An Overview: Dynamic Contrast Enhanced Imaging of Prostate Cancer

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Imaging philosophy

For many years, medical imaging focused on the anatomy of the body by taking a picture of the organs. Latest techniques allow us to investigate physiological and even molecular features of the imaged tissue. The interpretation of such images requires thus a thorough understanding of the imaging technique as well as a deep understanding of the biology and physiology of the healthy and diseased organ.

The switch to these new techniques represents a steep learning curve. To assist in this task we present some basic anatomy and physiology of the normal prostate. The many different types of diseases that are relevant make it difficult to give a complete picture in a couple of lines. Thus a summary of the most important findings is presented here. References to more detailed publications are also given.

A note of care:

MRI and in particular dynamic contrast enhanced (DCE) MRI is very sensitive to benign or malignant conditions of the tissue. This has increased the numbers of false positive radiological assessments. The false positive issue becomes even more critical when screening a population, i.e. when scanning a population which has a high probability of not having a malignant problem.

Researchers developing computer aided diagnostic tools have been pushed to change the investigation paradigm. The question now asked is “show me what is normal” rather than “let me find the tumour”.

Molecular and cellular research is in its infants shoes and the myriads of new findings in this field is lacking full understanding and is not correlated with radiological appearances. In practice, a radiologist is left with only little information from clinical studies to take decisions as to what could the diagnosis be.
Basic Anatomy

Several systems of terminology are available. With respect to MRI imaging, the zonal anatomy has mostly replaced lobar anatomy and in young men four zones can be differentiated: (1) peripheral zone (PZ), (2) transition zone (TZ), (3) central zone (CZ), and (4) anterior fibromuscular stroma (AFS) zone.

- The nonglandular anterior fibromuscular stroma (AFS) is an anterior band of fibromuscular tissue contiguous with the bladder muscle and the external sphincter.
- The peripheral zone (PZ) contains about 70% of the glandular tissue and forms the external layer of the prostate predominant at the apex and the posteriolateral side.
- The central zone (CZ) surrounds the ejaculatory ducts.
- The transition zone (TZ) is central and less prominent in younger men.

With increasing age, the TZ may become the dominant zone (hypertrophy) reducing the visibility of the CZ on T2 images and compressing the PZ. Therefore, the term central zone is often used to define the TZ hypertrophy clearly visible on ultrasound and MRI. The TZ, PZ, and the AFS are clearly defined on T2 MRI. Two papers explaining the anatomy of the prostate for imaging and radiotherapy treatment planning have recently been published (1) (2).

The neurovascular bundles contain the cavernous nerves responsible for potency. They are located in close proximity to the prostate gland on the posterolateral surface. Branches of the neurovascular bundles enter the prostate at the base (superior pedicle) and the apex (inferior pedicle) posterolaterally. They represent the main route of extraprostatic spread of cancer as they enable cancer cells to bypass the anatomical barrier of the prostate capsule. Extracapsular extension in the absence of perineural invasion is uncommon and is usually associated with large, high-grade tumors. Extracapsular extension most commonly occurs on the posterolateral surface of the prostate near the region of the neurovascular bundles. The distance from the prostate capsule to the neurovascular bundle is 2 to 5 mm at the apex (inferior pedicle) and 10 to 15 mm at the base (superior pedicle) on the posterolateral surface of the prostate.

Basic physiology

From a molecular point of view, the prostate gland consists of a duct system composed of epithelial cells overlying a fibromuscular stroma (3). The lining of the prostatic ducts is found to vary depending on how central they are positioned within the gland, making up the different zones. Indeed, the cells of the stroma vary from almost exclusively fibroblast distally to almost wholly smooth muscle at the proximal end of the ducts. The specific competences of these regions are not only due the structure, abundance and variety of the
stromal cells, but also due to the growth factors they generate and impose upon themselves.

To get a flavour of the complexity of the cellular physiology we have researched the two most common diseases and present a summary below.

**Benign prostatic hyperplasia (BPH)**

It is thought that BPH is a mesenchymal disease and results from the reawakening of embryonic inductive interactions between the prostatic stroma and epithelium (4). BPH is a truly hyperplastic process characterized by an increase in the total cell population, which is due to cellular proliferation and escape from the normal apoptotic process. BPH can progress to carcinoma, but it is rare. It seems that epithelial cells within BPH maintain their normal restriction to the basal cells. At an early stage, BPH is characterised by the hyperplasia of mainly stromal tissues around the urethra with excessive growth localised to the points where the ejaculatory ducts enter into the TZ of the prostate (5). As the prostate grows larger during BPH, hyperplasia of glandular tissue might predominate. In general, the heterogeneous nature of BPH nodules in different prostatic areas makes generalisation difficult. In addition, tissue composition of BPH can change with time. The histological appearance of epithelium in BPH is flattened with a decrease in mean epithelial height compared to normal TZ. In addition the intraluminal space is increased in BPH by 125%. The lymphatic vessels density has been reported
to be higher in BPH than in normal areas. Microvesseldensity (MVD) is lower in BPH than in cancer (6).

**Prostate Cancer (CaP)**

The activation of carcinoma is reported to be due to a genomic alteration in which the host microenvironment plays a key role (7). Indeed, it has been found that factors from the host rather than from the tumour can contribute angiogenesis and tumour formation. Growth factors produced by all cells of the organ act in a paracrine and autocrine way to promote the ability of cancer cells to acquire altered behaviours, e.g. progression to androgen independency and osteomimicry (leading to metastasis) (8). Unlike in BPH, CaP involves proliferation not only of the basal epithelial cells but also of e.g. luminal epithelial cells. Extracellular matrix remodelling and angiogenesis are prerequisites for cancer growth and metastasis. Indeed, an increase in microvessel density is seen in CaP (9). Several papers report no correlation between MVD and Gleason score (6) (10). On the other hand, a recent investigation reports destruction of lymphatic vessel in CaP but not at the tumour periphery (6).

Epidemiology and molecular research are gathering increasing evidence that recurrent prostate inflammation may initiate and promote cancer development (11).

**Imaging Prostate**

An overview of T1, T2 and DCE characteristics of prostatic tissue is given in Appendix 1.

**T2 images**

MRI provides the most accurate information about the anatomy and location of tumour compared to other imaging modalities like US and CT. So far it has the highest staging accuracy of any diagnostic imaging technique available. The detection T3b tumours invading the seminal vesicles could make a significant difference in planning radiotherapy treatment. Its routine use though in staging of all prostate cancers remains controversial, because of a wide range of reported accuracies. Diagnostic imaging requires knowledge as well as acquired skills and undoubtedly the experience of the radiologist plays a key factor in prostate MRI interpretation (12).

Prostate is best seen on T2-weighted images. The normal PZ shows high signal intensity on T2 images. It is surrounded by a slim low signal intensity rim representing the prostate capsule. The TZ and CZ present with lower and more heterogeneous signal intensities than the PZ. Prostate cancer usually induces lower signal intensity than the healthy surrounding tissue, but these changes are not entirely specific to cancer, as benign conditions such as haemorrhage, prostatitis, and the sequelae of radiation or hormone treatment produce a similar signal drop. MRI should not be performed during 4-6 weeks after biopsy to avoid diagnostic misinterpretations due to haemorrhage.
The diagnosis of cancer in the CZ and TZ is more complex because of the
difficult differentiation with nodules of hyperplasia. Confluent areas of low
signal intensity are most useful findings, suggesting central gland cancers.
While wedge shape diffuse extension without mass effect are indicative of
benignity (13).

There are acknowledged limitations in the detection and staging of cancer on
T2 images: cancer is not always identified in the PZ as a low intensity and the
detection of cancer in the CZ and TZ is a bigger problem mainly due to
inhomogeneous signal intensities due to the hyperplastic nodules.

T1-weighted images do not show the internal architecture of the prostate, but
the information can be used to to assess post-biopsy haemorrhage within the
prostate as well as aiding interpretation of the integrity of the prostate capsule.

**Dynamic Contrast Enhanced images**

Dynamic contrast enhanced (DCE) imaging has been introduced to
investigate the neovascularisation (angiogenesis) which is necessitated for
the growth of any new tissue i.e. cancer (14). DCE MRI has the potential to
detect cancer and any other disease involving angiogenesis. Since the
beginning of DCE MRI in the early 1990, imaging research has progressed
and spatial and temporal resolutions have been optimised to produce the best
results possible.

When investigating DCE MRI data, the PZ and the TZ are assessed
separately, due to their difference in anatomy, physiology and most probable
disease generation.

In the PZ, clinical studies report a higher accuracy of CaP detection with
dynamic parameters from DCE MRI compared to T2 images (15) (16) (17).
Kim presents good results with a wash-in rate, while Engelbrecht reports
highest discrimination between normal and malignant with relative peak
enhancement (tumour peak enhancement normalised to normal tissue peak
enhancement in PZ and CZ resp.).

Discrimination between benign and malignant in the inner part of the TZ on
the basis of DCE MRI alone remains a challenge. Additional information about
PSA and prostate size might aid differential diagnosis (17). Compared to PZ
tumours of similar size and grade, TZ cancers are associated with a
favourable prognosis due to natural barriers to extension (eg, urethra, anterior
fibromuscular stroma, fibrous plane between TZ and PZ) and inherent biologic
differences.

Interesting new work by Noworolski (18) gives indication about enhancement
pattern of stromal and glandular BPH in the CZ. According to her paper,
combined with T2 images a discrimination between CaP and BPH would be
possible (cf the table above).
DCE MRI is particularly suited to assist decision making in cases of suspected extracapsular extension. The enhancement pattern at the prostate edge itself might confirm or reject the suspicion of the radiologist.

After radiotherapy, prostate tissue demonstrates diffuse low signal intensity on T2 images. Recurrent tumour show poor contrast and cannot be distinguished from the post radiotherapy fibrosis. Rouviere (19) has shown that contrast enhanced MRI increase diagnostic accuracy from 0.60 to 0.79.

Padhani (20) has investigated the effects of androgen deprivation on DCE MRI. He reports a reduction in tumour volume and vascularisation due to fibrosis induced by androgen deprivation.

References


