diffusion imaging, perfusion (dynamic contrast-enhanced imaging) and spectroscopic imaging have been used in mp-MRI assessment of prostate cancer, but T2 morphologic assessment and functional assessment by diffusion imaging remains the mainstay for prostate cancer diagnosis on mp-MRI. Because assessment on mp-MRI can be subjective, use of the newly developed standardized reporting Prostate Imaging and Reporting Archiving Data System scoring system and education of specialist radiologists are essential for accurate interpretation. This review focuses on the present status of mp-MRI in prostate cancer and its evolving role in the management of prostate cancer.

Keywords: Diffusion imaging, functional imaging, MRI-guided biopsy, multiparametric-MRI, prostate cancer

INTRODUCTION

Currently, the diagnostic pathway for prostate cancer detection is initiated on prostate-specific antigen (PSA) level and digital rectal exam (DRE). Use of PSA as a screening tool followed by systematic transrectal ultrasound-guided (TRUS) biopsy has resulted in increased detection of prostate cancer with stage migration toward low-risk disease. About 233,000 new prostate cancers are estimated to be diagnosed in 2014 in the USA.[1] This has come with the risk of overdiagnosis and overtreatment, as many of these are clinically insignificant low-risk prostate cancer. On the other hand, anterior tumors tend to be missed by TRUS biopsy until they grow to a substantial size and reach within 15–20 mm from the posterior margin of the prostate, leading to delayed diagnosis. Systematic TRUS biopsy has historically shown to underestimate the final Gleason grade of tumor on histology following radical prostatectomy, leading to inaccurate risk stratification and selection of therapeutic options. For all these reasons, the US and the Canadian Task Force on Preventive Health Care recently released independent statements arguing that the risks of PSA tests outweigh the benefits.[2]

Multiparametric magnetic resonance imaging (mp-MRI), combining the morphological assessment of T2-weighted imaging (T2WI) with diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) perfusion imaging and spectroscopic imaging (MRSI), has been extensively studied in recent years.[3,4,5,6,7,8] In particular, T2WI and DWI have shown considerable promise in the detection, localization,

risk stratification and staging of prostate cancer.[9,10,11,12] This review will provide an overview of the different imaging sequences and discuss the current role of mp-MRI in the different aspects of management of prostate cancer.

MRI IMAGING TECHNIQUE

The recommended technique of MRI in prostate cancer is mp-MRI, which includes high-resolution T2WI and at least two functional MRI techniques.[13] T1-wegithed imaging is of limited use in assessing prostate morphology or in identifying tumor within the gland. Its main use is in detecting post-biopsy hemorrhage. Bowel motion artefacts should be reduced by administering anti-peristaltic agents. Prostate imaging at 3T benefits from higher signal to noise ratio. Use of endorectal coil (ERC) is not an absolute requirement for cancer detection protocol, but is preferable at 1.5T.[14] ERC use is recommended for staging purposes, although patient acceptability and increased costs remain its drawbacks. Air can be used to inflate the ERC balloon, but may cause distortion of DWI. Distention with liquids (perflurocarbon or barium suspension) will prevent susceptibility artefacts. Usually, about 60 cc of air or fluid is required to distend the balloon.

T2WI

T2-WI is the workhorse of prostate MRI. It provides high spatial resolution and defines the zonal anatomy differentiating the peripheral zone from the transition zone, the central zone, ejaculatory ducts, anterior fibromuscular stroma, seminal vesicles and the urethra.[15] The neurovascular bundles are also outlined on T2WI. The peripheral zone has high signal intensity on T2WI, reflecting its higher water content, and cancer in the peripheral zone appears as an area of lower signal [Figure 1a]. However, low T2 signal in the peripheral zone may also be seen in benign abnormalities, including prostatitis, fibrosis, scar tissue, post-biopsy hemorrhage or post-irradiation.

The heterogenous appearance with multiple BPH (benign prostate hyperplasia or benign enlargement of the prostate) nodules makes assessment for cancer more difficult in the transition zone, especially for the less-experienced reader.[16] Functional imaging is not always helpful in the assessment of transition zone tumor as areas of benign stromal or proliferating hyperplasia may show heterogenous enhancement on DCE and restricted diffusion on DWI.[17,18] Morphological features on T2WI, such as an “erased charcoal” appearance [Figure 2], indistinct margins of the nodule, extension of low signal into peripheral zone, lenticular shape, extension to fibromuscular stroma and local invasion, help to differentiate tumor from benign tissue, but again some BPH nodules may also not be clearly demarcated or encapsulated and therefore this remains a well-identified limitation of mp-MRI. As such, T2WI is considered the dominant of all the mp-MRI sequences for detection of cancer in the transition zone.[19]

The degree of intensity decrease on T2WI in the peripheral zone has been correlated with Gleason grade of tumor, with higher Gleason score components showing lower signal intensities, thereby playing a role in risk stratification of tumor.[20] The high spatial resolution of T2WI makes the sequence also the mainstay for local staging of disease.[21] Low signal intensity extension to seminal vesicles, obliteration of the recto–prostatic angle and extension to neurovascular bundles are signs of extracapsular extension (ECE) of tumor on T2WI [Figure 3]. Lawrence *et al.* recently reported that addition of DWI and DCE imaging to T2WI improved the accuracy of pre-operative detection of ECE.[11]

DWI

Diffusion-weighted MRI is a functional imaging tool that measures the random Brownian motion of water molecules in tissue. The apparent diffusion coefficient (ADC) on MRI or the net displacement of molecules quantifies the restriction of water diffusion and is measured by acquiring at least two set of images with different magnetic field gradient durations and amplitudes (b value). Performing DWI requires at least two b factors for the calculation of ADC. Multipoint b value analyses increase the accuracy of the calculated ADC at the expense of increased scanning time and decrease in signal to noise ratio (SNR). Earlier studies reported use of maximal b value of 1000 s/mm^2, but more recently it has been shown that a value of up to 2000 s/mm^2, which can be obtained on 3T scanners, may help to suppress signal from background normal prostate tissue and highlight the cancerous areas as hyperintense.[22]

Interpretation with high b values >1000 s/mm^2 is advocated for DWI in combination with ADC, with the hallmark of cancer being low ADC and iso to high signal on high b value DWI images (≥ 1400 s/mm^2). Limitations of DWI include increased noise and anatomic distortion of the image, especially at higher b values.

Studies have also shown an inverse correlation between quantitative ADC values and Gleason score, and may therefore help in assigning accurate risk stratification for selection of therapeutic options.[9,23,24] But, there is significant overlap in confidence intervals that ADC cannot be used as a surrogate for Gleason score at this time, although most clinically significant cancers have a ADC value of <1000.[17,25] DWI is a widely available technique and is considered to be the most important functional imaging sequence in mp-MRI. Functional imaging (DWI, DCE and magnetic resonance spectroscopic imaging [MRSI]), and in particular DWI, may help to differentiate cancer from benign abnormalities such as prostatitis, fibrosis, scar tissue, post-biopsy hemorrhage or post-irradiation in the peripheral zone [Figure 1b]; therefore, DWI is considered as the dominant sequence for identifying tumors in the peripheral zone.[26] It is also the most useful of all the functional imaging sequences for tumor detection in the transition zone. Multiple studies have shown DWI to be the most effective of the mp-MRI sequences for detecting prostate cancer, thereby improving the diagnostic performance of mp-MRI.[27,28,29,30,31]

DCE

DCE MRI relies on fast T1-weighted sequences before, during and after rapid intravenous (IV) administration (2–4 mL/s) of a bolus of a gadolinium-based contrast agent to assess tumor angiogenesis. During DCE MRI, tumors demonstrate early and high-amplitude enhancement followed by rapid washout in some cases compared with normal tissue. DCE MRI images can be evaluated by simple visual analysis in a qualitative manner on the raw data via scrolling through serial obtained images or on subtraction images, to look for early nodular and focal enhancement. Alternatively, semi-quantitative parameters such as upslope gradient, peak enhancement and washout gradient can be calculated to generate a slope curve (types A, B and C) for assessment. Quantitative metric assessment may also be performed using pharmacokinetic (Tofts) models to estimate contrast concentration within the tissue. It provides the transfer constant K_{trans}, which describes microvascular permeability and blood flow, and V_e, the extracellular–extravascular compartment volume fraction or leakage space.[32] For routine clinical assessment, visual analysis of images or semi-quantitative assessment of enhancement curve type are considered adequate for image interpretation. Quantitative assessment is valuable for assessing response to therapy when there are no changes to morphologic appearances.

Because of overlap of enhancement pattern with benign conditions such as prostatitis in the peripheral zone and BPH nodules in the transition zone, DCE MRI is not considered as a dominant imaging sequence in isolation for assessment of cancer, either in the peripheral zone or in the transition zone, and is often applied as an adjunct to T2WI and DWI findings in mp-MRI. It raises confidence in calling lesions identified on T2WI/DWI, helps make a final interpretation score in challenging cases when T2WI/DWI imaging is equivocal, provides useful information when other sequences are suboptimal (motion on T2WI or images distortion on DWI) and has the potential to draw attention to small foci at the time of read, which otherwise may have been overlooked. Unlike T2WI and DWI, studies have shown poor correlation of DCE MRI parameters with Gleason grade.

DCE MRI is however the dominant sequence for detecting residual/recurrent tumor following therapy. Early nodular enhancement on DCE MRI following focal therapy (post-treatment, the area becomes fibrotic and DWI is generally not useful in assessment) [Figure 4] and in the prostate bed following prostatectomy helps identify the site of local recurrence.[33]

Spectroscopic Imaging

On MRSI of the prostate, the dominant peaks in the spectra are from protons in citrate (resonates at 2.6 ppm), creatine (resonates at 3.0 ppm) and choline compounds (resonates at 3.2 ppm). Polyamine signals may also be identified. In cancer, choline signals are elevated while citrate signals decrease, in comparison with benign tissue. For image interpretation, the choline plus creatine-to-citrate ratio is often used as a metabolic biomarker, although it is more reliable in the peripheral zone, which has high citrate levels.

Several studies have shown the benefit of adding MRSI to MRI in the evaluation of prostate cancer.[34,35] Studies have shown the ability of MRSI to improve the cancer detection rate in patients with an elevated PSA[36] MRSI has shown promise in assessment of cancer aggressiveness[37,38,39] and is also a valid tool for detecting recurrence and monitoring therapy response.[40,41] Three-dimensional spectroscopic acquisition usually takes about 10–15 min. Considerable magnetic field distortions may occur from hemorrhage and therefore the exam has to be performed after sufficient delay following biopsy. MRSI needs more time and expertise than other MR functional techniques; therefore, its clinical application is limited.

OVERALL ACCURACY OF MP-MRI IN DETECTION OF PROSTATE CANCER

Although the individual sequences are useful, T2WI in combination with two functional sequences has been shown to provide better characterization of tumor in the prostate.[42,43,44] In a diagnostic meta-analysis of seven studies, de Rooij *et al.* revealed a high overall sensitivity and specificity on accuracy of mp-MRI using T2WI, DWI and DCE MRI. Pooled sensitivity and specificity were 0.74 and 0.88, respectively, with negative predictive value (NPV) ranging from 0.65 to 0.94.[45] In another study, mp-MRI showed good performance at detecting and ruling out clinically significant cancer, following at least one previous biopsy, with a NPV of 95% using transperineal template systemic biopsy as the gold standard.[46] The authors concluded that mp-MRI can therefore be used as a triage test following a negative biopsy and thereby identify patients who can avoid further biopsies. A recently published study reported clinical NPV of mp-MRI at 89.6% for significant cancer over a longitudinal follow-up period of 5 years.[47] Shakir *et al.* demonstrated that the benefit of MRI and targeted biopsy increases with increasing PSA levels and that the diagnostic usefulness and upgrading to clinically significant disease on biopsy occurred above a PSA threshold of 5.2 ng/mL.[48]

While several studies have shown the benefit of functional imaging in detection of prostate cancer in the peripheral zone,[26,31,49] functional imaging may have a limited role in evaluating cancers in the transition zone on mp-MRI because of the heterogenous appearance and enhancement secondary to benign prostatic hyperplasia. Hoeks *et al.*[19] reported that DCE-MRI in particular did not show any additional benefit over T2WI for detection of cancer in the transition zone. In their study, accuracy of mp-MRI for detecting Gleason grades 4 and 5 in the transitional zone was 79% for T2WI and 72% when combined with DWI and DCE MRI. For low-risk disease, the accuracy levels were 66% for T2WI and 62% when combined with functional imaging. In another study, the authors reported that adding DWI to T2WI improved the accuracy of detecting prostate cancer in the transition zone.[50]

Tumor volume is a documented prognostic factor for prostate cancer outcome, and is its correct estimation is mandatory for success of focal therapy,[51] the new organ-sparing treatment technique that aims to selectively ablate locally confined, clinically significant index lesions, while sparing the rest of the prostate gland and the surrounding structures. Histologic architecture of the tumor affects quantitative MRI findings and is known to be a major predictor of tumor visibility on mp-MRI.[52,53] Sparse or infiltrative tumor mixed with normal tissue may be present at the periphery of the MRI-visible “dense” tumor. Studies have shown that the greatest tumor volume on mp-MRI determined from images on any of the individual sequences provided a fairly accurate estimation of the tumor volume on whole-mount histology,[54] although estimation was more accurate for larger tumors over 10 mm[55] and >0.5 cc[56] in volume than for small tumors.[51]

Because prostate MRI interpretation can be subjective and inconsistent, suspicion scores for prostate cancer on MRI (Prostate Imaging and Reporting Archiving Data System [PI-RADS]) have been developed on a 1- to 5-point scale (based on fixed criteria) for improved standardization of MRI interpretation and reporting.[13] The Likert scoring system is based on an overall impression of the reader and is a more subjective form of evaluation. Studies have shown higher interobserver reproducibility in the experienced readers than for less-experience readers for both the PI-RADS and the Likert scoring systems.[16] A recent meta-analysis of 14 studies evaluating use of the PI-RADS scoring system for prostate cancer detection on mp-MRI showed good diagnostic accuracy.[57] However, the PI-RADS scoring system is work in progress and PI-RADS version 2 has recently been published.[58]

ROLE OF MP-MRI IN BIOPSY NAÏVE PATIENTS

Use of mp-MRI in men with no previous biopsy has been studied, but the cost-effectiveness and the true value in this patient population is yet to be determined. Recently, the National Health Services in the United Kingdom has demonstrated that prostate MRI even in biopsy-naïve patients may be cost effective.[59] De Rooij *et al.*[60] compared the quality of life and health care costs for the TRUS-guided biopsy strategy and the imaging-based strategy where MRI and directed MR-guided biopsies were performed, modeled to a period of 10 years following initial referral for biopsy. Their results suggested comparable healthcare costs in the two strategies but an improved quality of life (QoL) in the imaging arm. The benefit in QoL is derived from decrease in overdiagnosis and overtreatment in the imaging arm.

In a recently reported randomized prospective study by Panebianco *et al.*,[3] prostate cancer was detected in 215/570 (38%) patients in the TRUS biopsy arm. Of the 355/570 patients in whom TRUS biopsy was negative, mp-MRI after the biopsy showed a suspicious focus in 208 patients, of which 186 were positive on biopsy (i.e., 52% of patients after an initial negative biopsy). In the imaging arm, 440/570 patients had a positive MRI, of whom 417 were positive on biopsy. In the 130 patients in the imaging arm who had a negative MRI, none had Gleason 7 disease on saturation biopsy. In another study, Haffner *et al.* reported a cancer detection rate of 54% in the systematic biopsy arm versus 63% in the MRI arm.[61] Several studies have shown detection of more clinically significant tumors in the MRI arm compared with systematic biopsy, even though the overall cancer detection rate may not be higher in the imaging arm, thereby improving the biopsy performance and benefitting the diagnosis of cancer.[61,62,63,64]

MP-MRI FOLLOWING BIOPSY

In a meta-analysis including 14 studies and 698 patients, the mean cancer detection rate following a negative biopsy was 37.5% (range 19.2–68.3%).[65] The pooled sensitivity and specificity by site analysis was 57% and 90%, respectively. The positive predictive value of mp-MRI in these studies ranged from 17 to 92. However, in many of these studies, biopsies were obtained by visual/cognitive assessment following mp-MRI. Hoeks *et al.* reported a cancer detection rate of 25% (108/438) in patients who had at least one previous negative biopsy for increased PSA and underwent subsequent mp-MRI and MRI guided in bore biopsy, with 87% of these cancers found to be clinically significant.[66] The positive predictive value of mp-MRI in this study was 41% (108/265) by patient analysis and 33% (123/368) by site analysis. Similarly, Vourganti *et al.* reported a cancer detection rate of 37% (73/195) following a previous negative biopsy and suspicious mp-MRI. In their study, targeted biopsy using MRI-TRUS fusion upgraded in 28 patients and detected additional significant cancer in 12 patients, not detected by systematic biopsy. Recently, Sonn *et al.*[67] also detected cancer in 34% (36/105) of patients using MRI-TRUS fusion following initial negative biopsy, with 72% of these being clinically significant. The positive predictive value of mp-MRI for highly suspicious lesions (PI-RAD scores of 4 and 5) was 50% (24/48 patients).

ROLE OF MP-MRI IN ACTIVE SURVEILLANCE (AS)

Different studies have shown a wide range of upgrading (range 17–72%) following targeted biopsy in men with low-risk disease on initial biopsy and therefore improves the assignment of appropriate treatment options.[68] Margel *et al.* reported that 32% of patients were reclassified as higher risk disease following mp-MRI-directed targeted biopsy in a cohort of 60 active surveillance patients.[69] Turkbey *et al.* retrospectively assessed 133 patients who underwent mp-MRI prior to radical prostatectomy. Mp-MRI had a sensitivity of 93%, positive predictive value of 57% and overall accuracy of 92%, thereby demonstrating the capability to improve the appropriate selection of therapeutic option (AS versus radical treatment).[70] The absence of a visible lesion on mp-MRI in patients with low-risk disease has been suggested as a good prognostic indicator for men on AS and in reducing the number of unnecessary biopsy episodes.[71] MRI in lieu of biopsies as a surveillance tool for detection of clinically significant cancer holds promise.

CONCLUSION

The targeted biopsy “flight” has taken off and the benefits of targeted biopsy have been repeatedly shown in several studies. There is mounting evidence along with the recent literature suggesting that effectiveness of mp-MRI when used along with PSA, followed by targeted biopsy of the MRI-visible lesion, is a better alternative to systematic TRUS biopsy in the diagnostic pathway for prostate cancer detection and therefore benefits the diagnosis of cancer. The largest benefit may come from reduction of unnecessary

biopsies (NPV of mp-MRI for clinically significant cancer), which could in turn prevent overdiagnosis and overtreatment. It also has the potential to decrease the number of missed clinically significant cancers and improves risk stratification; therefore, it provides a more accurate therapeutic option to the patient. As we move toward personalized medicine, use of MRI to biopsy each man's prostate differently rather than based on a pre-defined 12 core seems to be supported in the recent literature.

Footnotes

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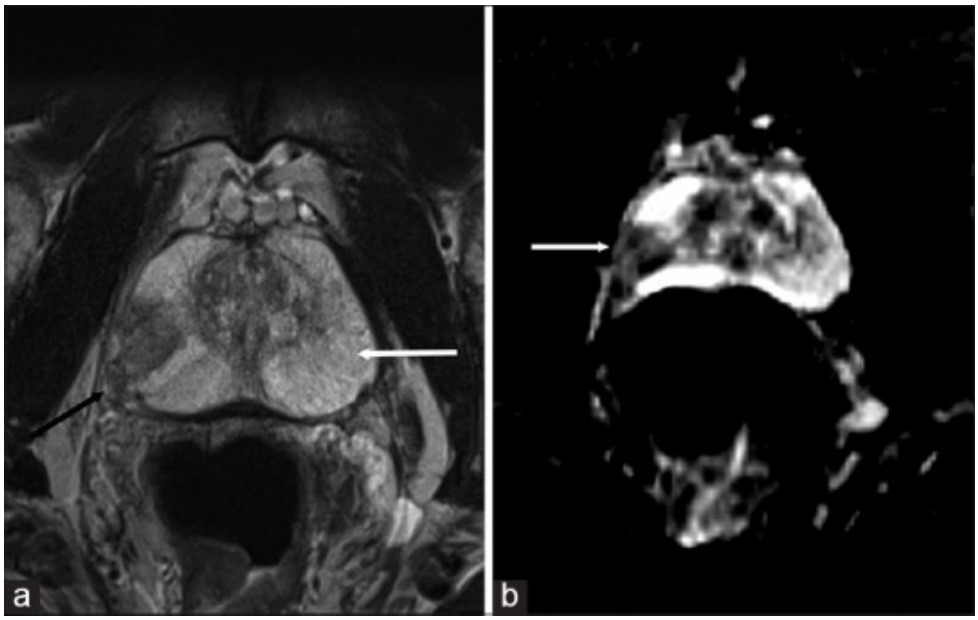
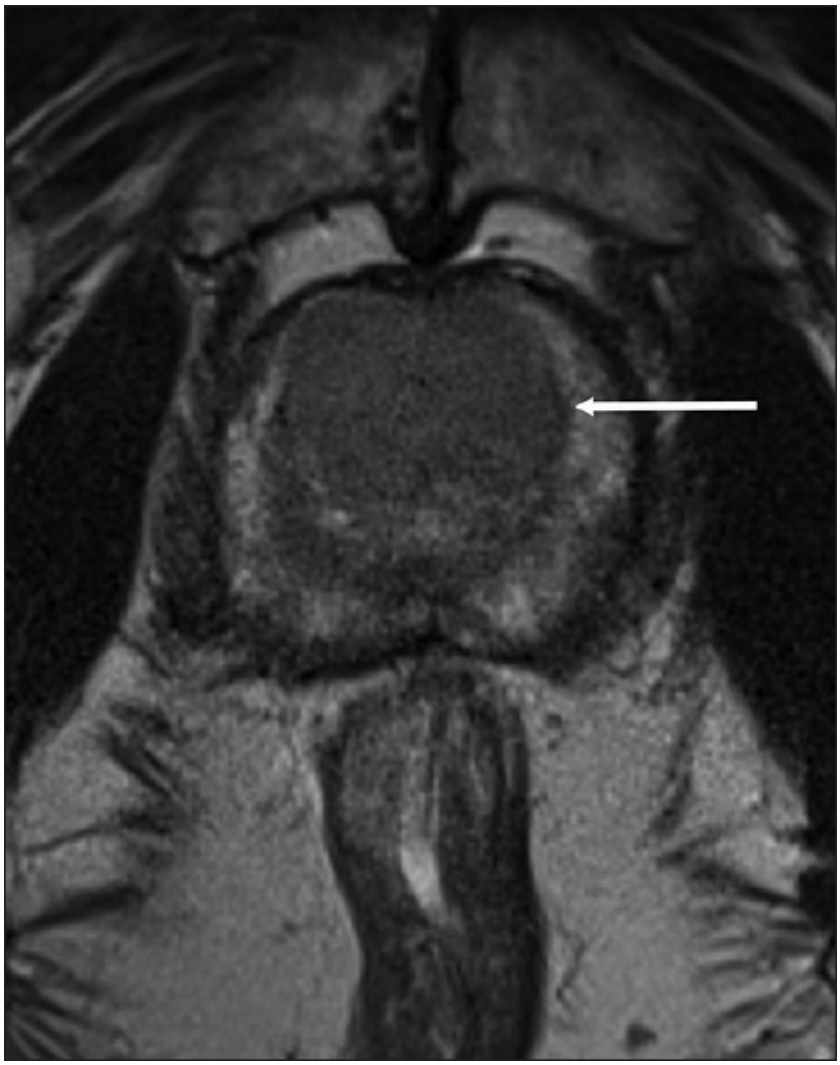
Figures and Tables

Figure 1



A 55-year-old man with Gleason 7 (4 + 3) prostate cancer. (a) Axial T2-weighted image (T2WI) shows the normal hyperintense T2 signal in the peripheral zone (white arrow) from the high water content with cancer (black arrow) appearing as an area of low signal on T2WI. (b) Apparent diffusion coefficient map at the same level showing low signal from the restricted diffusion at the site of cancer (arrow)

Figure 2



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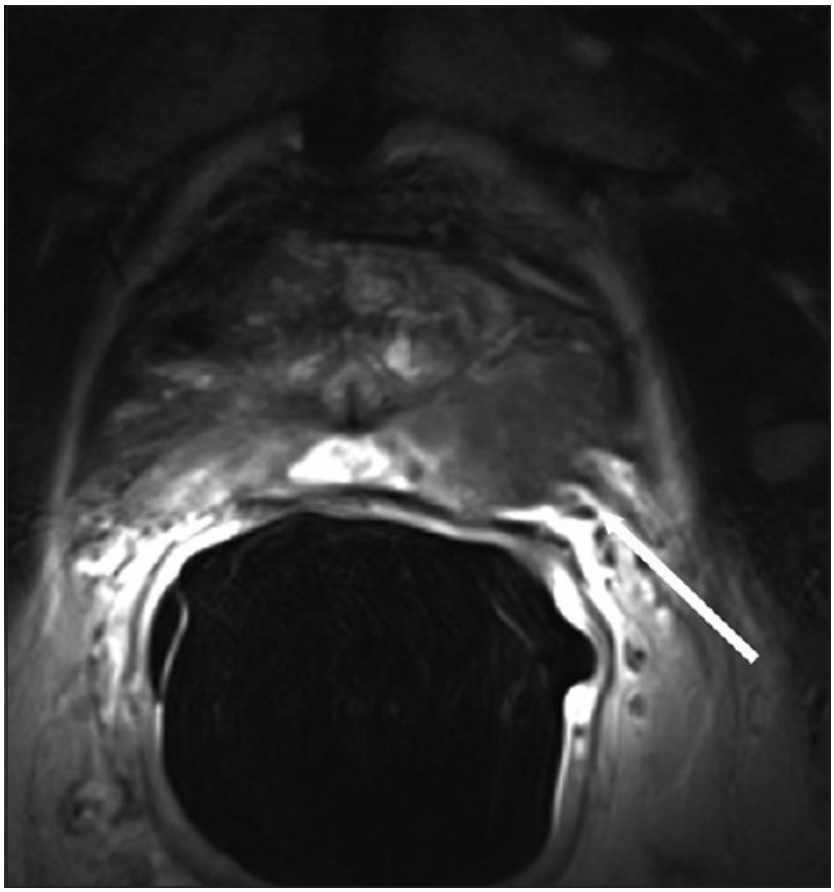
Transition zone tumor. A 54-year-old male with biopsy-confirmed Gleason 8 prostate carcinoma. The T2-weighted image showing a typical “erased charcoal” (arrow) appearance in the transition zone

Figure 3



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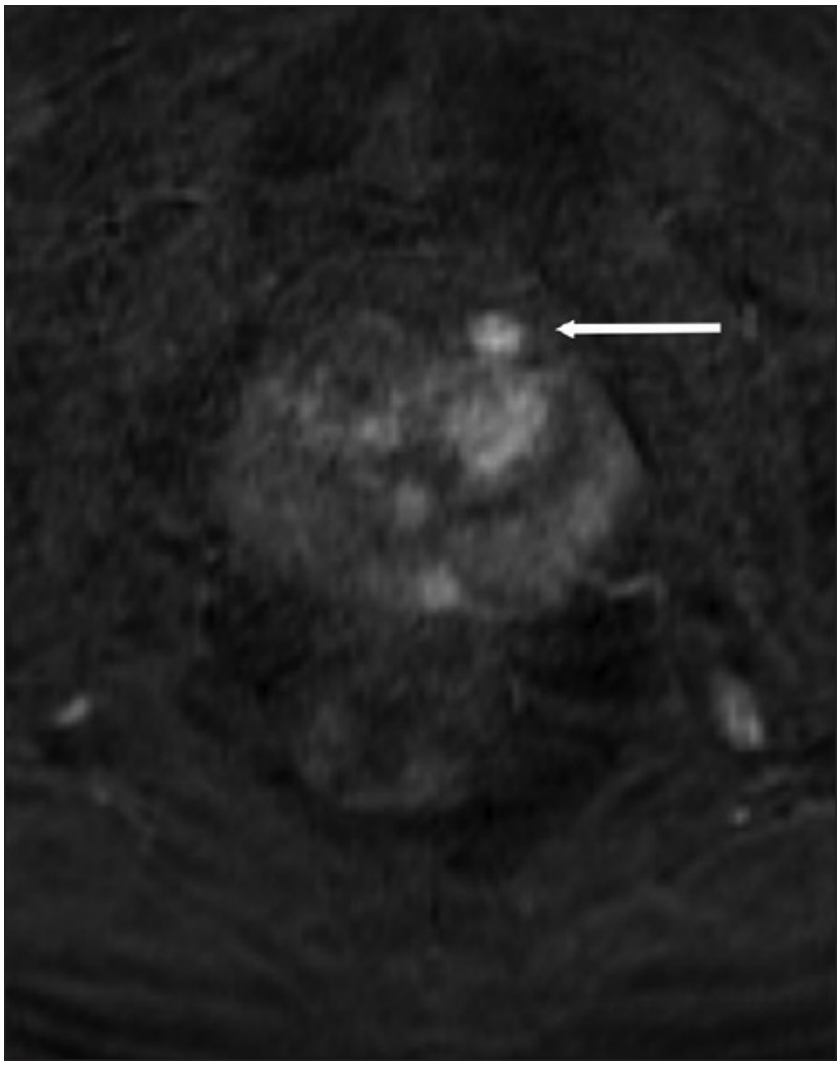
Extracapsular extension of tumor. A 64-year-old male with biopsy-confirmed Gleason 7 (3 + 4) prostate carcinoma. Axial T2-weighted image obtained with the endorectal coil shows the low signal tumor in the left peripheral zone with minimal extension along the left neurovascular bundle (arrow)

Figure 4



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Residual tumor following focal therapy. Dynamic contrast-enhanced axial subtraction image 6 months following focal therapy shows a nodular area of enhancement at the margin of the treatment. Magnetic resonance-directed fusion biopsy of the area was performed, which revealed Gleason 6 disease