

Multi-parametric MRI of the Prostate

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Introduction

One in six men will develop prostate cancer in their lifetime [1]. The most consistent risk factors for the development of prostate cancer are advancing age, family history and race [2]. Interestingly, men in South East Asian countries have a lower incidence of prostate cancer that increases rapidly after immigration to the West suggesting that the pathogenesis of prostate cancer reflects both hereditary and environmental components [2]. It has been suggested that chronic inflammation might be important in prostate carcinogenesis. Intraprostatic inflammation might be caused by infections such as sexually transmitted agents; cell injury from exposure to chemical or physical trauma from urine reflux and prostatic calculi formation; hormonal variations or exposures and dietary factors such as charred meats. This may directly injure the prostate epithelium, resulting in histological lesions known as proliferative inflammatory atrophy (PIA). Transitions between areas of PIA and high grade prostatic intraepithelial neoplasia and adenocarcinoma have been observed [2]. Furthermore, PIA lesions may be a manifestation of the 'field effect' caused by environmental exposures [2]. In fact, prostate cancer is histologically heterogeneous and multifocal in as many as 85% of patients [3].

Clinical screening of the prostate is performed with

digital rectal examination (DRE) and serum prostate specific antigen (PSA) measurement. DRE has a low sensitivity in the detection of prostate cancer while elevated PSA has a high sensitivity but low specificity in the detection of cancer with elevated levels seen in the presence of prostatitis, benign prostate hypertrophy (BPH) and post-instrumentation [4]. Positive predictive values for the detection of early prostate cancer have been reported as 21% for DRE and 32% for PSA [4]. In patients with abnormal DRE or elevated PSA, trans-rectal ultrasound (TRUS) guided biopsies are performed for histological diagnosis and to determine Gleason grade which is an indicator of tumour aggressiveness. These systematic random biopsies are prone to undersampling with 35% of cancers missed on first biopsy [5] and underestimation of Gleason grade in 46% of cases [6].

Hence, multi-parametric magnetic resonance imaging (MRI) plays an increasingly important role in the evaluation of prostate carcinoma. A combination of anatomic imaging with T1- weighted imaging (T1WI) and T2-weighted imaging (T2WI) and functional imaging with diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) map calculation and dynamic contrast-enhanced MRI (DCE-MRI) are routinely performed. MR spectroscopic imaging (MRSI) may also be performed as an optional technique.

Indications for MRI

MRI plays a vital role in the detection and staging of

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prostate carcinoma. A combination of T2WI, DWI and DCE-MRI has an increased sensitivity of 81% and specificity of 96% in prostate cancer detection compared to use of T2WI alone which has a sensitivity of 61% and specificity of 91% [7]. MRI is particularly helpful in guiding repeat TRUS biopsies in patients with elevated PSA and negative initial biopsies as sometimes seen with anterior and apical tumours which are easily missed on random biopsy. MRI is used to determine extracapsular and locoregional tumour infiltration, this is vital in treatment planning, for instance in planning of nerve and continence sparing surgery or focal therapy. Functional MRI can also be used to determine tumour volume and foci of more aggressive disease enabling targeted TRUS biopsies for more accurate estimation of Gleason grade. Studies have shown that ADC values have an inverse relationship with Gleason grade in peripheral zone prostate cancers [8]. MRI is also vital in the detection of post-prostatectomy and post-radiotherapy tumour recurrence.

Normal Anatomy of the Prostate

The normal prostate weighs 15 to 20g and is shaped like an inverted pyramid with its base directed superiorly and its apex inferiorly. It surrounds the urethra between the neck of the urinary bladder superiorly and the urogenital diaphragm inferiorly. Laterally the prostate borders the middle portion of the levator ani muscles. The paired seminal vesicles extend from the top of the prostate in a superolateral direction. Inferior to the seminal vesicles the neurovascular bundle fibres penetrate the prostate capsule posteriolaterally. The prostate is separated from the rectum by the Denonvilliers fascia. Anterolateral to the prostate there is an extensive venous complex [9]. These structures should be evaluated when determining locoregional tumour spread.

The prostate can be divided into several zones with the urethra as the anatomical landmark. Anterior to the

urethra is the fibromuscular zone (FMZ) which is histologically non-glandular. Posteriolaterally is the glandular part of the prostate consisting of an inner periurethral glandular region and transitional zone (TZ) which is at the level of the proximal urethra above the seminal colliculus; the central zone (CZ) posteriorly is wedge shaped and surrounds the ejaculatory ducts and extends from the seminal colliculus to the bladder neck; the peripheral zone (PZ) is contiguous with the CZ at the base while its distal portion from below the seminal colliculus to the prostate apex surrounds the urethra. The CZ and TZ are commonly referred to as the central gland as it cannot be differentiated on MRI while the PZ is referred to as the peripheral gland. A pseudocapsule separates the central gland from the peripheral gland while the true prostate capsule surrounds the peripheral gland [9].

Many prostate diseases have a zonal distribution, for example 70% of adenocarcinomas arise in the PZ, with 20% in the TZ and 10% in the CZ [3]; BPH usually involves the TZ [3].

MRI of the Normal Prostate

MRI of the prostate can be performed with a body phased-array coil. The following sequences are performed: Axial T1WI of prostate; Axial T2WI of whole pelvis; Axial, sagittal and coronal T2WI of prostate; Axial DWI of prostate with b-value of 1000 s/mm² with ADC map calculation; Axial DCE-MRI of prostate following administration of gadolinium-based contrast medium with image acquisition continued for 5 minutes for analysis of dynamic enhancement curves; Axial post contrast image of whole pelvis at 5 minutes. MRSI is not routinely performed. Bowel motion artifact can be reduced by administration of an anti-peristaltic agent.

On T1WI the prostate has homogeneously intermediate signal intensity slightly hyperintense to muscle. The prostate zonal anatomy is best appreciated on T2WI, the

PZ is homogeneously hyperintense, the central gland has heterogeneous areas of high and low signal intensity and the FMZ is isointense to muscle. The prostate capsule is seen as a line of hypointensity surrounding the PZ in the low and mid portions of the prostate. The neurovascular bundles are seen as triangles at the posteriolateral margins of the prostate [9]. The seminal vesicles are isointense to the prostate on T1WI. They are better evaluated on T2WI where the lobular glandular configuration with hyperintense content and hypointense borders of the tubules and capsule are better appreciated [9].

MRI of Prostate Carcinoma

The European Society of Urogenital Radiology (ESUR) published guidelines for prostate imaging in 2012 [10]. The guidelines recommend three MRI scanning protocols for tumour detection, local staging and node and bone metastases evaluation. The ESUR propose a PI-RADS scoring system which relays the probability of a lesion being a clinically significant cancer. The scoring criteria include T2WI for the PZ and TZ, DWI, DCE-MRI and extra-prostatic disease. MRSI is given as an optional technique. A 5 point scale is allocated for each imaging sequence with a score of 1 indicating that clinically significant cancer is highly unlikely to be present and a score of 5 indicating that clinically significant cancer is highly likely to be present. Each lesion is then given an overall score to predict its chance of being a clinically significant cancer.

On T2WI, a round or ill-defined homogeneously hypointense focus in the PZ is suspicious for cancer. Bulging of the capsule, broad contact of more than 1.5cm with the capsule or extracapsular extension increases likelihood of malignancy [10] (Figure 1). A linear, wedge shaped or geographic area of hypointensity in the PZ which is usually not well demarcated is more likely to represent a benign process [10]. This may be seen in cases of prostatitis, atrophy,

scarring or post treatment change.

Detection of prostate cancer in the TZ is more challenging as signal characteristics of normal TZ and cancer overlap. On T2WI, a homogeneously hypointense mass with indistinct margins giving an 'erased charcoal sign', a lesion which is lenticular or 'water drop' in shape or invasion of the pseudocapsule, anterior-FMZ or anterior horn of the PZ is more likely to represent malignancy [10] (Figure 1). This should be differentiated from heterogeneous TZ adenomas with well defined margins referred to as 'organized chaos' or areas of homogeneous hypointensity with retained well defined margins originating from the TZ, this is seen in BPH [10] (Figure 2).

Prostate cancer demonstrates restricted diffusion with hyperintensity on DWI and hypointensity on ADC maps [11-12]. However normal prostatic tissue, especially in the TZ, may have restricted diffusion mimicking a tumour, using very high b values of $> 1000\text{s/mm}^2$ has been recommended to overcome this [10]. A focal area or mass having restricted diffusion on high b-values is more likely to represent malignancy (Figure 1). A diffuse area with no focal features or an area that is linear, triangular or geographic demonstrating restricted diffusion is more likely to represent benign disease [10].

DCE-MRI is an evaluation of tissue vascularity. A region of interest (ROI) is drawn on suspicious tumour foci and dynamic contrast enhancement curves evaluated. Cancer typically demonstrates early contrast enhancement with high peak relative enhancement and contrast washout (Figure 1). However, hypervascular BPH nodules can have similar enhancement characteristics, hence it is always interpreted in combination with T2WI and DWI [10].

Biopsy related haemorrhage commonly causes artifacts that mimic cancer limiting sensitivity of MRI. This should be recognized on T1WI as areas of hyperintensity, preventing misinterpretation (Figure 3).

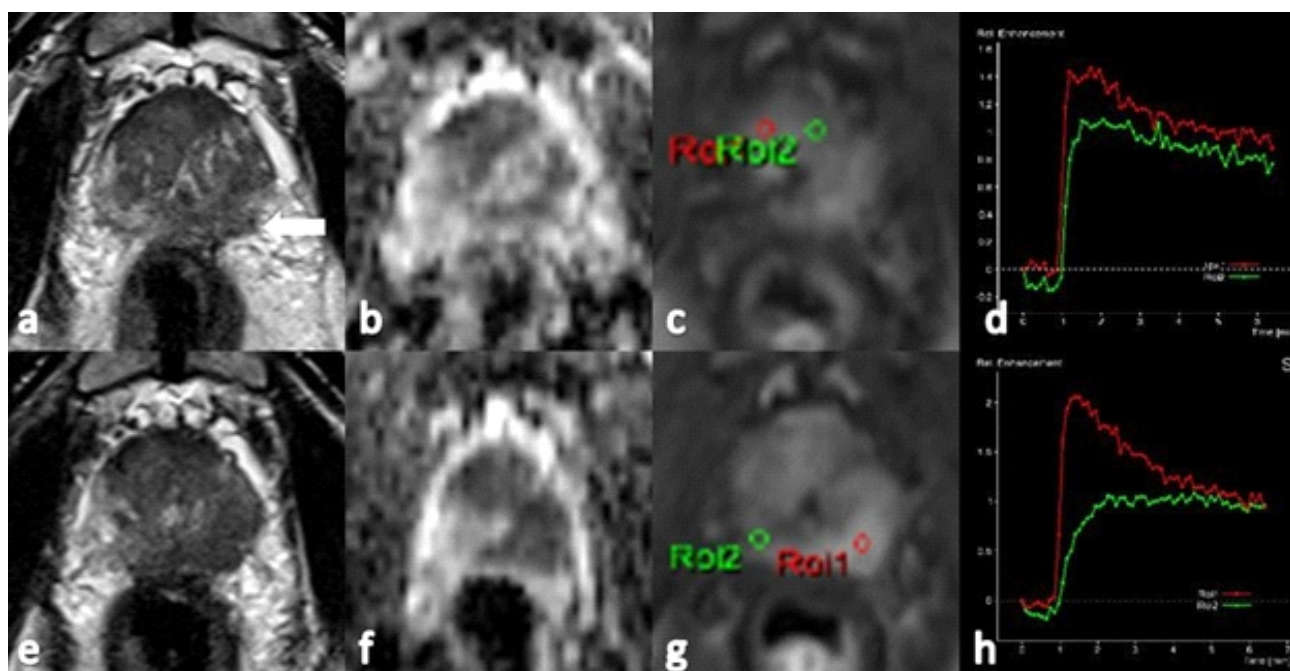


Figure 1. 76-yr-old man with raised PSA. TRUS biopsy confirmed prostatic acinar adenocarcinoma, Gleason grade 3+4=7. (a) Axial T2WI shows lenticular shaped area with 'erased charcoal sign' in the right anterior central gland invading the FMZ likely representing cancer. A second hypointense lesion is seen in the left PZ with irregularity of the prostate capsule and thickening of the left neurovascular bundle (arrow) in keeping with tumour infiltration. (b) ADC map shows both lesions have restricted diffusion. (c) DCE-MRI with two ROIs placed on the central gland lesion. (d) Graph of relative enhancement versus time. The dynamic enhancement curves show rapid contrast enhancement with high peak relative enhancement and contrast washout in keeping with carcinoma. Note that ROi1 has been placed on part of the lesion with lower ADC value and has a higher peak relative enhancement and washout in keeping with a more aggressive focus of cancer. (e) Axial T2WI more inferiorly in the prostate again shows the lesion in the central gland with irregular margins. The second lesion in the left PZ is seen as a rounded mass with bulging of the capsule consistent with capsular infiltration. (f) ADC map shows both lesions have restricted diffusion involving a large volume of the prostate. (g) DCE-MRI with ROi1 placed on the lesion in the left PZ and ROi2 placed on contralateral lobe for comparison. (h) Graph of relative enhancement versus time. ROi1 shows rapid enhancement with high peak relative enhancement and contrast washout in keeping with cancer. In comparison ROi2 in the contralateral lobe has gradual enhancement with low peak relative enhancement and no significant contrast washout in keeping with benign PZ.

A time interval of 4-6 weeks between biopsy and MRI has been recommended [13], however if significant haemorrhage is still seen, postponing the study for a further 3-4 weeks to allow resolution of the haemorrhage is recommended [10].

Extracapsular extension of tumour is best evaluated on T2WI. Capsular breach by tumour may manifest as tumour abutment, bulging, loss of definition and irregularity of the prostate capsule [10]. Thickening of

the neurovascular bundle, measurable extra-capsular disease and obliteration of the recto-prostatic angle may be evident [10]. Seminal vesicle infiltration may manifest as expansion, hypointensity on T2WI, filling in of the prostate-seminal vesicle angle, abnormal enhancement and restricted diffusion [10]. Tumour adjacent to the bladder neck, loss of low T2W signal of the bladder muscle and abnormal enhancement extending into the bladder neck is indicative of bladder

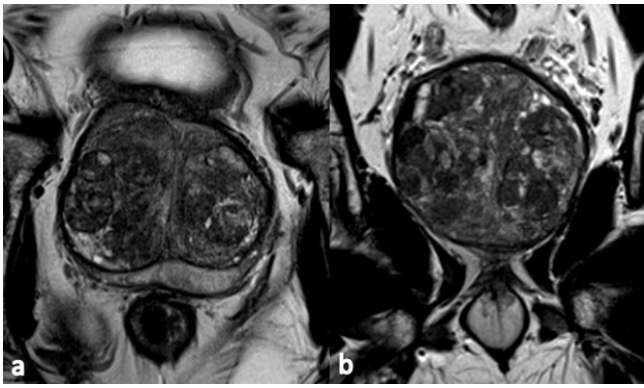


Figure 2. (a) Axial T2WI and (b) Coronal T2WI show enlarged TZ with multiple well margined nodules of varying intensities in keeping with 'organised chaos' of BPH. Note normal PZ of homogeneous hyperintensity.

neck invasion [10]. Similar imaging features may be seen in local tumour infiltration of the levator ani or rectum (Figure 4). Lymph node staging of prostate cancer on MRI is unreliable as 70% of metastatic lymph nodes are less than 8mm [10].

In post- prostatectomy patients with rising PSA, a focal

lesion in the surgical bed, having restricted diffusion and typical dynamic contrast enhancement curve would most likely represent tumour recurrence.

On MRSI, the relevant metabolites are citrate which is a marker of benign tissue, creatine which is insignificant for diagnosis but difficult to resolve from choline and choline which is a marker of malignancy. In quantitative analysis, a choline-plus-creatine-to-citrate (CC/C) ratio is estimated, with ratios of >0.86 in the PZ and >0.94 in the central gland indicative of malignancy [10]. In qualitative analysis the peak heights of citrate and choline are visually compared. A choline peak height exceeding a citrate peak height by >1 times is likely to represent clinically significant cancer [10].

Conclusion

Clinical screening for prostate cancer with DRE and PSA measurements has its limitations. Random TRUS-guided biopsies may miss cancers and may

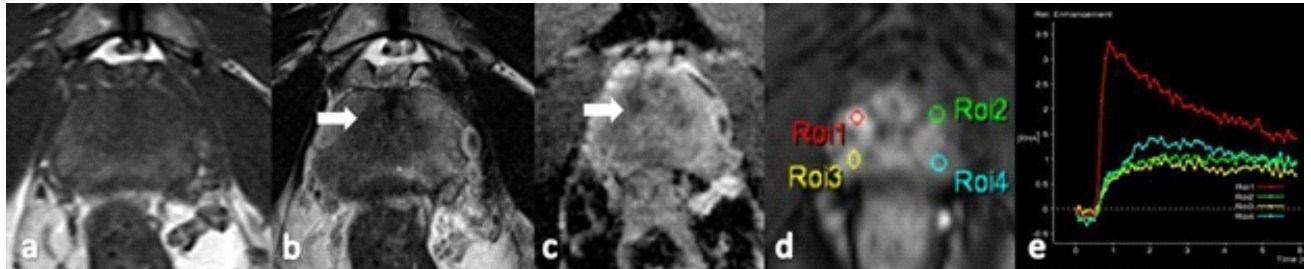


Figure 3. A 60-yr-old asymptomatic man with raised PSA on health screening. TRUS biopsy confirmed prostatic acinar adenocarcinoma, Gleason grade 3 +4=7 (a) Axial T1WI shows diffuse hyperintensity in the PZ and right central gland consistent with post biopsy haemorrhage. (b) Axial T2WI shows several hypointense foci in the PZ, more on the right, with irregularity of the prostate capsule. This corresponds to areas of haemorrhage seen on T1WI, mimicking carcinoma. However a small focus of relatively lower signal intensity is seen anteriorly in the right PZ (arrow), this was noted to extend inferiorly to the prostate apex suspicious for cancer. (c) ADC map shows mild restricted diffusion of the haemorrhagic foci in the PZ. A small focus of more intense restricted diffusion anteriorly in the PZ (arrow) corresponds to the suspicious lesion seen on T2WI. (d) DCE-MRI, ROi1 has been placed on the suspicious lesion in the right anterior PZ, while ROi2-4 have been placed in the remaining PZ for comparison. (e) Graph of relative enhancement versus time. ROi1 enhancement curve shows rapid contrast enhancement with high peak relative enhancement and contrast washout in keeping with cancer. ROi2-4 show gradual contrast enhancement with low peak relative enhancement and no contrast washout in keeping with benign process. The patient had a radical prostatectomy and histology confirmed tumour involvement of both lobes with a tumour volume of 15%. The remnant sites of tumour are probably obscured by post biopsy haemorrhage on MRI.

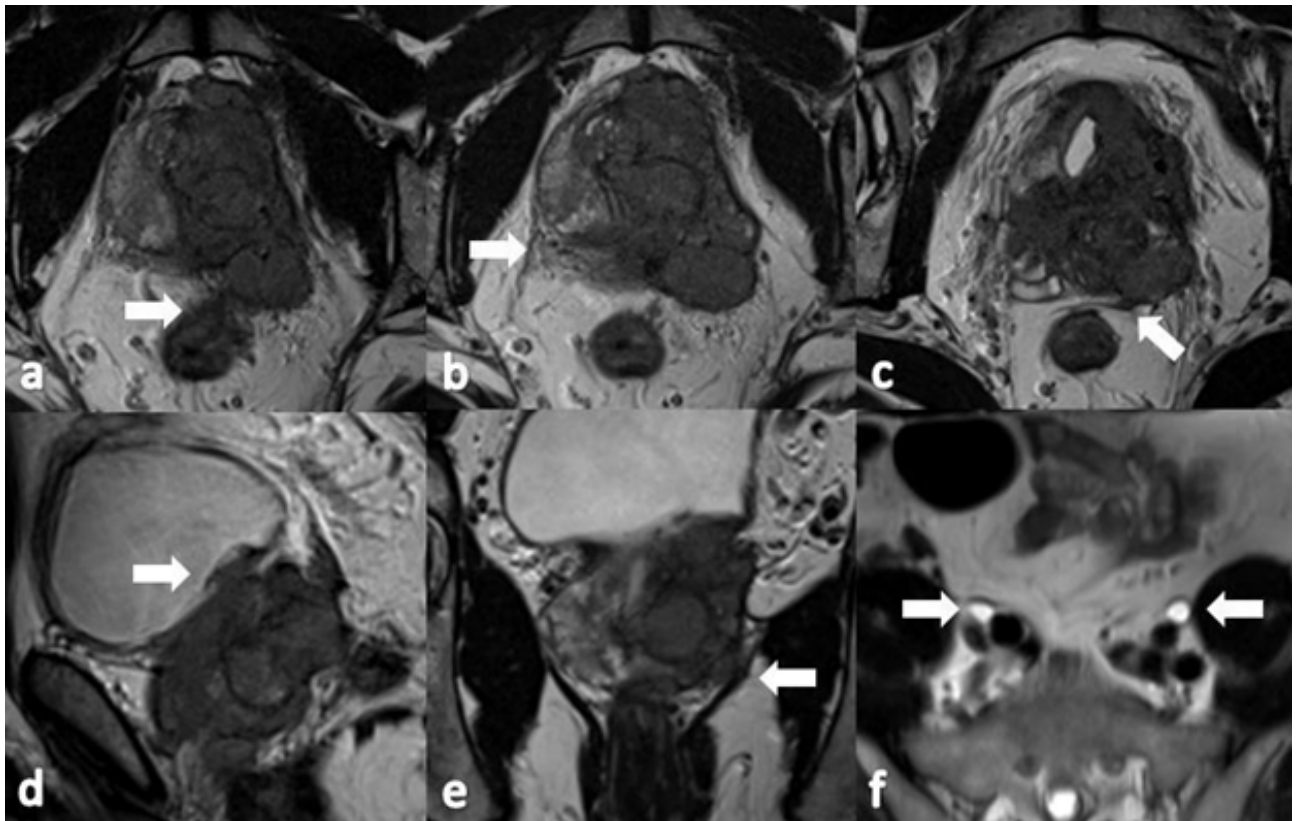


Figure 4. 57-yr-old man with gross haematuria and lower urinary tract symptoms. Cystoscopy and biopsy confirmed prostatic adenocarcinoma, Gleason grade 4+4=8. (a) Axial T2WI shows large prostate cancer of the left lobe with extracapsular tumour infiltration. Posteriorly there is loss of fat plane with the rectum with soft tissue stranding of the mesorectum (arrow) in keeping with rectal serosal infiltration. Anteriorly tumour infiltration of the venous plexus on the left is seen. (b) Axial T2WI shows large tumour mass invading the left neurovascular bundle, note normal neurovascular bundle on the right (arrow). (c) Axial T2WI shows tumour invasion of both seminal vesicles, more on the left, with nodular tumour infiltration of the mesorectal fascia (arrow). (d) Sagittal T2WI shows thickening and abnormal signal of the bladder neck in keeping with tumour invasion (arrow). (e) Coronal T2WI shows tumour indenting the left levator ani which is thickened with abnormal hyperintensity in keeping with tumour infiltration (arrow). (f) Axial T2WI of the pelvic inlet shows bilateral hydroureters (arrows) secondary to tumour involvement of both vesicoureteric junctions.

underestimate tumour aggressiveness. A combination of anatomical and functional MRI techniques is vital in the detection, staging and follow up of clinically significant prostate cancer.

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