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Multiparametric 3T MR imaging of the prostate - acquisition protocols and image evaluation

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Learning objectives

LEARNING OBJECTIVES

1. To discuss acquisition protocols and image evaluation of multiparametric MR imaging of the prostate at 3T, including dynamic contrast-enhanced imaging, diffusion-weighted imaging, and proton MR spectroscopy.

2. To describe the integrated interpretation of anatomic and functional MR imaging techniques based on the experience of our department.

3. To briefly review the current literature on the pros and cons of these imaging techniques in localization and local staging of prostate cancer.

Background

BACKGROUND

Epidemiology and Prostate Cancer Diagnosis

Prostate cancer (PCa) is a major global health problem being currently the most common cancer in men and the second cause of death by cancer in Portugal. Worldwide it is the second most frequently diagnosed cancer and the sixth leading cause of cancer related death in men (1).

Around 95% of prostate cancers are adenocarcinomas that develop in the acini of the prostatic ducts.

At present, screening for PCa relies on prostate-specific antigen (PSA) level and digital rectal examination (DRE). Definitive diagnosis is obtained by transrectal ultrasound (TRUS)-guided systematic random biopsy of the prostate (2). Histopathological analysis of biopsy samples provides information on the Gleason score that correlates with prostate cancer prognosis (3). Gleason score is based on the degree of differentiation of tumour architecture from 1 to 5, from least to most aggressive. Prostate carcinoma tends to be

multifocal and often presents multiple patterns of different grades. The Gleason score is obtained by adding the grades of the two most common tumour patterns (4).

These screening methods have several limitations. DRE has a low positive predictive value and a high inter-observer variability (5) and PSA levels have a low specificity owing to false-positive increase under benign circumstances like benign prostatic hyperplasia (BPH) (6).

Systematic random biopsy is prone to under-sampling and underestimation of the Gleason grade in 46% of cases (7) because PCa is often heterogeneous and has areas with different grades of differentiation in the same patient.

Newly diagnosed PCa is stratified according to the risk of tumor progression after radical treatment defined by the D'Amico criteria. This nomogram is based on the combination of PSA level and TRUS-guided biopsy findings, including the Gleason score and the amount of cancer tissue present on biopsy (8) (figure 1).

Low risk	Intermediate risk	High risk
PSA level ≤ 10 ng/ml *and* Biopsy: Gleason < 7 No more than two adjacent sectors positive for cancer Cancer volume in biopsy cores: total length of cancer < 10mm and < 7mm in any core; less than 1/3 of cores positive for cancer	PSA level 11-20 ng/ml *or* Biopsy: Gleason = 7 (3+4) *or* Gleason < 7, with cancer volume in biopsy cores greater than that of low risk group	PSA level > 20 ng/ml *or* Biopsy: Gleason > 7 (3+4)

Fig. 1: D'Amico criteria defining risk of progression after radical treatment of prostate cancer
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

The limitations of the aboved mentioned diagnostic tools for detecting and localizing prostate cancer are stimulating research in the field of magnetic resonance imaging (MRI).

MRI allows the detection of clinically significant PCa and can be used to identify areas of greater likelihood of cancer to be sampled during TRUS-guided biopsies, decreasing the number of false-negative results.

Prostate Anatomy

The prostate gland is divided into four parts according to McNeal's anatomic concepts: the peripheral zone (the lateral and posterior part of the prostate), the transitional zone, the central zone, and the anterior non-glandular fibromuscular stroma (figure 2) (9).

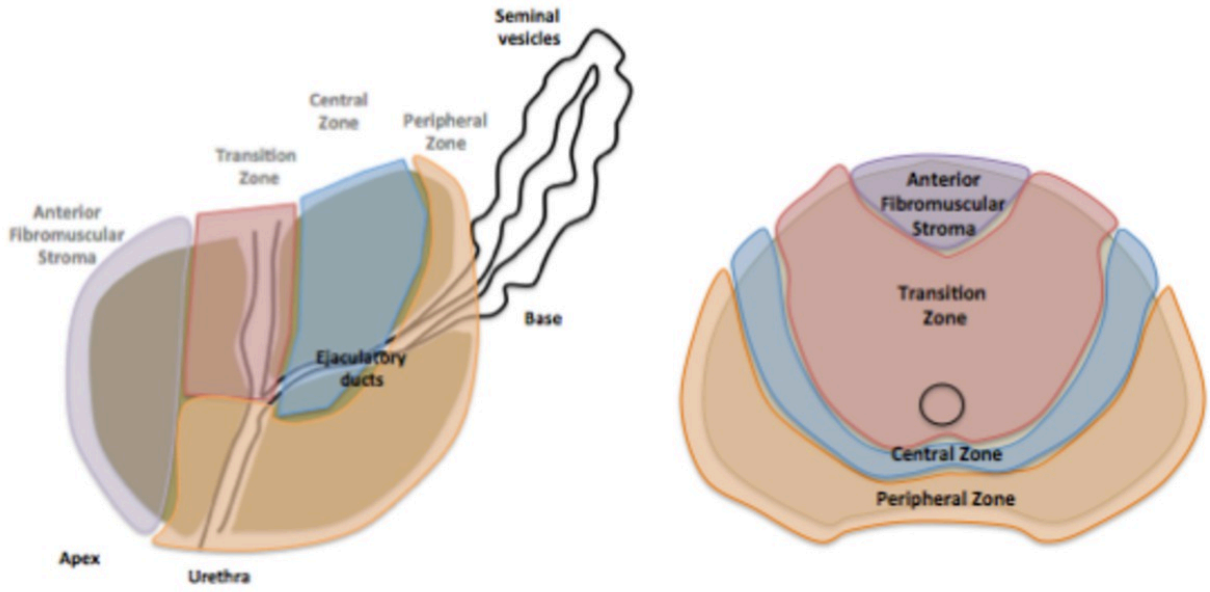


Fig. 2: Anatomy of the prostate (McNeal's zonal classification)
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

The percentage of carcinoma in a given zone is determined by the proportion of glandular tissue it contains. So, as the peripheral zone comprises 70-80% of the glandular tissue, 70% of prostate cancers arise in this zone (9).

It should be stressed that the zonal anatomy of the prostate changes with age: the transition zone tends to increase due to benign prostatic hyperplasia and exerts pressure on the surrounding central zone.

Findings and procedure details

FINDINGS AND PROCEDURE DETAILS

Nowadays, recommended use of MRI in prostate cancer consists of multi-parametric MRI (mpMRI), that combines anatomical images from T2-weighted (T2W) sequences and functional information obtained from diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCEI) and MR spectroscopy (MRS) (at least 2 functional MRI techniques should be used) (10).

Both 1.5T and 3T scanners are currently employed. Current receiver coil technology includes pelvic phased-array coils with or without the addition of an endorectal coil. In our department the mpMRI of the prostate is done at a 3T equipment. As the endorectal coil adds discomfort, time, and cost to the MR examination we perform it with the pelvic phased-array coils.

At our institute, a standard protocol is followed (figure 3). Spectroscopy is also routinely performed.

Sequence	T2 FSE	DWI	DCEI	MRSI
Plane	Axial / Coronal / Sagittal	Axial	Axial 3D	Axial
ET (ms)	126 / 126 / 127	75	1,74	145
RT (ms)	3600 / 3600 / 4400	3700	4,97	750
Section thickness (mm)	3	3	3,6	---
FOV (mm)	160	300	240	70x84x84
Matrix	256x256	128x128	192x115	---
Acquisitions	3	8	1 (measurements 75)	6
Acquisition time	4:28 / 4:28 / 4:34	5:09	6:25	9:54
Angle			12	90
b- value		0, 100, 500, 1000		

Fig. 3: Acquisition parameters of the prostate MR protocol in our 3T unit
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

MRI Techniques

High-resolution T2W Sequences

T2W images provide the best depiction of the prostate's zonal anatomy. This sequence is used for prostate cancer detection, localization and staging. In our department this sequence is obtained in 3 planes.

In this sequence the peripheral zone (PZ) of the prostate is hyperintense, whereas the central (CZ) and transitional zones (TZ) have low signal and cannot be distinguished being called collectively the central gland (CG), which is separated from the peripheral zone by a thin pseudocapsule (figure 4). The central gland may appear heterogeneous due to the presence of nodules and cysts (figure 5).

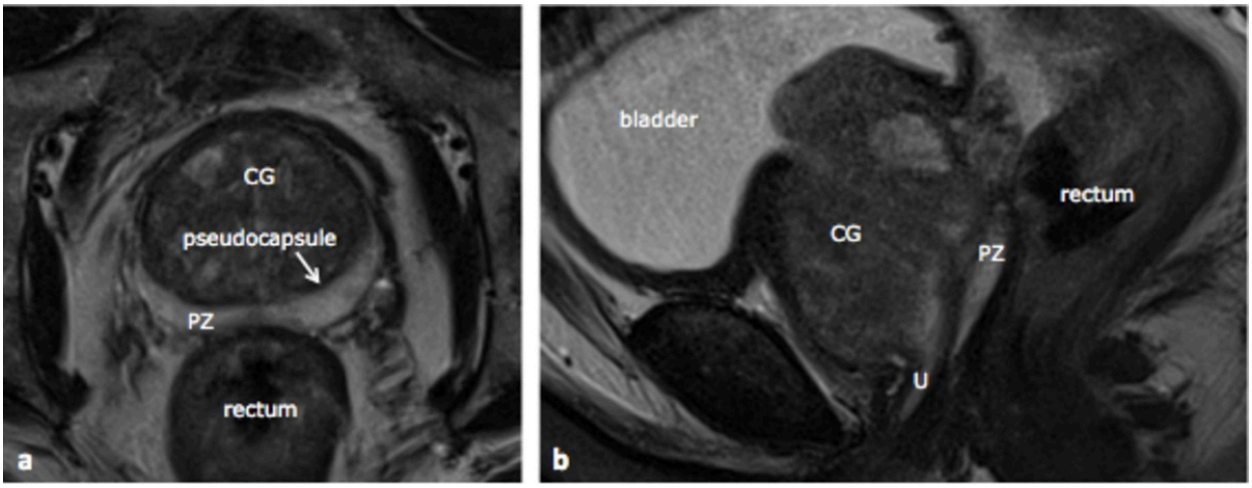


Fig. 4: Axial (a) and sagital (b) T2W images show normal zonal anatomy of the prostate. PZ: peripheral zone, CG: central gland, U: urethra.
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

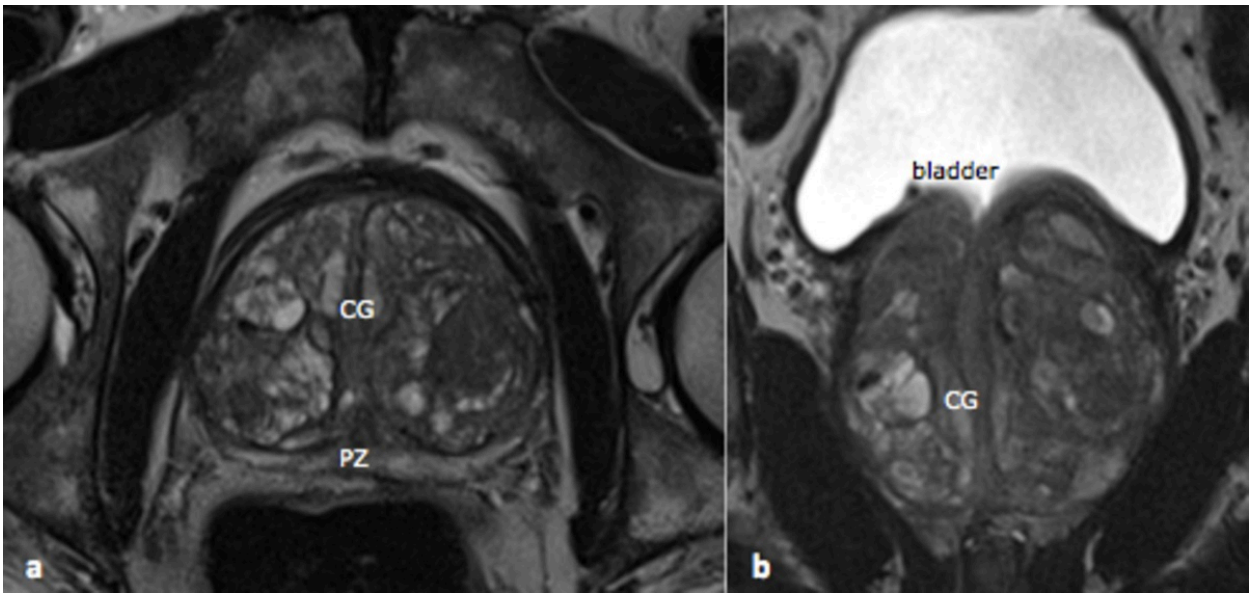


Fig. 5: Axial (a) and coronal (b) T2W images demonstrate the enlarged central zone to be heterogenous in signal with multiple nodules and cysts in a pattern called "organized caos". Note that an intact low signal pseudocapsule around its periphery is present. Features such as well-defined margins, visible capsule, and round shape favor a diagnosis of benign prostatic hyperplasia (BPH) nodules. The anterior fibromuscular stroma can be invaded by transitional zone tumors. BPH nodules, on the other hand, may displace but do not invade the fibromuscular stroma. PZ: peripheral zone, CG: central gland
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

The capsule is also demonstrated as a low-intensity line surrounding the gland. This capsule is an important imaging landmark in prostate cancer as extracapsular extension (ECE) can upstage the tumor to T_3.

Neurovascular bundles can usually be seen on axial images at 5 and 7 o'clock positions and they serve as pathways for extension of the tumor outside the capsule. The seminal vesicles are elongated fluid-filled structures with thin septae and possess high signal intensity on T2W images (figure 6). Medial to the seminal vesicles the vas deferens could be appreciated with low T2 signal intensity.

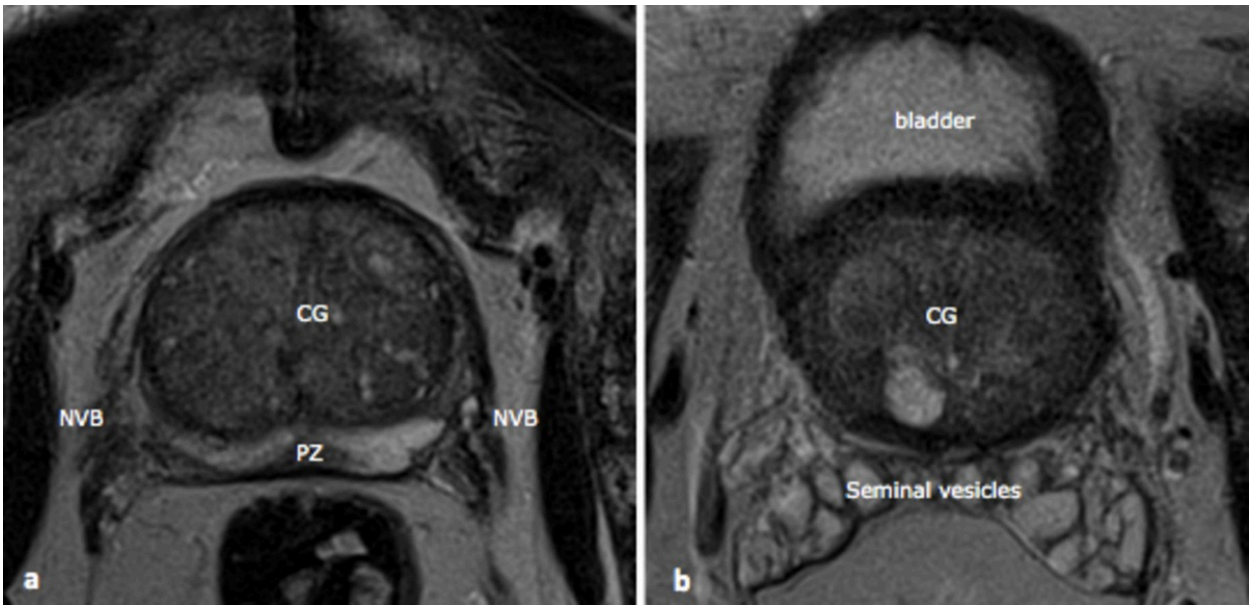


Fig. 6: Axial (a and b) T2W images. Neurovascular bundles (NVB) at 5 and 7 o'clock positions and normal appearance of the seminal vesicles. PZ: peripheral zone, CG: central gland.
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

T1-weighted (T1W) contrast in the prostate is very low and is not possible to appreciate the different anatomic prostatic zones. However, T1W images enables the determination of the presence and location of hemorrhage in patients submitted to prior biopsy sampling, that could mimic the presence of cancer as both appear as hypointense areas on T2W images. Preferably, MR imaging of patients suspected of having prostate cancer should be avoided for at least 8 weeks after prostate biopsy to allow reduction of artifacts due to post-biopsy hemorrhage.

Prostate cancer usually manifests as a round or ill-defined area of low signal-intensity, frequently in the peripheral zone (PZ) (figure 7).

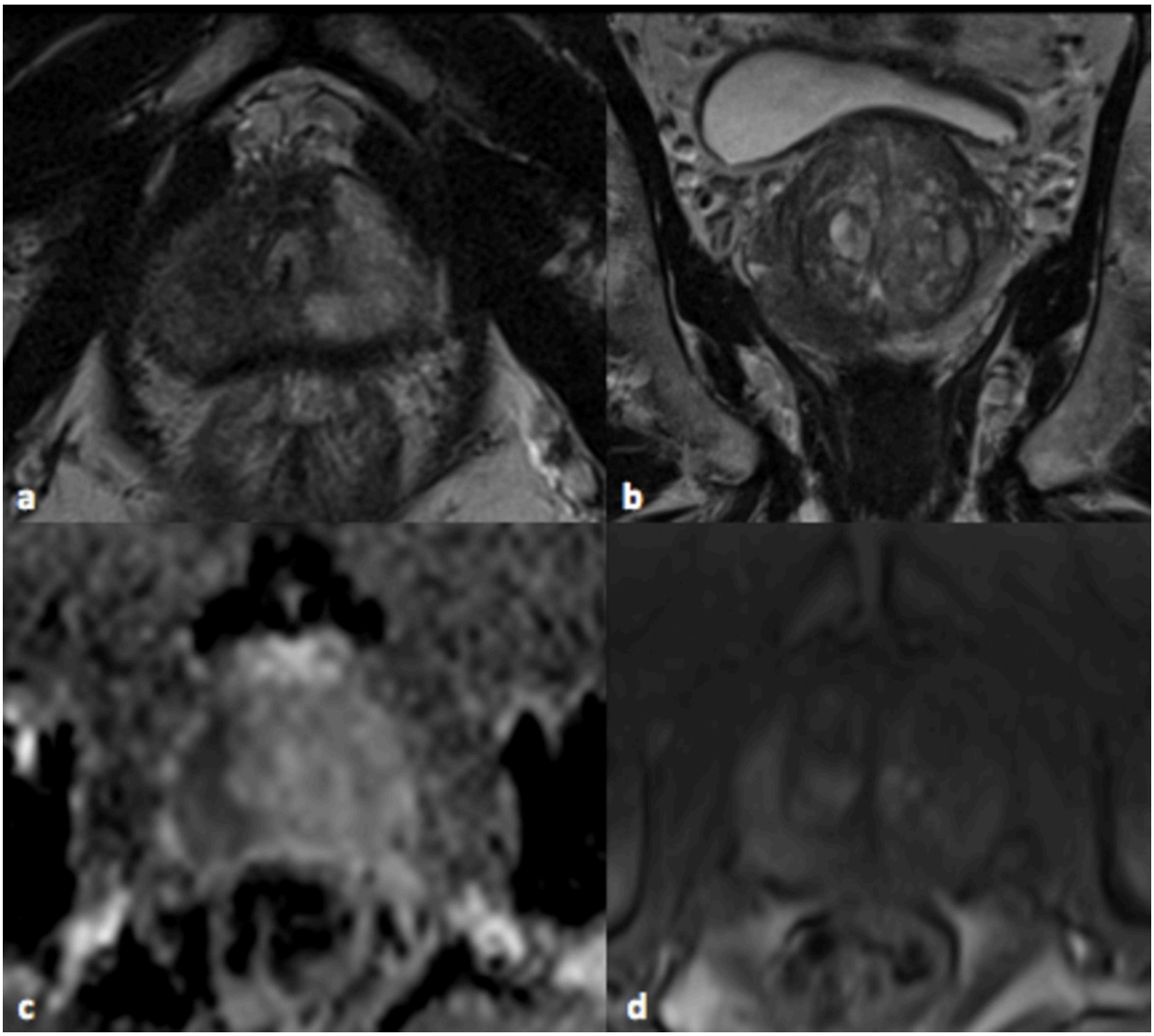


Fig. 7: Axial (a) and coronal (b) T2W images: low signal in the peripheral zone on the right. ADC map (c): low signal area in right peripheral zone. Perfusion image (d): high signal area in right peripheral zone. 75 years old, PSA 119 ng/ml. 3 negative random biopsies. Gleason by biopsy oriented by MRI 8 (4+4).
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

Besides cancer and hemorrhage, other benign abnormalities such as chronic prostatitis, atrophy, scars, post-radiation or hormonal treatment effects can result in low signal intensity areas on the T2W images and can be misdiagnosed as cancer. The predictors of benignity in those cases are the absence of mass effect and the linear or wedge shaped morphology (11) (figure 8).

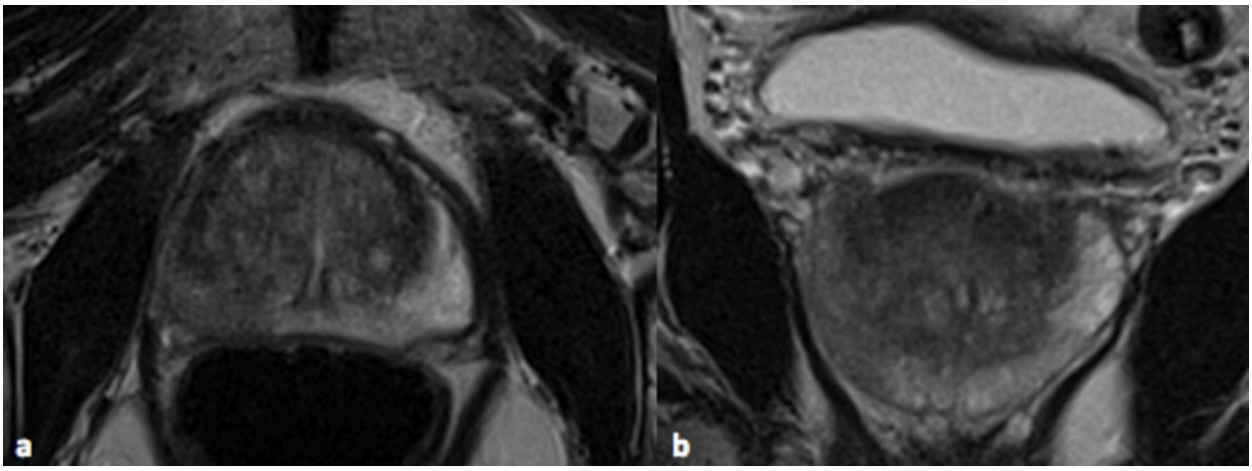


Fig. 8: Low signal intensity on T2-weighted images (a - axial; b - coronal) in peripheral zone on the right. Note the absence of mass effect. Young man with slight increase in PSA levels, proved to have prostatitis. T2W images are very sensitive but have low specificity.
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

Cancer located in the TZ are more difficult to detect because their signal intensities usually overlap. Moreover, the presence of benign prostatic hyperplasia (BPH) may have signal intensity similar to that of prostate cancer on T2-weighted images. In the TZ the lesion features suggestive of malignancy are a homogeneous low T2W signal intensity and unsharp borders (the so called "erased charcoal sign"), the absence of capsule, a lenticular shape and the extension into the urethra or the anterior fibromuscular stroma (11) (figure 9).

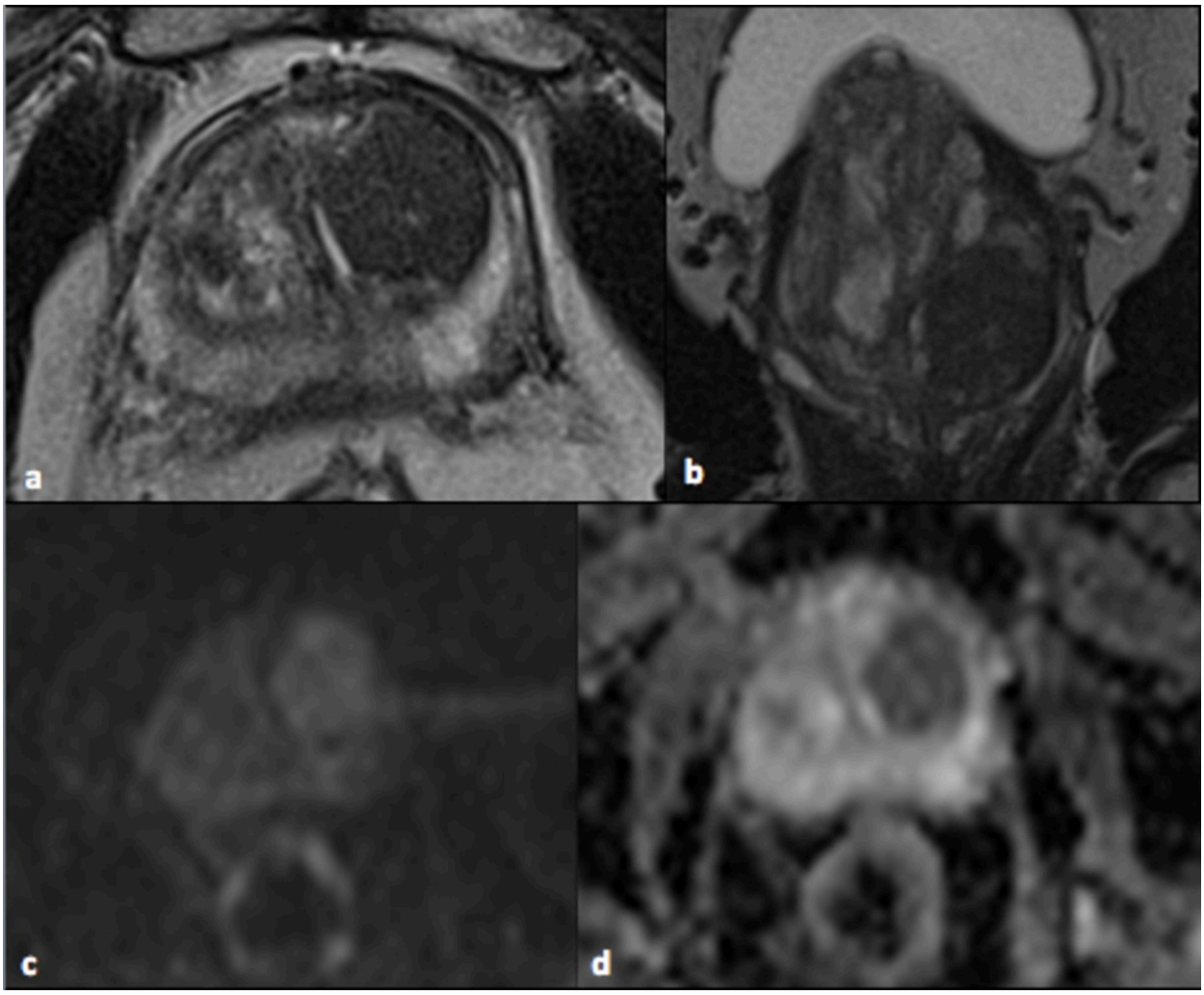


Fig. 9: T2-weighted axial (a) and coronal (b) images show a nodular area of hypointense signal in the left transitional zone. The corresponding DWI (c) and ADC map (d) shows restricted diffusion in the same area, most consistent with PCa. Histopathology showed a tumor with a Gleason score of 7.
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

The T2W sequence can also be used to estimate the aggressiveness of the tumour as the degree of signal intensity decrease may differ with the Gleason score: higher Gleason score components have shown lower signal intensities than do lower Gleasons score components (12).

Once a focal lesion is detected, an evaluation of the overall stage of the tumor is required. The most important overall assessment is whether the tumor is confined to the gland (T#2) or extends beyond the gland (T#3) (figure 10).

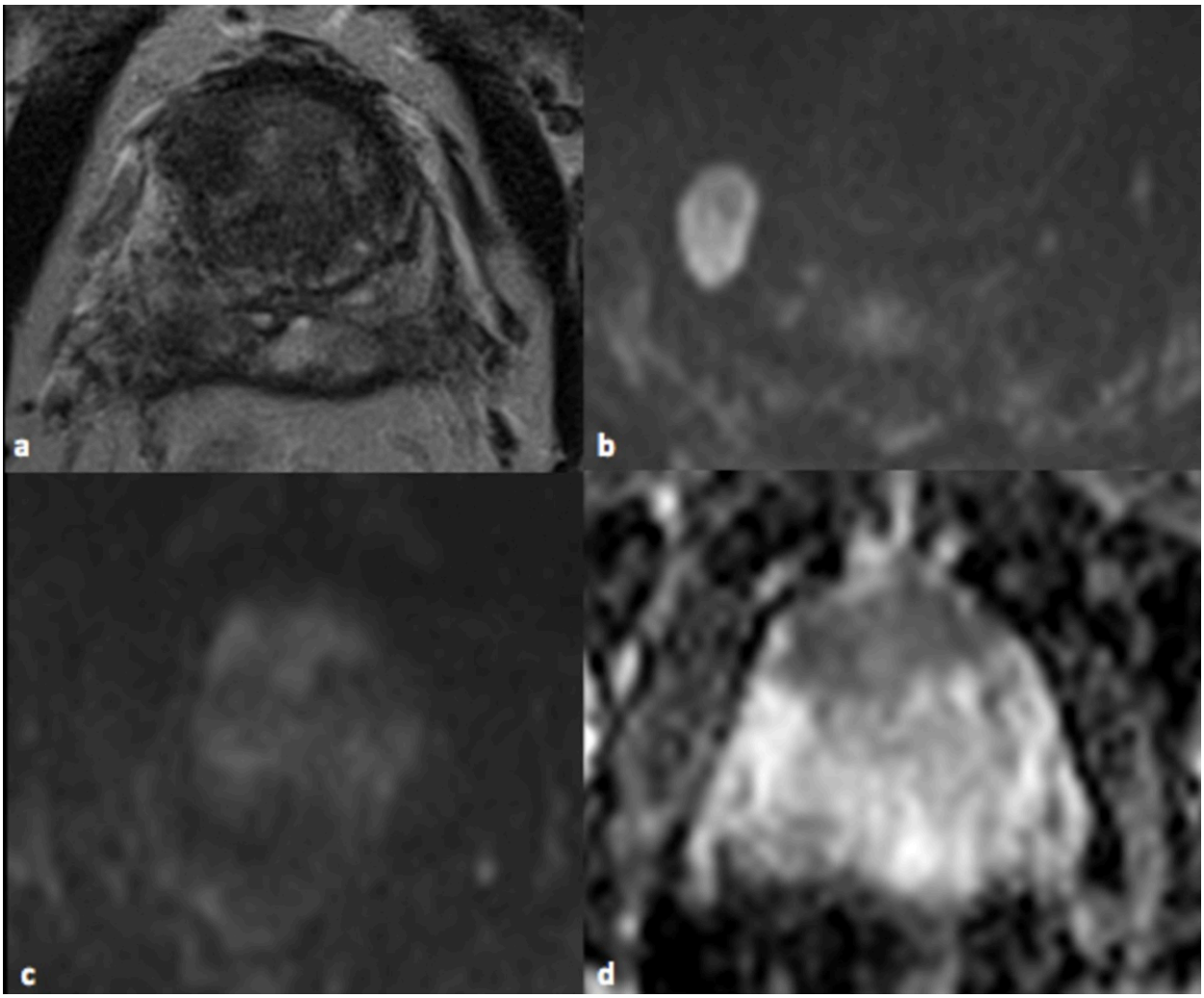


Fig. 10: A 62-year-old man with Gleason 8 (4+4) PCa involving the TZ and the anterior fibromuscular stroma at prostatic base. Axial T2W image (a) shows a hypointense tumor involving predominantly the right anterior base with indefinition of prostatic contour, indicating extraprostatic extension of cancer, which was confirmed at pathology following the prostatectomy. DWI (b) shows a right internal iliac metastatic adenopathy. The prostatic lesion is hyperintense on the trace DWI (c) and hypointense on the ADC map (d). The identification of a lesion on both the ADC map and trace DWI is a more specific finding than is the identification of the lesion on either image alone.
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

Diffusion-Weighted Imaging (DWI)

The diffusion technique is based on the random translational movement (Brownian motion) of protons of water molecules in the extracellular matrix. The degree of diffusion restriction is inversely related to the cellularity of the tissue and the integrity of cell

membranes. Therefore, diffusion tends to be more restricted in tissues with a high cellular density and a narrow extracellular space, such as neoplastic tissue. Apparent diffusion coefficient maps are generated from the index DWI data on the MR console itself and could be analyzed qualitatively and quantitatively (13,14).

In PCa, the normal glandular architecture is replaced by tumour cells and fibrous stroma, which inhibit the movement of water macromolecules, restricting diffusion and reducing the apparent diffusion coefficient (ADC) in tumour tissue. So, cancerous lesions will generally appear hypointense on ADC maps but hyperintense on the DWI high b-value image (figure 11).

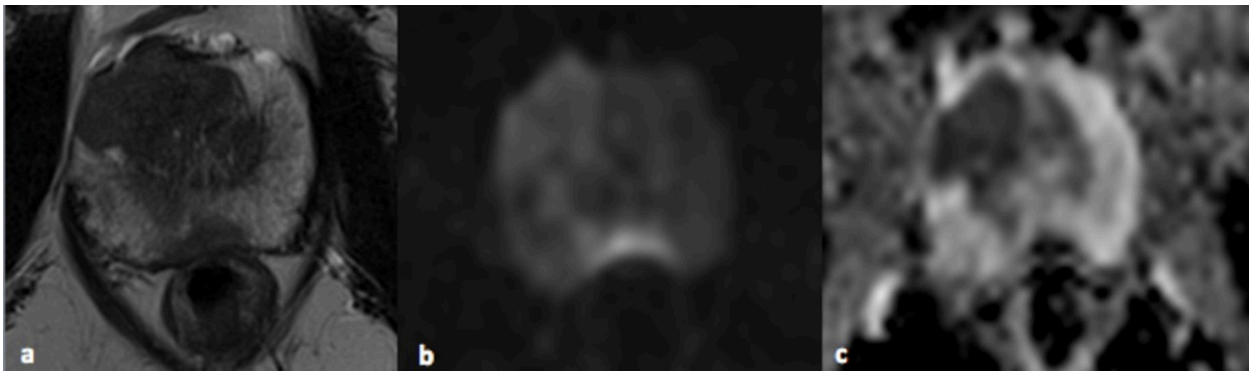


Fig. 11: Axial T2W image (a) shows an ill-defined homogeneous low-signal intensity area in the right transition zone with low signal intensity on the ADC map (c). Note that the lesion is slightly hyperintense on the trace DWI with b1000 s/mm2 (b). TRUS-guided biopsy showed a Gleason grade 8 (4+4) prostate adenocarcinoma on the corresponding position.
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

Because ADC values are lower in BPH than in the peripheral zone, the accuracy for detection of PCa in the transition zone is significantly lower and even lower in the prostate base (13).

The sensitivity of the DWI sequence to molecular motion can be adjusted by modifying the *b value* parameter (the *b value* depends on the amplitude duration, and time interval between the paired gradients used to generate the DWI sequence).

Diffusion sequences can be obtained by various techniques. In our center, we use an echo-planar sequence with the following parameters: TR: 3700, TE: 75, and b: 0, 100, 500 and 1000, in the axial plane with a slice thickness of 3 mm.

In general, diffusion sequences provide low spatial resolution so it is essential combining those images with those from T2-sequences. The advantages of diffusion sequences are the short acquisition time and higher sensitivity and specificity for tumour detection.

Moreover, DWI reflects cellular density, which makes the technique potentially suitable to determine tumor aggressiveness. Recently, some studies have shown a correlation between the ADC and the Gleason score, with lower ADCs values corresponding to increasing Gleason scores (15).

Dynamic Contrast Enhanced Imaging (DCEI)

It is well known that the number of vessels increases in cancerous tissue (neoangiogenesis) and that the newly formed tumor vessels have an increased flow, blood volume and greater permeability.

As the prostate as a whole is highly vascularized, a simple comparison of pre and post-gadolinium images is usually insufficient to discern prostate cancer, so DCEI is used. This is the method most commonly used to evaluate tumour vascularity.

DCEI consists of a series of axial 3D T1W spoiled gradient echo sequences, with a high temporal resolution (between 5-10 sec), covering the entire prostate before, during and after rapid injection (3ml/s) of a bolus of a gadolinium-based contrast medium (0,1mmol/Kg).

In our department we use very short TR periods of 4,97ms, which can acquire 192x115 3D matrix data with acquisition time of 5s each measurement. We generally perform about 75 such measurements consecutively, with the contrast material automatically infused following pre-contrast baseline acquisitions with different flip angles to obtain T1 map, resulting in DCEI image acquisition lasting about 6:25 min.

This technique exploits the dynamic uptake and rapid washout of a gadolinium chelate contrast agent to show the typical pharmacokinetics of cancerous tissue (14).

There are several different approaches to DCEI: quantitative pharmacokinetic modeling, semi-quantitative, qualitative and simple visual analysis. In our department we perform all these approaches (figure 12 and 13).

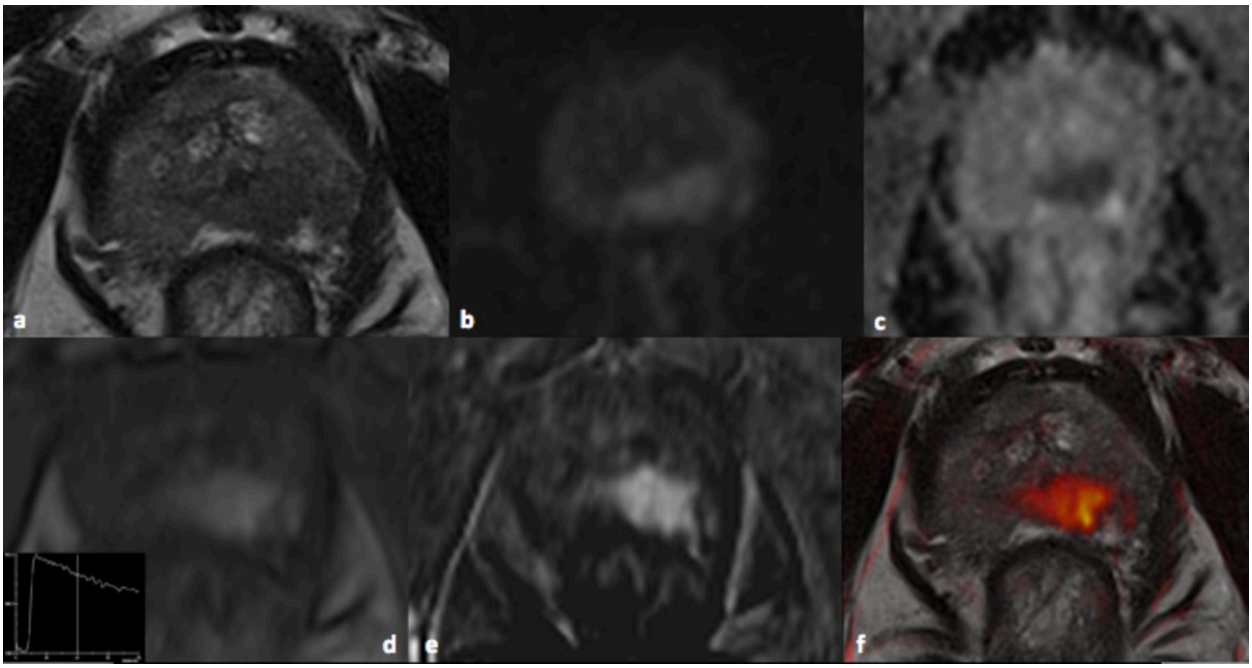


Fig. 12: T2W image (a) shows a ill-defined low-signal intensity area in the left posterior peripheral zone causing slight rectoprostatic angle effacement. The lesion has high signal on DWI trace (b) and low signal intensity on the ADC map (c). In early-phase DCE image (d), the lesion shows strong enhancement. Signal intensity curve of the lesion shows a type 3 curve. Subtraction image (d) confirmed high vascularization of the lesion. (e) Fusion image (T2W + DWI trace). TRUS-guided biopsy revealed PCa, Gleason 7 (3+4).
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

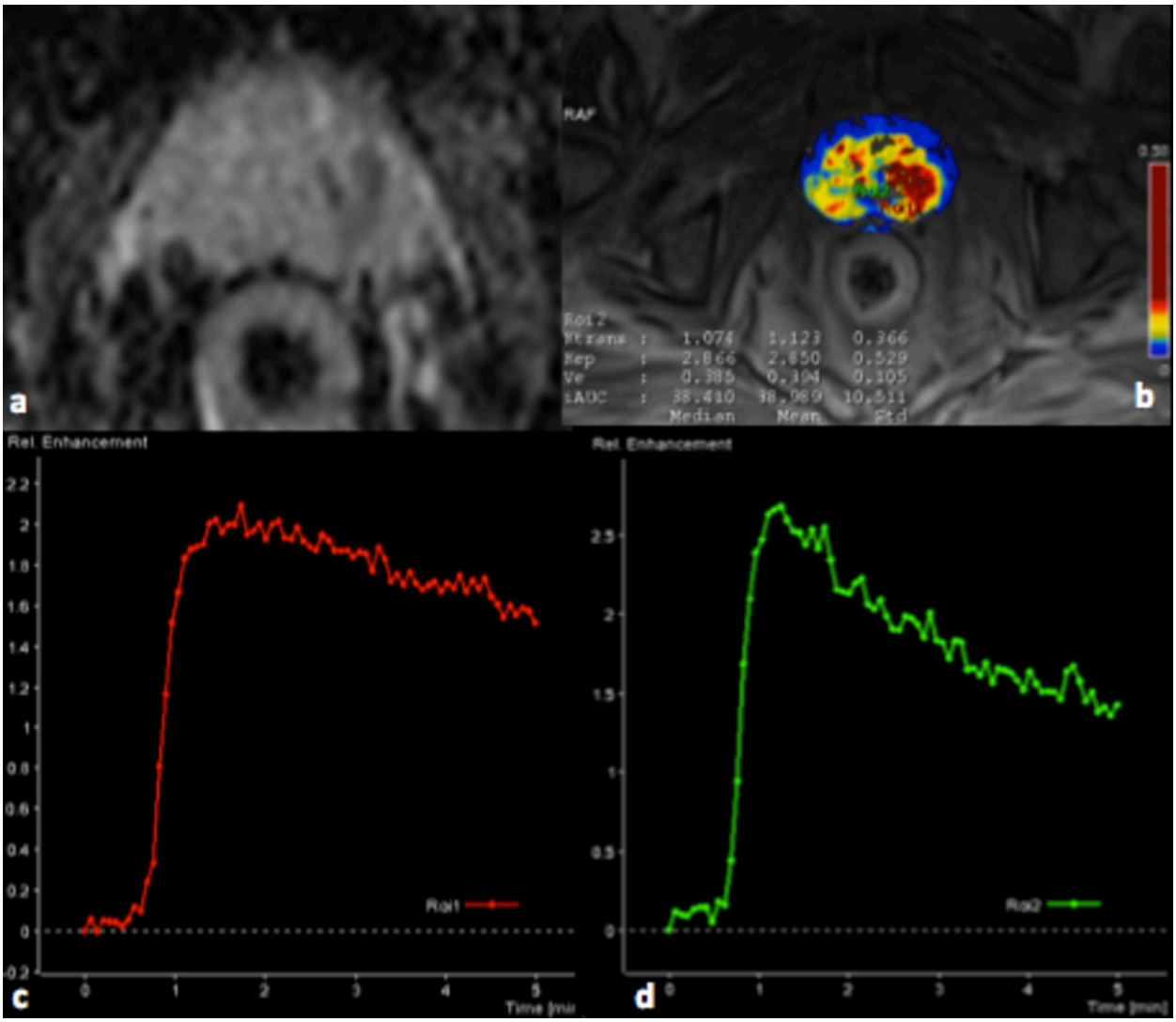


Fig. 13: 78-year-old patient with PSA level of 40 ng/mL and previously negative TRUS-guided biopsy. ADC map (a) shows restricted diffusion in the lesion with low mean ADC. Ktrans map (b) for the same level as the suspicious region in (a) reveals focal enhancement (red indicate higher levels of enhancement). Kinetic curves of gadolinium concentration versus time for the tumor regions (c and d) shows an early enhancement peak, followed by washout in the tumor area - type III curve. Overall, the region suspicious for tumor demonstrates lower mean ADC, higher Ktrans, and greater enhancement (higher maximum concentration of contrast reached, as seen in the kinetic curves). Biopsies showed a Gleason 7 (3+4) prostate adenocarcinoma.
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

One of the limitations of dynamic contrast-enhanced MR imaging is related to discrimination of cancer from prostatitis in the peripheral zone and from highly vascularized BPH nodules in the transition zone, as well as the shortage of uniform commercially available tools for pharmacokinetic analysis and the lack of consensus in acquisition protocols.

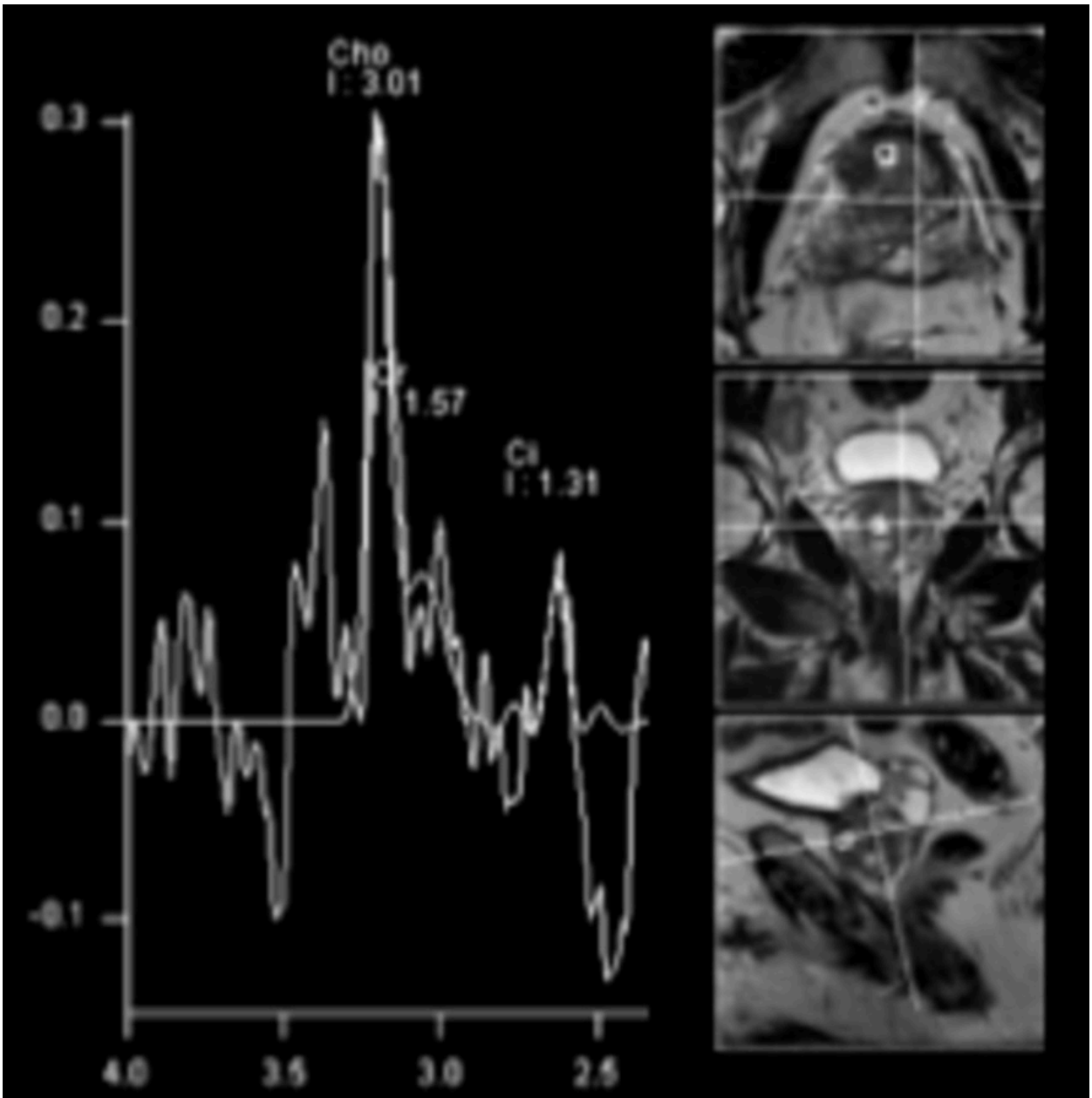
Magnetic Resonance Spectroscopic Imaging (MRSI)

MRSI provides information on the gland metabolism and is used to spatially detect deviations from normal biochemistry that occur in tumor tissue.

MRSI is preformed with a 3D chemical shift imaging protocol. The volume of interest (VOI) is aligned to axial T2W images to maximize coverage of the whole prostate. After post-processing, spectral information is overlaid on T2W images.

The dominant peaks observed in these spectra are from protons in citrate (approximately 2.60 ppm), creatine (3.04 ppm) and choline compounds (approximately 3.20 ppm).

Compared with healthy peripheral tissue or BPH tissue, citrate signals are reduced and those of choline compounds are often increased in prostate cancer tissue (figure 14) (10,11,16). The lower citrate (marker of benign tissue) peak in cancer tissue is probably caused by altered metabolism, as well as by a reduction of luminal space, which commonly occur in prostate cancer. On the other hand, an increased cell-turnover in prostate cancer results in an increased concentration of free choline-containing molecules (marker of malignant tissue) within the cytosol and the prostate interstitial tissue as they are important in the build-up and maintenance of cell membranes process (10,11,16). The creatine is insignificant for diagnosis but is difficult to resolve from choline. So, in quantitative analysis, the peak of all metabolites are estimated by means of the choline+creatine to citrate ratio (CC/C). A ratio CC/C > 0,72 in at least 2 adjacent voxels are considered to indicate malignant tissue, whereas a ratio between 0,58 and 0,72 are equivocal. In qualitative analysis the peak heights of citrate and choline are visually compared in at least 3 adjacent voxels and a lesion is suspect of cancer if the choline-creatine peak is higher than the citrate peak (10).



Metabolite	Pos./ppm	Integral	Ratio
Cr	3.06	1.57	1.20
Cho	3.20	3.01	2.30
Ci	2.63	1.31	1.00
Cho+Cr	3.13	4.58	3.50

Fig. 14: Despite some background noise MR spectrum shows pathological Cho+Cr/Ci ratio. The selected voxel of interest demonstrates metabolite peaks as follows: choline (Ch) at 3.2 ppm, creatine (Cr) at 3.09 ppm, citrate (Ci) at 2.6 ppm. Note elevated choline and decreased citrate, a characteristic metabolic signature of prostate cancer. The ratio of Cho+Cr/Ci is 3.5.
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

MR spectroscopic imaging is an accurate technique, although time consuming, that may be used for predict the presence or absence of tumour, lesion aggressiveness and to detect cancer recurrence and monitoring treatment response (10).

Scoring system for mpMRI (PI-RADS) (10)

We should always keep in mind that no single technique is able to adequately detect and characterize PCa and that a mpMRI should be employed with that purpose.

According to the ESUR prostate MR guidelines, prostate MRI examination should include the use of T2W images plus 2 functional techniques.

The ESUR prostate MR guidelines also suggest a unified scoring system for mpMRI imaging named Magnetic Resonance Prostate Imaging Reporting and Data System (MR PI-RADS), that we follow in our department. In this scoring system each lesion is score on a 5-point scale for each sequence employed (figure 15), and each lesion is given an overall score that indicates its likelihood of being a clinically significant cancer.

Prostate Imaging Reporting and Data System scoring system

LIKERT SCALE

Score 1 – Clinically significant disease highly unlikely to be present
Score 2 - Clinically significant cancer unlikely to be present
Score 3 - The presence of clinically significant cancer is equivocal
Score 4 - Clinically significant cancer likely to be present
Score 5 - Clinically significant disease highly likely to be present

T2WI for the peripheral zone

Score	Description
1	Uniform high signal intensity
2	Linear, wedge-shaped, or geographic areas of lower signal intensity, usually not well demarcated
3	Intermediate appearances not in categories 1/2 or 4/5
4	Discrete, homogeneous low-signal focus/mass confined to the prostate
5	Discrete, homogeneous low–signal intensity focus with extracapsular extension/invasive behavior or mass effect on the capsule (bulging), or broad (>1.5-cm) contact with the surface

T2WI for the transition zone

Score	Description
1	Heterogeneous transition zone adenoma with well-defined margins: ''organized chaos''
2	Areas of more homogeneous low signal intensity, well marginated, originating from the transition zone/BPH
3	Intermediate appearances not in categories 1/2 or 4/5
4	Areas of more homogeneous low signal intensity, ill defined: "erased charcoal sign"
5	Same as 4, but involving the anterior fibromuscular stroma or the anterior horn of the peripheral zone, usually lenticular or water-drop shaped

DWI

Score	Description
1	No reduction in ADC compared with normal glandular tissue; no increase in SI on any high–b value image (≥ b800)
2	Diffuse, hyper signal intensity on ≥ b800 image with low ADC; no focal features; however, linear, triangular, or geographic features are allowed
3	Intermediate appearances not in categories 1/2 or 4/5
4	Focal area(s) of reduced ADC but isointense signal intensity on high–b value images (≥ b800)
5	Focal area/mass of hyper signal intensity on the high–b value images (≥ b800) with reduced ADC

DCEI

Score	Description
1	Type 1 enhancement curve
2	Type 2 enhancement curve
3	Type 3 enhancement curve
+1	For focal enhancing lesion with curve type 2–3
+1	For asymmetric lesion or lesion at an unusual place with curve type 2–3

Quantitative MRS

Score	Description
1	(Col+Cr)/Citrate ≤ 0.44 peripheral zone and ≤ 0.52 transition zone
2	(Col+Cr)/Citrate 0.44–0.58 peripheral zone and 0.52–0.66 transition zone
3	(Col+Cr)/Citrate 0.58–0.72 peripheral zone and 0.66–0.80 transition zone
4	(Col+Cr)/Citrate 0.72–0.86 peripheral zone and 0.80–0.94 transition zone
5	(Col+Cr)/Citrate > 0.86 peripheral zone and > 0.94 transition zone

Qualitative MRS

Score	Description
1	Citrate peak height exceeds choline peak height >2 times
2	Citrate peak height exceeds choline peak height times >1, <2 times
3	Choline peak height equals citrate peak height
4	Choline peak height exceeds citrate peak height >1, <2 times
5	Choline peak height exceeds citrate peak height 2 times

Fig. 15: Scoring system for Multiparametric Prostate MRI (PI-RADS): ESUR prostate MR Guidelines 2012 - Adapted from reference 10.
References: Medical Imaging Department and Faculty of Medicine, University Hospital of Coimbra, Portugal

Conclusion

CONCLUSION

Multiparametric MRI is an invaluable tool that should be performed in order to best achieve information regarding volumetry, localization, staging and assessment of the aggressiveness profile of prostate cancer.

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