Magnetic Resonance Imaging of Prostate Cancer: Approach, Local Staging and Therapeutic Impact

Poster No.: C-2270
Congress: ECR 2014
Type: Educational Exhibit
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Keywords: Genital / Reproductive system male, Anatomy, Management, MR, MR-Functional imaging, Diagnostic procedure, Staging, Education, Neoplasia, Cancer, Outcomes
DOI: 10.1594/ecr2014/C-2270

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Learning objectives

To describe and illustrate prostate anatomy.

To present the latest classification of prostatic cancer staging.

To emphasize the role of magnetic resonance imaging (MRI) in prostate cancer detection, local staging and therapeutic implications.

Background

Prostate cancer is the most frequently diagnosed noncutaneous cancer in males, with increasing incidence in older age groups, and the second most common cause of death from cancer in men. 1 in 6 men will be diagnosed with prostate cancer in their lifetime. This neoplasm accounts for annually 350,000 cases, which corresponds to 25% of all new malignancies diagnosed in European males.

ANATOMY

The prostate is divided from superior to inferior into the base (just below the urinary bladder), the midgland, and the apex (Figure 1 and 2). In the axial plane, the prostate is divided into four zones: the anterior fibromuscular stroma, without glandular tissue; the transition zone surrounding the urethra, which contains 5% of the glandular tissue; the central zone, which contains 20% of the glandular tissue; and the outer and peripheral zone, which contains 70% to 80% of the glandular tissue, increasing from the base to the apex of the gland (Figure 1 and 2).
Fig. 1: Diagram of the prostate shows distribution and proportions of the tissue layers composing the prostate. Illustration of prostate zonal anatomy in the sagittal plane and corresponding axial sections from the base (1), midgland (2), and apex (3). Note the anterior fibromuscular stroma (purple line), peripheral zone (orange), central zone (blue), and transition zone (green).

References: Radiology, Instituto Portugues de Oncologia de Lisboa Francisco Gentil E.P.E. - Queluz/PT

95% of prostate cancers are adenocarcinomas, which develop from the acini of the prostatic ducts. Therefore, prostate cancers arise in the glandular tissue, with approximately 70% originating in the peripheral zone, 25% in the transition zone, and 5% in the central zone. The transition zone cannot be separated from the central zone on imaging; this way, these two zones are often described to together as the central gland (Figure 2). There is no prostatic true capsule, and only an outer band of concentric fibromuscular tissue which is an element of prostatic stroma, corresponding to a thin hypointense layer of tissue that is on T2-weighted images. This outermost fibromuscular tissue layer is an important landmark for assessment of extraprostatic tumor extension, since irregularities, bulges, and disruptions of this tunic are signs of tumor invasion or spread outside the prostate boundaries.
Fig. 2: Anatomy of the prostate on MR images obtained at 1.5 T. (a) Sagittal T2-weighted shows division of the prostate into three sections in the craniocaudal direction. The superior one-third of the prostate below the bladder is the base. The middle one-third is the midgland. The distal one-third is the apex. (b) Axial T2-weighted image shows the base of the prostate. The anterior fibromuscular stroma (arrow) consists of nonglandular tissue and appears dark. Note the symmetric homogeneous muscular stroma layer (arrowheads) in the posterior prostate base. (c) Axial T2-weighted image of the midprostate shows the homogeneously bright peripheral zone (arrowheads) surrounding the central gland (white arrows). The central gland is composed of the transition zone and central zone, which cannot be resolved at imaging. Therefore, they are referred to jointly as the central gland. Note the neurovascular bundles at the 5-o’clock and 7-o’clock positions (black arrows). (d) Axial T2-weighted image of the prostatic apex shows the homogeneous peripheral zone (arrowheads) surrounding the urethra (U). Note that the volume of the peripheral zone increases from the base to the apex.

References: Radiology, Instituto Portugues de Oncologia de Lisboa Francisco Gentil E.P.E. - Queluz/PT

The periprostatic neurovascular bundles course posterolateral to the prostate bilaterally. At the apex and base, the nerve bundles send penetrating branches through the "capsule", which provide a route for extraprostatic tumor extension.
PROSTATE CANCER DIAGNOSIS AND IMAGING APPROACH

Nowadays, the diagnostic tools for prostate cancer are the following: digital rectal examination (DRE); serum prostate specific antigen (PSA), which is a non-specific blood test; trans-rectal ultrasound (TRUS) guided biopsy, frequently with an invisible target.

Despite all these methods, there is a need for further evaluation with magnetic resonance imaging (MRI), which is key modality in prostate cancer evaluation because of its high resolution and soft-tissue contrast.

Progress in MRI has shown improvement in the detection and characterization of prostate cancer, by the application of a multi-parametric approach, which combines anatomical and functional information. This technique also improves local staging, assessment of cancer aggressiveness, and treatment decision.

PROSTATE CANCER STAGING

The most widely used system for prostate cancer staging is TNM system.

The fundamental aspect of prostate cancer local staging is differentiation between organ-confined disease (stage T1 or T2) and early advanced disease in the form of extracapsular extension or seminal vesicle invasion (stage T3). With the advances in MRI techniques a more accurate differentiation between stage T2 and T3 prostate cancer is possible than with other imaging modalities, being the former preferred for prostate cancer local staging.

The latest staging system (7th) of the American Joint Committee on Cancer (AJCC) for prostate cancer (Figure 3 and 4), includes the major following changes:

- Extraprostatic invasion with microscopic bladder neck invasion (T4) is included in T3a;

- Gleason Score is now recognized as the preferred grading system;

- Prognostic factors have been incorporated in the Anatomic Stage/Prognostic Groups:
- **Gleason Score**;
- **Preoperative prostate-specific antigen (PSA)**.

**Fig. 3**: Diagram of T staging for prostate cancer. T1 tumors are clinically unapparent (neither palpable nor visible at imaging), T2 tumors are confined within the prostate gland, T3a tumors extend beyond the prostatic capsule, T3b tumors invade the seminal vesicle, and T4 tumors are fixed to or invade adjacent structures other than seminal vesicles (eg, bladder, rectum, pelvic wall).

**References**: Radiology, Instituto Portugues de Oncologia de Lisboa Francisco Gentil E.P.E. - Queluz/PT
Fig. 4: TNM Staging of Prostate Cancer.


Findings and procedure details

CLINICAL APPLICATION OF MRI IN PROSTATE CANCER

- **Multi-parametric MRI**
In the past few years, MRI of the prostate has evolved with the development of advanced multi-parametric MR imaging (mp-MRI) techniques, which include the combination of high-resolution T2-weighted images (T2WI), and at least two functional MRI techniques, like dynamic contrast enhanced MRI (DCE-MRI), diffusion weighted imaging (DWI) and MR spectroscopic imaging (MRSI). In addition to T2WI, which mainly assesses anatomy, DWI and MRSI add specificity to lesion characterization, while DCE-MRI has a high sensitivity in cancer detection.

**Clinical value of MRI and in Treatment Options**

In prostate evaluation, the presence of an elevated PSA (>3-4 ng/mL) or a suspicious DRE, requires a TRUS-guided biopsy, which may allow cancer detection, and estimation of lesion volume, extension and aggression. An increased PSA is not equivalent for a tumor, because PSA has low specificity (36%). On the other hand, a normal PSA does not exclude a tumor. Another important point is that TRUS-guided biopsy underestimates the extent and grade of prostate cancer. This way, prostate cancer treatment approach should be determined by the integration of PSA findings, DRE results and histopathological findings at TRUS biopsy.

Selection of the optimal treatment modality for each case of prostate cancer is based primarily on the initial clinical stage (Figure 4) and the risk of biochemical failure (the likelihood of recurrence after locoregional treatment) (Figure 5). Estimated life expectancy, comorbidities, potential side effects, and patient preferences are also taken into account when selecting treatment. In general, patients should have a life expectancy of >10 years before definitive treatment is recommended.
Fig. 5: Risk of Treatment Failure in Prostate Cancer and Treatment Recommendations.


The standard treatment of choice for early-stage prostate cancer (T1-T2 disease) is surgery or radiation therapy (RT), while active surveillance is being investigated. Recently, local ablation techniques such as cryoablation, photodynamic therapy, and high-intensity focused ultrasound have been introduced for targeting tumors in patients with localized prostate cancer. In locally advanced prostate cancer (T3-T4 disease), either RT combined with ADT or surgical resection combined with adjuvant RT is offered, depending on the severity of local extension.

- MRI Determining Tumor Aggression and Grading Prostate Cancer with the Gleason System

Mp-MRI techniques add high accuracy in detecting prostatitc tumor and prostatic areas of higher aggressiveness. The correlation with histologic Gleason grading system is best achieved with DWI and MRSI relative to T2WI and DCE-MRI. Mp-MRI also allows detection of adverse prognostic factors like tumor volume, and higher grade tumors, special in anterior and apical locations.

The association of T2WI with DCE-MRI and DWI or with MRSI have a high perceptiveness in identifying tumors with a volume >0.5 cc.

MRI PROTOCOL FOR PROSTATE EVALUATION

- T2-weighted MR imaging

T2-weighted imaging (T2WI) gives the best evaluation of the prostate anatomy. This sequence is applied for prostate cancer detection, localization and staging.

T2WI alone is sensitive but not specific for prostate cancer and should be improved by applying two functional techniques, which improve accuracy.

Prostate cancer usually corresponds to a round or ill-defined, low-signal-intensity lesion in the peripheral zone (Figure 6 and 7). In T2WI high-grade cancers usually are
associated with lower SI than low-grade cancers. Prostate intra-epithelial neoplasia, prostatitis, haemorrhage, atrophy, scars and post-treatment changes can simulate cancer on T2WI.

**Fig. 6:** Prostate cancer of the left peripheral zone of the midgland in a 65-year-old man with a Gleason score of 4+3. On (a) sagittal and (b) axial T2-weighted images a low signal lesion is seen in the left peripheral zone of the mid-prostate (blue arrows). (c) DCE study demonstrates an early hyperenhancement of the lesion. On (d) DWI evaluation with b 1000 s/mm² and on (e) ADC map the lesion is hyperintense and hypointense, respectively, this way showing restriction, also seen on (f) fusion image from T2-weighted image and DWI with b-value 1000 s/mm².

**References:** Radiology, Instituto Portugues de Oncologia de Lisboa Francisco Gentil E.P.E. - Queluz/PT
Fig. 7: Prostate cancer of the left peripheral zone of the midgland in a 61-year-old man with a Gleason score of 3+3. On (a) axial and (b) coronal T2-weighted images an oval and low signal lesion is seen in the left peripheral zone of the mid-prostate (blue arrows). (c) DCE study demonstrates an early hyperenhancement of the lesion. On (d) ADC map the lesion is hypointense, showing restriction, also seen on (e) fusion image from T2-weighted image and DWI with b-value 1000 s/mm2.

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**Tumors** located in the transition zone (TZ) are more difficult to detect, because signal intensity of TZ and cancer is usually similar. An imaging clue for detection of **TZ tumors** is the presence of a **homogeneous signal mass** with **indistinct margins** ("**erased charcoal sign**"). A **lenticular** or **"water-drop" shape** is also characteristic (Figure 8 and 9).
Fig. 8: Suspicious prostate central gland lesions in a 65-year-old man, classified as a PI-RADS 4 (probably malignant). (a) Coronal and (b) axial T2-weighted images show bilateral ill-defined homogeneous hypointense areas with a lenticular or "water-drop" shape characteristic of transition zone tumors (blue arrows). (c) On fusion image from T2-weighted image and DWI with b-value 1000 s/mm2, these areas show restriction, and appear (d) hyperintense on DWI with b-value 1000 s/mm2 and (e) hypointense on ADC map. (f) DCE MR imaging demonstrates in a selected area of the left central gland (ROI, blue arrow in f) a rapid enhancement and progressive washout posteriorly, a finding suggestive of malignancy.

References: Radiology, Instituto Portugues de Oncologia de Lisboa Francisco Gentil E.P.E. - Queluz/PT
Fig. 9: Suspicious prostate central gland lesions in a 66-year-old man, classified as a PI-RADS 4 (probably malignant). (a) Axial T2-weighted image shows bilateral ill-defined homogeneous hypointense areas with a lenticular or "water-drop" shape characteristic of transition zone tumors (blue arrows). (b) On DWI with b-value 1000 s/mm² these areas are hyperintense and on (c) ADC map appear hypointense, in concordance with restriction. (d) DCE MR imaging demonstrates in a selected area of the left central gland (ROI) a rapid enhancement and progressive washout posteriorly, a finding suspicious of malignancy.

References: Radiology, Instituto Portugues de Oncologia de Lisboa Francisco Gentil E.P.E. - Queluz/PT

Extra-capsular tumor extension should always be characterized, which may correspond to contorn abutment and irregularity (Figure 10); capsular loss or enhancement; seminal vesicles expansion, with low T2 signal intensity (Figure 11), enhancement and impeded diffusion; effacement of the prostate-seminal vesicle angle; neurovascular bundle thickening; obliteration of the recto-prostatic angle; and measurable extra-capsular disease (Figure 12).
Fig. 10: Prostate cancer of the left peripheral zone of the midgland in a 69-year-old man with a Gleason score of 4+3. On axial T2-weighted image an ill-defined hypointense lesion is seen in the left peripheral zone of the mid-prostate (blue arrow), with extraprostatic tumor extension (yellow arrows) involving the left neurovascular bundle (green arrow).

References: Radiology, Instituto Portugues de Oncologia de Lisboa Francisco Gentil E.P.E. - Queluz/PT
Fig. 11: Prostate cancer of the left posterolateral peripheral zone at the base and midgland in a 71-year-old man with a Gleason score of 3+4. (a) Sagittal and (b) coronal T2-weighted images show an left base prostatic ill-defined hypointense lesion (blue arrows) extending along the left seminal vesicle, in relation with seminal vesicle invasion (yellow arrows).

References: Radiology, Instituto Portugues de Oncologia de Lisboa Francisco Gentil E.P.E. - Queluz/PT
Fig. 12: Diffuse prostatic cancer in a 70-year-old man with a Gleason score of 3+4. (a) Sagittal and (b) coronal T2-weighted images show a diffuse substitution of the prostate gland by a tumor (blue arrows), and evident extra-prostatic extension with loss of low T2 signal in bladder muscle, compatible with bladder invasion (yellow arrows).

References: Radiology, Instituto Portugues de Oncologia de Lisboa Francisco Gentil E.P.E. - Queluz/PT

- Dynamic contrast enhanced MRI

Prostate tumor vascularity is frequently evaluated by dynamic contrast enhanced (DCE) MRI after the administration of gadolinium-based contrast medium. This is best achieved by high temporal resolution DCE-MRI (<10 s). DCE-MRI consists of a series of axial T1WI gradient echo sequences encompassing the whole prostate during and after IV bolus injection (2-4 mL/s) of gadolinium-based contrast medium.

The increased vascularity of prostate cancer leads to early hyperenhancement (higher and earlier peak enhancement than in normal tissue) and to rapid washout of contrast material from the tumor, in relation with normal prostate tissue (Figure 8 and 9). Microvascular alterations and neovascularity are commonly more severe in prostate
cancer, in comparison with other processes in the prostate such as BPH or prostatic intraepithelial neoplasia.

**DCE-MRI imaging data** can be valued in three ways: *qualitatively, semi-quantitatively* or *quantitatively*. Available studies suggest that **DCE-MRI** is superior to **T2WI alone** for **prostate cancer localization** and **local staging**, and it should always be **combined** with **T2WI** and **DWI**, for a **better differentiation** from prostatitis, BPH and TZ prostate cancers.

- **Diffusion weighted MRI**

**Diffusion weighted imaging (DWI)** is a **primordial parameter** of **mp-MRI**, providing **qualitative** and **quantitative information** about **tumor aggressiveness**, through the calculation of **apparent diffusion coefficient (ADC) maps**. It is also associated with **higher specificity** in **prostate cancer detection** compared with **T2WI** alone.

**DWI** should be acquired in the **axial plane** with **b-values of 0, 100, and 800-1000 s/mm²**, and with **additional b-value of 500 s/mm²** for **optimal evaluation**. ADC maps must be analyzed qualitatively and quantitatively.

**Prostate cancer** demonstrates **high signal intensity on DWI high b-values** and **low signal intensity/value on ADC maps** (Figure 6, 7, 8 and 9). In **qualitative evaluation** **high b-value (800-1000 s/mm²)** DW images and ADC maps should be **applied**, and interpreted in **association with T2WI**, for anatomical correspondence. In **quantitative assessment** **ADC values** are used, which vary with different field strengths, different b-values, different models to fit the data, patient characteristics.

**Normal prostatic tissue**, particularly the **TZ**, may have high signal intensity on DWI and low ADC, **simulating a tumor**, which can be **avoided** by using **very high b-values** (>1000 s/mm²).

- **MR spectroscopic imaging**

**Magnetic resonance spectroscopic imaging (MRSI)** can be used to predict the presence or absence of cancer, through identification of **lower levels of citrate** and **higher levels of choline**, characteristic of **prostate cancer** in contrast to benign tissue.
This technique also provides information about lesion aggressiveness, but does not give staging information because of its poor spatial resolution.

MRSI results from a 3D chemical shift imaging protocol. The volume of interest (VOI) is overlaid on axial T2WIs to encompass the whole prostate gland and minimize surrounding tissue interference.

MRSI permits the identification of some important metabolites, which are citrate, a marker of benign tissue; choline, a marker of malignant tissue; creatine, insignificant for diagnosis, but difficult to resolve from choline). In quantitative analysis, the peak integrals of all metabolites are estimated by means of the choline-plus-creatine-to-citrate (C+C/C) ratio, and an increased ratio is often used as a marker of malignancy in prostate cancer and increases the specificity of diagnosis, being more reliable in the PZ (Figure 13). So, cancer in PZ and TZ should present in at least two adjacent voxels a C+C/C ratio exceeding respectively 2 and 3 standard deviations above the mean ratio. In qualitative analysis, the peak heights of citrate and choline are visually compared.
**Fig. 13:** Diffuse prostate cancer in a 70-year-old man with a Gleason score of 3+4. MR spectroscopic image at 1.5 T of a selected area of the right midgland shows a malignant spectral pattern, with increased choline level (Ch) and reduced citrate level (Ci) (and thus an increased [choline + creatine]/citrate ratio) in an area of low T2 signal intensity in the right midgland, in opposition to the benign spectral pattern, which has relatively high citrate level and low choline level.

**References:** Radiology, Instituto Portugues de Oncologia de Lisboa Francisco Gentil E.P.E. - Queluz/PT

**COMMUNICATION OF PROSTATE MP-MRI FINDINGS**

- **Scoring system for mp-MRI (PI-RADS)**

Until recently, there were no uniform recommendations for the reports of *mp-MRI* finding. To improve the quality of this procedure, the European Society of Urogenital Radiology (ESUR) published a structured reporting scheme for *MRI of the prostate (PI-RADS)* in analogy to the BI-RADS classification for breast imaging, and based on a Likert scale, with scores ranging from 1 to 5 (Figure 14). This *reporting system* offers the advantage of a *standardized* and *easy communication* of *mp-MRI findings* to other doctors.
A1. T2WI for the peripheral zone (PZ)
1. Uniform high signal intensity (SI)
2. Linear, wedge shaped, or geographic areas of lower SI, 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 behaviour or mass effect on the capsule (bulging), or broad (>1.5 cm) contact with the surface

A2. T2WI for the transition zone (TZ)
1. Heterogeneous TZ adenoma with well-defined margins: “organised chaos”
2. Areas of more homogeneous low SI, however well margined, originating from the TZ/BPH
3. Intermediate appearances not in categories 1/2 or 4/5
4. Areas of more homogeneous low SI, ill defined: “erased charcoal sign”
5. Same as 4, but involving the anterior fibromuscular stroma or the anterior horn of the PZ, usually lenticular or water-drop shaped.

B. Diffusion weighted imaging (DWI)
1. No reduction in ADC compared with normal glandular tissue. No increase in SI on any high b-value image (≥8000)
2. Diffuse, hyper SI on ≥8000 image with low ADC; no focal features, however, linear, triangular or geographical features are allowed
3. Intermediate appearances not in categories 1/2 or 4/5
4. Focal area(s) of reduced ADC but iso-intense SI on high b-value images (≥8000)
5. Focal area/mass of hyper SI on the high b-value images (≥8000) with reduced ADC

C. Dynamic contrast enhanced (DCE)-MRI
1. Type 1 enhancement curve
2. Type 2 enhancement curve
3. Type 3 enhancement curve
4. +1 For focal enhancing lesion with curve type 2–3
5. +1 For asymmetric lesion or lesion at an unusual place with curve type 2–3

D1. Quantitative MRS for 1.5 T. Diagram references [50, 70]

Choline + Creatine/Citrate Ratios for the Different Tissues in the Prostate on a 5-Point Scale

<table>
<thead>
<tr>
<th>Rating</th>
<th>Peripheral Zone</th>
<th>Central Gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Definitely benign tissue</td>
<td>0.44</td>
<td>0.52</td>
</tr>
<tr>
<td>2. Probably benign tissue</td>
<td>0.54–0.75</td>
<td>0.52–0.66</td>
</tr>
<tr>
<td>3. Possible malignant tissue</td>
<td>0.76–0.82</td>
<td>0.62–0.70</td>
</tr>
<tr>
<td>4. Probably malignant tissue</td>
<td>0.72–0.86</td>
<td>0.30–0.94</td>
</tr>
<tr>
<td>5. Definitely malignant tissue</td>
<td>&gt;0.86</td>
<td>&gt;0.94</td>
</tr>
</tbody>
</table>

D2. Qualitative magnetic resonance spectroscopic imaging (MRSI)
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

In qualitative analysis, the relative peak heights of citrate and choline are visually compared (pattern analysis), rather than quantified. The criteria apply for 1.5: for at least three adjacent voxels
Score 1 = Clinically significant disease is highly unlikely to be present
Score 2 = Clinically significant cancer is unlikely to be present
Score 3 = Clinically significant cancer is equivocal
Score 4 = Clinically significant cancer is likely to be present
Score 5 = Clinically significant cancer is highly likely to be present
Fig. 14: PI-RADS scoring system.


Mp-MRI data is structured in a simple reporting scheme, which consists in the following items:

- **PI-RADS score** based on the *probability* of cancer risk and its aggressiveness;

- **Location** and probability of extra-prostatic disease;

- **Pertinent incidental findings**.

In *scoring system for prostate mp-MRI (PI-RADS)* every lesion should be assessed in the different *methods* of mp-MRI, which are *T2WI, DCE-MRI, DWI* and *MRSI* (Figure 14), and evaluated in a *standardized graphic prostate scheme* with at least 16, better 27, sector. For each lesion, a **score range between 1 and 5** is to be assigned per method: **Score 1** - Clinically significant disease is highly unlikely to be present, **Score 2** - Clinically significant cancer is unlikely to be present, **Score 3** - Clinically significant cancer is equivocal, **Score 4** - Clinically significant cancer is likely to be present, **Score 5** - Clinically significant cancer is highly likely to be present. This is used to calculate the **total score**, which reflects the probability of the presence of clinically relevant cancer. The **total score** is then converted to the relevant PI-RADS score, with the advantage that the **final PI-RADS score** is independent of the number of mp-MRI techniques used and can be easily communicated.

**Extra-prostatic involvement** should also be scored on a five-point scale (Figure 15). This should include: extra-capsular extension, seminal vesicle infiltration, distal sphincter, rectal wall, neurovascular bundles and bladder neck.
Fig. 15: Scoring of extraprostatic disease.


Conclusion

Accurate local staging of prostate cancer is crucial in selecting the most appropriate therapeutic approach.

Multi-parametric MRI techniques play a primordial role in this important step, through the application of PI-RADS structured reporting system, increasing both the quality and the diagnostic value of prostate MRI.

Therefore, radiologists should be aware of the advantages and limitations of this technique in order to optimize the interpretation of imaging findings.

Personal information

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References


