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PREOPERATIVE LOCAL STAGING OF PROSTATE CANCER

ASPECTS ON PREDICTIVE MODELS, MAGNETIC RESONANCE IMAGING AND INTERDISCIPLINARY TEAMWORK

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“One, remember to look up at the stars and not down at your feet.
Two, never give up work. Work gives you meaning and purpose and life is empty without it.
Three, if you are lucky enough to find love, remember it is there and don't throw it away.”
— *Stephen Hawking*

“Do not spoil what you have by desiring what you have not; remember that what you now have was once among the things you only hoped for.”
— *Epicurus*

To my beloved family: Gabi, Miranda, Noel and Esther

ABSTRACT

In prostate cancer surgery the two issues at stake are the removal of the tumour on one hand and functional outcome i.e. urinary continence and sexual function on the other. A nerve preserving procedure will optimise the functional outcome but introduces the risk of positive surgical margins by accidentally leaving small tumour remnants behind, thus risking a poor oncological outcome. Preoperative knowledge of tumour aggressiveness, location and whether local growth is confined to the prostate is of outmost importance for an optimal outcome. Currently available tools that provide the surgeon with preoperative information on which to base the treatment decision and surgical technique are far from perfect.

The overall aim of this thesis was to explore ways to improve preoperative local staging of prostate cancer, including the development of a prediction tool and the use of magnetic resonance imaging (MRI) in the decision of surgical method.

In *Paper 1* we found that of men who underwent surgery with preoperative characteristics implicating very low risk disease, one third had adverse pathology outcome i.e. non-organ confined tumours and/or more aggressive tumour features at pathology. Sixteen percent had positive surgical margins and only 40% were urinary continent and sexually potent 12 months after surgery. The findings describe both the shortcomings of the preoperative work-up and the risks linked to surgery. It also gives support to active surveillance, where active treatment is deferred, as an option for men with very low risk, albeit after careful risk stratification where MRI should play an important role to rule out maleficent tumours.

Patients with tumour that on clinical examination are classified as organ-confined will in approximately one third of the cases subsequently be reclassified at pathology as non-organ confined. In *Paper 2* the development of a prediction tool from preoperative variables, predicting non-organ confined disease, is described. The accuracy of the final model was only moderate and when validated on an external group showed even lower performance. We found that the probable cause of the low performance was due to variability between pathologists in judgement of our primary outcome measure, tumour stage. This underlines the need for validation before the use of an externally derived prediction model.

Paper 3 investigated the additional value of a three-dimensional (3D) T2-weighted sequence with radial reconstructions, in local staging of patients receiving a preoperative prostate MRI. A radial reconstruction overcomes the partial volume effect encountered at the curved portions of the prostate seen with conventional imaging methods. The outcome however showed no benefits of adding the 3D sequence but rather introduced an uncertainty when comparing assessments from two radiologists, with an inter-rater correlation of 0.17 (poor agreement) compared to traditional sequences of 0.42 (moderate agreement).

In *Paper 4* we compared outcome measures from pathology regarding positive surgical margins between (A) men who had performed a preoperative MRI discussed at an interdisciplinary consensus conference between surgeons and a radiologist and (B) men who were operated on without a preoperative MRI. The group receiving MRI and a conference showed a significant reduction in positive surgical margins but at the cost of less nerve sparing procedures, compared to those men not receiving a preoperative MRI.

The findings of this thesis highlight the difficulties encountered at prediction of local tumour stage in prostate cancer at all stages of the preoperative investigation. This implicates the need for improvements, with tuning and standardisation of the different preoperative investigational modalities for better oncological and functional outcome in men undergoing treatment with curative intent. This should be carried out in a multi-disciplinary setting, to optimize and increase the knowledge of all specialists involved in the care of prostate cancer patients.

LIST OF SCIENTIFIC PAPERS

I. **Oncological and functional outcomes one year after radical prostatectomy for very low risk prostate cancer. Results from the prospective LAPPRO trial.**
Carlsson S, **Jäderling F**, Wallerstedt A, Nyberg T, Stranne J, Thorsteinsdottir T, Carlsson SV, Bjartell A, Hugosson J, Haglind E, Steineck G
British Journal of Urology Int. 2016 Aug;118(2):205-12.
Epub 2016 Mar 18. DOI: 10.1111/bju.13444

II. **Accurate prediction tools in prostate cancer require consistent assessment of included variables.**
Jäderling F, Nyberg T, Blomqvist L, Bjartell A, Steineck G, Carlsson S
Scandinavian Journal of Urology. 2016 Aug;50(4):260-6
Epub 2016 Mar 29. DOI: 10.3109/21681805.2016.1145736

III. **Accuracy in local staging of prostate cancer by adding a three-dimensional T2 weighted sequence including radial reconstructions in magnetic resonance imaging**
Jäderling F, Nyberg T, Öberg M, Carlsson S, Skorpil M, Blomqvist L
Submitted Manuscript.

IV. **Preoperative staging using magnetic resonance imaging and risk of positive surgical margins after prostate cancer surgery**
Jäderling F, Akre O, Aly M, Björklund J, Olsson M, Adding C, Öberg M, Blomqvist L, Nyberg T, Wiklund P, Carlsson S
Submitted manuscript.

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LIST OF ABBREVIATIONS

AFS	Anterior fibromuscular stroma
AUC	Area under the curve
CZ	Central zone
DRE	Digital rectal examination
DWI	Diffusion weighted imaging
EPE	Extraprostatic tumour extension
ePLND	Extended pelvic lymph node dissection
MRI	Magnetic resonance imaging
mpMRI	Multi-parametric magnetic resonance imaging
NS	Nerve sparing
NVB	Neuro-vascular bundle
PI-RADS	Prostate Imaging-Reporting and Data System
PLND	Pelvic lymph node dissection
PSA	Prostate specific antigen
PSM	Positive surgical margins
PZ	Peripheral zone
OR	Odds ratio
RARP	Robot assisted radical prostatectomy
ROC	Receiver operating characteristic
RR	Relative risk
SIPW	Stabilized inverse probability weighting
SM	Surgical margins
SNR	Signal-to noise ratio
SVI	Seminal vesicle invasion
T1w	T1 weighted
T2w	T2 weighted
TRUS	Trans-rectal ultrasound
TZ	Transition zone

1 BACKGROUND

1.1 THE PROSTATE

The prostate is a gland located just beneath the urinary bladder, enveloping the urethra (Figure 1). The size is often compared to the size of a walnut, but usually becomes larger with older age giving impairment of micturition. The apex of the prostate is the inferior part of the prostate and the base is located superiorly, like a pyramid turned up side down. From the testicles the left and right spermatic cords (vas deferens) confluence with the ducts from the seminal vesicles on the dorsal aspect at the base of the prostate, forming the ejaculatory ducts that traverse through the prostate to the urethra at the seminal colliculus.

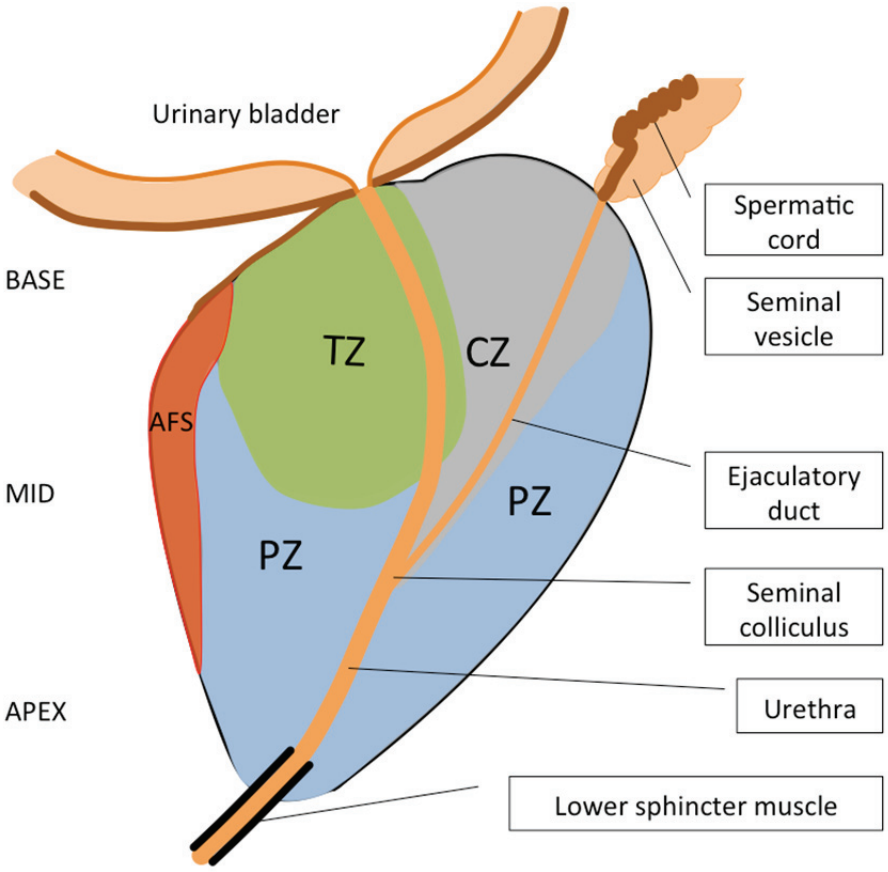


Figure 1. Zonal anatomy of the prostate: peripheral zone (PZ), transition zone (TZ), central zone (CZ), anterior fibromuscular stroma (AFS).

The prostate is divided into three major zones: the central, transitional and peripheral zone. The central zone surrounds the ejaculatory ducts and the transitional and the peripheral zones are located anterior and posterior to the prostatic part of the urethra respectively.

The prostate has no true capsule but rather a layer of fibro-muscular fascicles comprised mainly of smooth muscles inseparable from the prostatic stroma [1]. The “capsule” is not present at the upper portion of the base, the apex and the anterior aspect of the prostate. The confinement of the anterior aspect of the prostate is called the anterior fibromuscular stroma (AFS). The urethra extends from the apex and is surrounded by an inner smooth muscle layer and the external sphincter, a striated muscle [1]. The nerves supporting erectile function originate from the inferior hypogastric plexus and run on the dorsolateral aspect of the seminal vesicles on each side [2]. The nerves run from the seminal vesicles spreading in a mesh-like manner down the dorsal, dorsolateral and lateral aspect on each side of the prostate. The main bulk of the nerves reside dorsolateral together with small blood vessels also known as the neurovascular bundle (NVB), an important landmark in surgery. Saving the NVB during surgery is crucial to increase the chance of retaining erectile function and to some extent urinary continence.

Prostate specific antigen (PSA), a protein produced by the glands in the prostate, leaks in small amounts into the bloodstream. PSA is a protease and a part of the seminal fluid where its function is degradation of the clot forming proteins from the seminal vesicles [3]. This leads to a liquefaction of the clot, facilitating the motility of the spermatozoa [4]. The PSA level in blood may rise in both benign and malignant conditions.

1.2 PROSTATE CANCER

The research field in prostate cancer has from the turn of the century obtained great interest. This can be seen in the number of scientific publications on PubMed, rising from 36,776 noted in the year 2000 and today reaching the number of 139,495 (September 2016). It is a vast field including diagnostics, prediction models, treatments, genetics as well as patient’s experiences and health.

Prostate cancer is the most common soft tissue tumour in Swedish men, with a prevalence that has steadily increased since 1990, affecting 93,000 men in 2013. Approximately 11,000 new cases were found in 2014, accounting for 2,500 deaths that same year [5]. The rising incidence can be attributed to more frequent use of prostate specific antigen (PSA) testing, leading to a higher frequency of men undergoing trans-rectal ultrasound (TRUS) guided biopsies, but also the fact that mean age at death is rising. The high prevalence probably reflects diagnosis of many indolent cancers that most men die with and not from. In an autopsy study of men dying from other causes, 65% of men over 80

years had latent prostate cancer [6]. The death rate from prostate cancer has declined in the last decades [7].

What causes prostate cancer is still not fully elucidated but older age, racial, hereditary, dietary and lifestyle factors are discussed [8-11]. Most cancers arise in the peripheral zone (70-80%) but also appear in the transition zone (≈25%) and rarely in the central zone (≈5%) [12], adenocarcinoma being the most common type of cancer.

At the diagnosis of prostate cancer the patient faces different treatment options depending on tumour extent and biological behaviour of the tumour with the aim of giving a treatment with best possible net outcome. Curative treatment balances between oncological and functional outcome. A combination of both good oncological and functional outcome means disease free together with retained erectile function and urinary continence. A poor oncological outcome means increased risk of recurrence with additional treatment, reduced quality of life and at the far end death, whereas a poor functional outcome means lost erectile function and urinary incontinence. In low risk disease the patient can opt for active surveillance. The patient is then carefully monitored with periodical PSA tests, DRE and systematic biopsies so as that curative treatment can be started at the suspicion of disease progression. In intermediate and high-risk patients with localized or locally advanced disease radiotherapy (RT) in combination with hormonal treatment or surgery are the most common treatment options with curative intent. RT is given as external RT with or without brachytherapy (several slender tubes are placed in the prostate via perineum and the radioactive source is placed in each tube for a certain amount of time = internal RT).

Local treatment techniques is another option such as high-intensity focused ultrasound (HIFU) and radio frequency (RF) ablation both using heat to destroy the cancer cells with side effects of harming the adjacent structures [13]. Irreversible electrophoresis (IRE) is another technique using high voltage through needles placed outside the tumour volume to turn the tumour cells into apoptosis without damaging neighbouring nerves and vessels. The long-term efficacies of such treatments are still under investigation [14,15].

In metastatic prostate cancer combination treatments are available. Radiotherapy or surgery can be used for local control in combination with systemic treatment such as hormones or cytotoxic drugs.

1.3 PROSTATE CANCER DIAGNOSIS

The traditional course of establishing the prostate cancer diagnosis is through a blood sample measuring prostate specific antigen (PSA). The PSA cut-off levels in Sweden are age dependent; men < 50 years 2.0-2.99 ng/mL and a normal DRE should be followed with a PSA test every other year. For men < 70 years the PSA cut-off level is set at < 3.0 ng/mL, for men aged 70-80 < 5.0 ng/mL and for men over 80 years ≥ 7.0 ng/mL [16]. The PSA is bound to macromolecules in blood, but a small fraction exists in its free form (f). The ratio of f/total PSA is lower in men harbouring prostate cancer than in men with a high PSA value due to benign prostate hyperplasia [17]. The ratio of f/total PSA can also be low after urinary tract infection as well [18]. If an elevated PSA is detected, benign causes are ruled out first e.g. benign prostate hyperplasia, prostatitis or urinary tract infection. Digital rectal exam (DRE), palpation of the dorsal aspect of the prostate with the index finger via rectum, is clinical routine in prostate cancer diagnostics. The findings of the DRE is graded according to the T in the TNM classification (T=Primary tumour clinical, N=Regional lymph nodes, M= Distant metastasis) [19] (Table 1).

Table 1. T classification of prostate cancer

T Primary tumour		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1		Clinically inapparent tumour neither palpable nor visible by imaging
	T1a	Tumour incidental histologic finding in 5% or less of tissue resected
	T1b	Tumour incidental histologic finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (for example, because of elevated PSA)
T2		Tumour confined within prostate
	T2a	Tumour involves one-half of one lobe or less
	T2b	Tumour involves more than one-half of one lobe but not both lobes
	T2c	Tumour involves both lobes
T3		Tumour extends through the prostate capsule
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4		Tumour is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

If palpation raises the suspicion of cancer and/or PSA level is elevated the patient is recommended systematic trans-rectal ultrasound (TRUS) guided biopsies. The biopsies are obtained under local anaesthesia in a systematic manner with 10-12 cores with an 18G biopsy needle to cover the essential dorsal parts of the prostate. The biopsies are histologically graded according to the Gleason grading system [20] (explained under Chapter 1.7.1 PATHOLOGY).

Based on findings from this clinical evaluation each patient is stratified to a risk category established by the Swedish National Health Group for Prostate cancer, based on the D'Amico risk criteria [21]:

Very low risk	T1c, Gleason sum ≤6, 1-4/8-12 biopsy cores, ≤8 mm total cancer length, PSA density <0.15 ng/mL/cm^3
Low risk	T1a-T2a, Gleason sum ≤6, PSA ≤10 ng/mL
Intermediate risk	T2b and/or Gleason sum 7 and/or PSA 10-19.9 ng/mL
High risk	T2c-T3 and/or Gleason sum ≥8, or extensive growth 4+3 in more than 50% of cores taken and/or PSA ≥20 ng/mL

There is no optimal cut-off value for PSA receiving both a high sensitivity and a high specificity. In the large randomised Prostate Cancer Prevention Trial (PCPT) men with initial PSA ≤ 3.0 ng/ml and normal DRE were randomised to either finasteride (reduces the conversion of testosterone to dihydrotestosterone and may relieve the symptoms of benign prostate hyperplasia) or placebo. Men not diagnosed with cancer during the study period were recommended an end-of-study prostate biopsy. In the placebo arm a low PSA value of 1.1 ng/ml showed sensitivity for detection of any cancer as high as 83% while specificity was only 39% and at 3.1 ng/ml sensitivity dropped to 32% with a specificity of 87% [22]. At low PSA levels < 4 ng/ml, 15% of the men will have prostate cancer and 2% will have significant disease (Gleason sum ≥ 7) [23].
The positive predictive value of DRE in a screening setting was only 5%, 14% and 29% at PSA levels of 0-1.0 ng/ml, 1.1-2.5 ng/ml and 2.6-4.0 ng/ml respectively [24].

TRUS is not recommended as a detection tool for cancer since a large proportion of tumours are iso-echoic, but is used to assess prostate volume and to direct the systematic biopsies. TRUS systematic biopsies under-samples by missing tumours in 30-36% at first biopsy [25,26], may under-sample tumours by inadequate targeting with up-grading at final histology in as much as 46% of the cases [27] and over-sample by targeting minute cancers of

low grade that do not need treatment in 17% [28]. Systematic TRUS biopsies inflict a risk of urinary tract infections, seen in 6% of patients and with sepsis leading to hospitalisation in 1% between 2006-2011 in Sweden [29], but was seen in 2.8% of the patients in a French study including 2,718 patients [30]. The strongest predictor for sepsis was noncompliance to recommendations of the use of prophylactic antibiotics. All men undergoing TRUS biopsies are recommended prophylactic antibiotics [16]. Bacterial resistance to antibiotics is another reason for an increasing proportion of men having biopsy related infections and has become a global concern [31].

1.4 MAGNETIC RESONANCE IMAGING (MRI)

1.4.1 MRI HISTORY

In 1952 the two scientists Felix Bloch and Edward Mills Purcell were awarded the Nobel Prize *"for their development of new methods for nuclear magnetic precision measurements and discoveries in connection therewith"*[32]. Their work made it possible to distinguish the contents of different molecules in solids and liquids using nuclear magnetic resonance [33].

Medical doctor and scientist Raymond Damadian published in 1971 the discovery that cancer and normal tissues have different relaxation time in hydrogen nuclear magnetic resonance (NMR) [34]. This is due to the fact that normal tissues contain more water than cancer tissue and therefore have shorter relaxation time. There were also predecessors to his findings that studied proton resonance emissions from other tissues and cell water [35-37].

In 1973 chemist Paul Lauterbur created the first NMR image of a test tube. Mathematics behind creating magnetic resonance images was improved by Peter Mansfield who also introduced echo-planar imaging making image acquisition much faster. They were both awarded the Nobel Prize in Physiology or Medicine in 2003 for their work [38].

MRI has since then evolved rapidly including diffusion weighted imaging first published by Le Bihan in 1986 where he describes imaging of intravoxel incoherent motion in the human brain [39].

1.4.2 PROSTATE CANCER IMAGING

Several imaging methods are used in the assessment of prostate cancer for tumour detection, local staging, active surveillance and diagnosing distant spread and recurrent disease. In MRI *morphological* imaging techniques include T2-weighted and T1-weighted

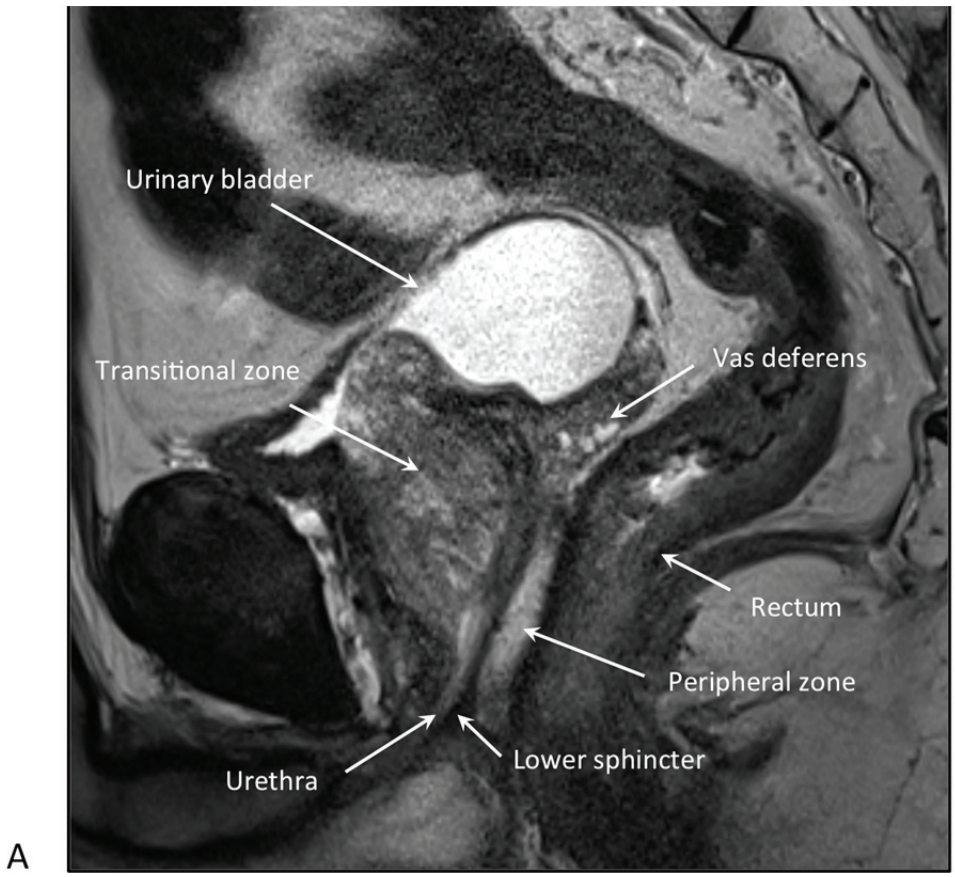
imaging (described below) to assess tumour growth pattern, suspicious lymph nodes in the small pelvis and local bone marrow metastasis. Reaching beyond the anatomical assessment to improve the accuracy of tumour detection, *functional* imaging techniques such as diffusion weighted imaging (DWI), dynamic contrast enhancement (DCE) and spectroscopy all provides additional information. Multi-parametric MRI (mpMRI) includes both morphological and functional sequences and can be compared to a jigsaw puzzle where each piece designates a sequence and all the pieces are needed to get the full picture to rule in or out significant disease. MRI is an excellent tool to detect and localise the tumour, useful in targeted biopsies (see Chapter 1.4.6 TARGETED BIOPSIES). The negative predictive value of mpMRI is as high as 90% that is if no tumour suspicious lesions are found the likelihood of harbouring a cancer is only 10% [40]. Computed tomography (CT), positron emission tomography (PET) in conjunction with either CT or MRI (PET-CT and PET-MRI) and skeletal scintigraphy are techniques used to diagnose distant spread and recurrent disease. The staging algorithm of a patient with prostate cancer depends on PSA level and Gleason score from systematic biopsies. Swedish national guidelines recommend patients with high-risk disease and curative intent to undergo skeletal scintigraphy to rule out skeletal metastasis and an MRI of the small pelvis can be considered for local tumour staging and detection of suspicious lymph nodes prior to treatment.

To avoid post-biopsy bleeding residuals in the prostate that may mimic tumours [41] and deteriorate diffusion weighted imaging (DWI), thereby decreasing accuracy of tumour detection [42], an MRI examination should be performed at the earliest 6-8 weeks after the biopsy procedure [43].

1.4.3 MORPHOLOGIC MRI

1.4.3.1 T2-weighted imaging (T2w)

Morphological imaging of the prostate rests heavily on high resolution T2w imaging. The in-plane spatial resolution of T2w images with a phased array coil at 3T is usually 0.5 x 0.5 mm and with endo-rectal coil 0.3 x 0.3 mm. Images are acquired in three orthogonal planes: the axial, sagittal and coronal plane (Figure 2, page 13 and 14).



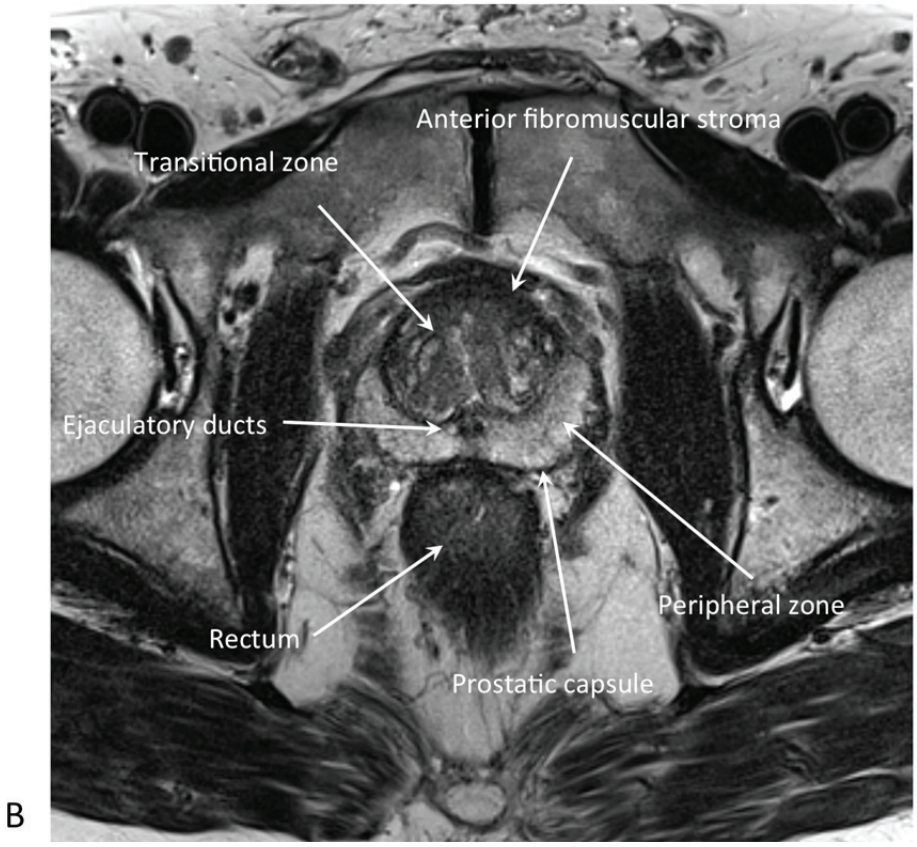


Figure 2. T2-weighted magnetic resonance images of the prostate in the sagittal (A) and axial plane (B) with anatomical landmarks.

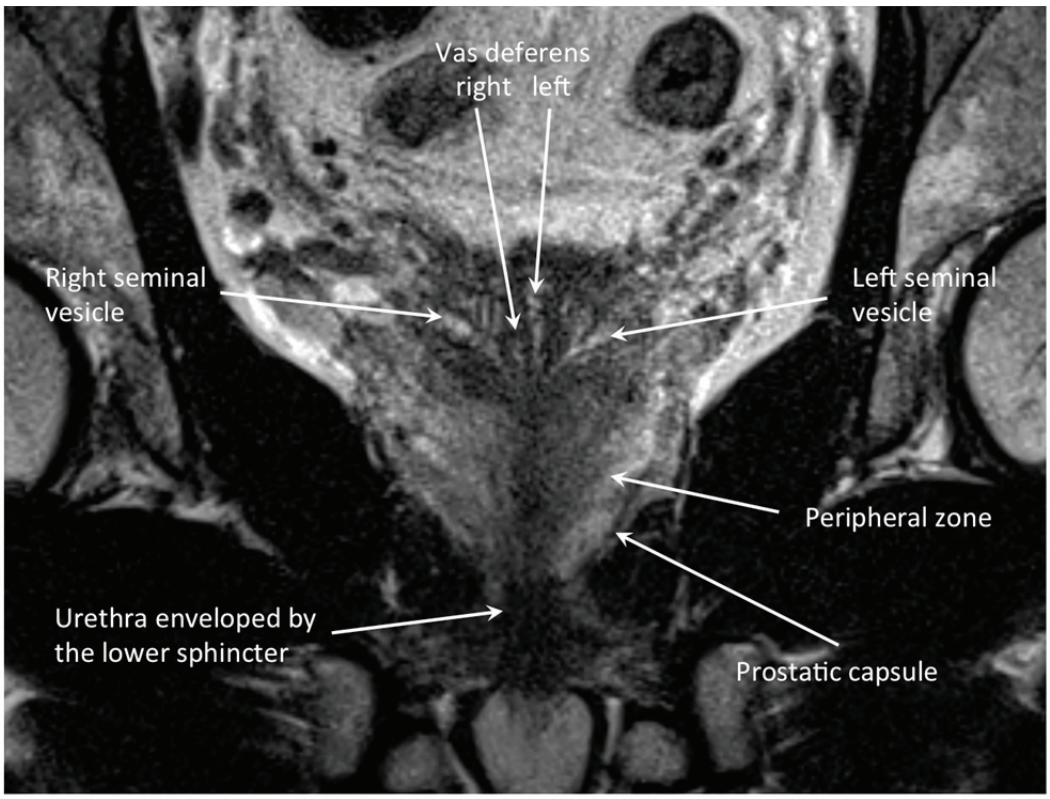


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Figure 2 continued. T2-weighted magnetic resonance images of the prostate in the coronal plane with anatomical landmarks (C).

The normal peripheral zone appears, due to high water content, with intermediate to high signal surrounded by a low signalling thin capsule. A tumour in the peripheral zone usually appears dark to the surrounding normal tissue (Figure 3). The decrease in signal intensity correlates to tumour Gleason score showing lower signal intensity with higher Gleason grade [44]. If the tumour growth pattern is sparse the signal intensity difference between normal peripheral zone and tumour tissue can be indistinguishable and therefore missed on T2w images [45]. The sparse growth pattern is characterized by malignant glandular tissue intermixed with normal glands and loose stroma. Every low signalling area in the peripheral zone is not cancer, which is a limitation of the sequence. Bleeding residuals after biopsies can appear either as bright or dark areas, depending on the stage of degradation. Chronic prostatitis with fibrosis appears dark on the images and the morphology is often linear or wedge shaped and usually bilateral [46]. Hormonal treatment and previous radiotherapy will also affect the peripheral zone in reducing the water content in the glandular tissue often making the signalling pattern homogenously dark, rendering tumour distinction impossible without functional imaging [47].

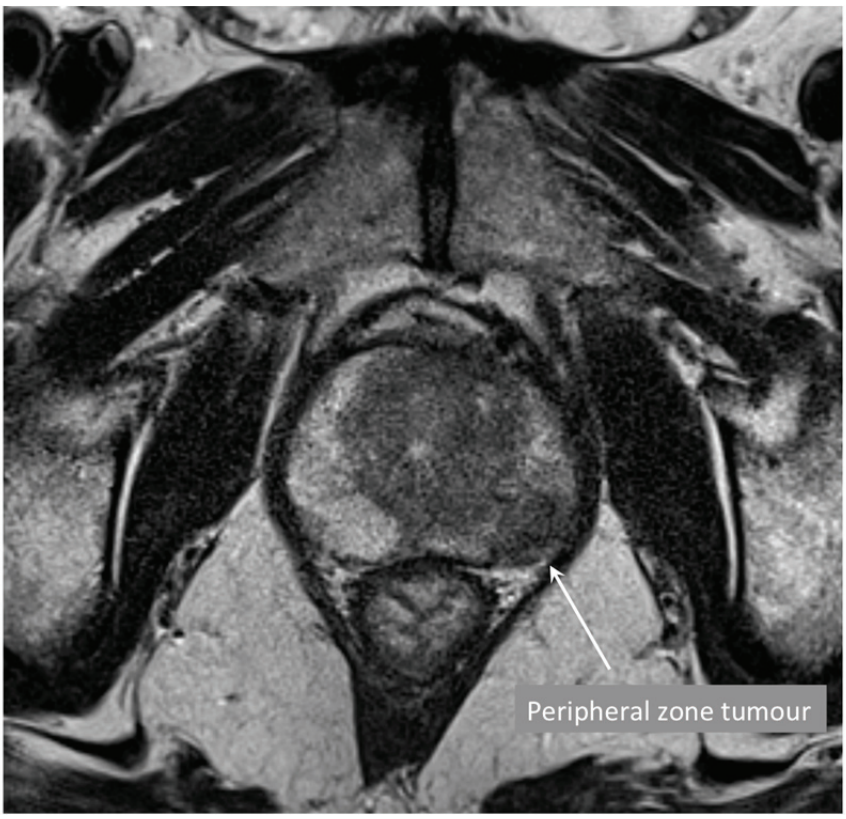

Figure 3. Axial T2-weighted magnetic resonance image with a tumour in the left peripheral zone. Note the disruption of the capsule adjacent to the tumour indicating extraprostatic tumour growth.

A relatively thick, low signalling capsule, earlier referred to as the surgical capsule, surrounds the transition zone. Due to benign prostate hyperplasia (BPH) the transition zone varies greatly in size between men. The appearance of the benign transition zone on T2w images is heterogeneous with different sized, adenomatous nodules each with a well defined capsule, internally with mixed high and low signal. The nodules are interspersed by high and low signalling ill defined areas of cystic and simple atrophy [48]. T2w imaging plays the key role in tumour detection in the transition zone, since functional imaging (DWI and DCE, described below) has low specificity for cancer. Tumours are more often localized in the anterior part of the transition zone with homogenous low T2 signal, lack of capsular encasement with ill-defined borders, lenticular shape and invasion of the anterior fibro-muscular stroma [49] (Figure 4). Transition zone cancers generally have higher PSA levels but a lower proportion of biochemical recurrence than peripheral zone cancers [50,51]. Tumours in the transition zone generally have a lower Gleason score and are more often organ confined [52]. Adenomatous nodules sometimes appear in the peripheral zone and must not be mistaken for a cancerous lesion. These nodules are surrounded by a well-defined capsule and can show both early enhancements on DCE imaging and appear dark on the ADC-map.

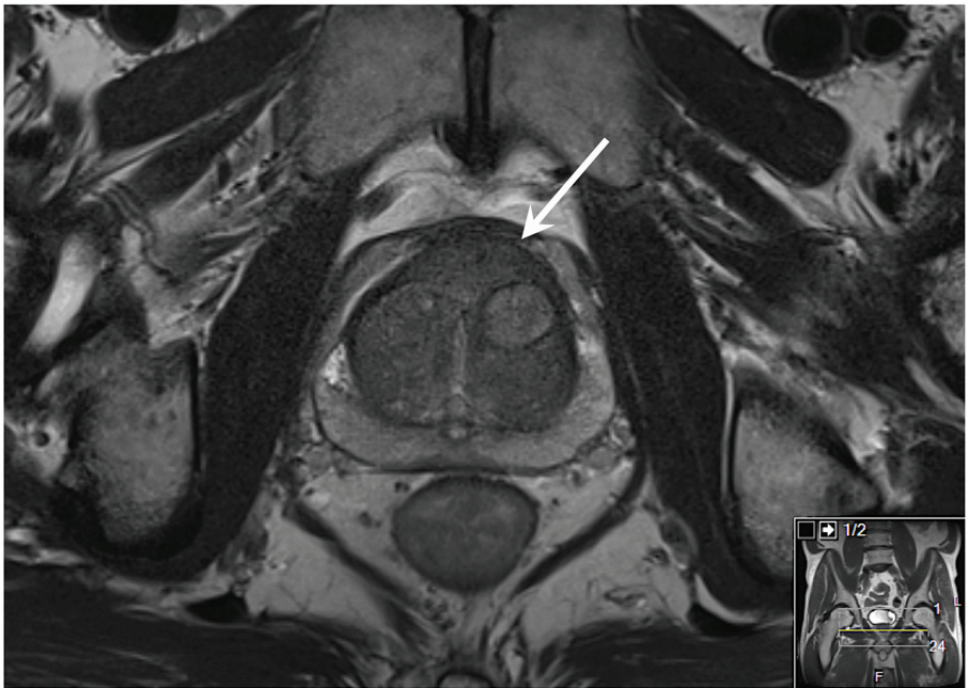

Figure 4. T2w image with a large bulging tumour, with homogenous signal at the anterior aspect of the prostate (arrow) invading the anterior fibromuscular stroma.

The mainstay in local staging of prostate cancer is the T2w images. Reporting on tumour growth pattern is of great importance for the surgeon in deciding whether to perform a nerve sparing or a non-nerve sparing procedure or for the oncologist to guide what type of therapy would be suitable. The assessment includes to rule in or out tumour breaching the prostatic confinement, with growth through and beyond the so-called capsule. The extraprostatic tumour extension (EPE) outside the capsule is often minute < 0,5 mm, falling out of the range of detection on MRI, making local staging overall very challenging. Direct signs of EPE, often described as extensive at pathology, is a measurable tumour mass outside the prostatic confinement, as obliteration of the recto-prostatic angle and asymmetry at the neurovascular bundle [53]. Indirect signs of EPE include broad tumour abutment to the capsule, bulging, irregularity, capsular thickening and tiny dark strands outside the capsule [54,55]. In tumours at the base, tumour growth into the seminal vesicles or the bladder neck is also assessed. The seminal vesicles normally have high signal due to high fluid content. Seminal vesicle invasion appears as lack or loss of architecture or low signalling areas often with a mass effect whenever the tumour grows 'per continuitatem' into the vesicles [56]. In direct over-growth from EPE at the base, wall thickening of the seminal vesicles and obliteration of the angle between the prostate and the base of the seminal vesicles is seen [56]. Assessing bladder neck invasion is challenging and indirect sign as adjacent tumour growth is used. Sometimes at extensive tumour growth, areas with higher

signal in the lower signalling bladder neck muscle are seen as a sign of invasion. At the apex, especially close to the lower sphincter muscle and the anterior aspect of the prostate where no capsule is present, tumour growth also has to be carefully assessed to exclude invasion of the muscle.

1.4.3.2 T1-weighted imaging (T1w)

T1w imaging is used both in morphological and functional imaging (dynamic contrast enhanced MRI=DCE-MRI). For morphology the T1w images are used for detecting post biopsy bleeding residuals in the peripheral zone. The impact on tumour detection and staging of blood residuals has been debated and several reports state that deferring time from biopsy to MRI does not improve tumour detection or local staging when used in conjunction with functional imaging [57-59]. This has been opposed by other studies where tumour detection was deteriorated by haemorrhage when MRI was performed less than 4 weeks after biopsy [60] and both tumour detection and staging performance was poorer with a short time interval between biopsy and MRI [61]. An interval of 6 weeks between biopsy and MRI for staging purposes is recommended by the PI-RADS document [62]. In some instances haemorrhage can be an aid in tumour detection in the so-called 'haemorrhage exclusion sign'. The tumour area is void of haemorrhage residuals due to quicker washout of blood remnants, since small vessels, as a consequence of angiogenesis, are abundant. A corresponding low signal in the T2w images can confirm the finding [63] (Figure 5).

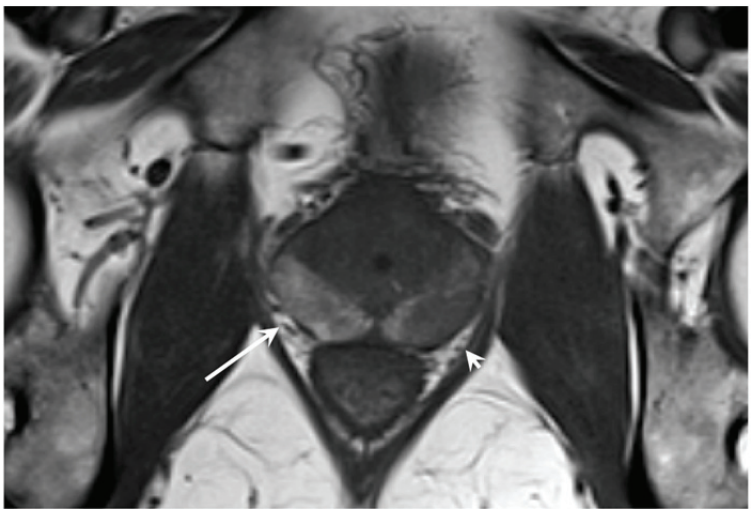

Figure 5. Haemorrhage exclusion sign. T1-weighted image with post biopsy haemorrhage in the right peripheral zone (long arrow) and void of blood remnants in the left peripheral zone (arrowhead) were the patient had biopsies positive for cancer.

T1w imaging should include the small pelvis from the aortic bifurcation including the whole pelvis and is also useful in detection of enlarged lymph nodes that could be metastatic (Figure 6). Bone marrow metastases are also detectable on the T1w images but usually require further work-up (Figure 6) and a confirmatory fine-needle aspiration or biopsy is sometimes needed.

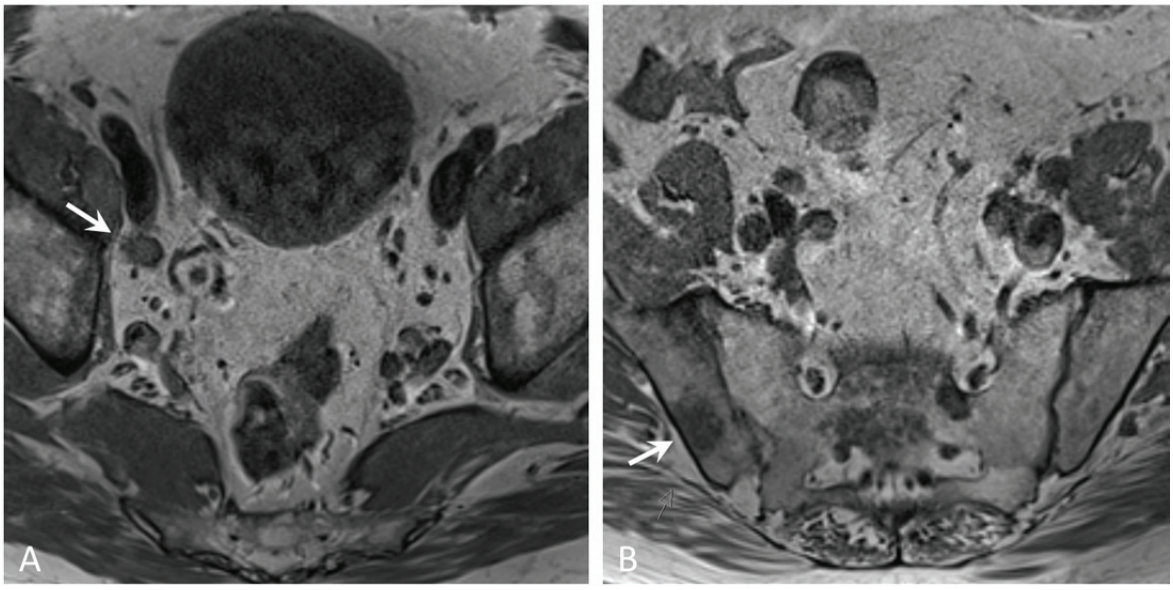

Figure 6. A: T1-weighted image with an enlarged lymph node (arrow) with indistinct border dorsal to the external iliac vein, giving the suspicion of metastatic disease. B: T1-weighted image with low signalling bone marrow lesion in the right os ilium (arrow) suspicious for metastasis.

1.4.4 FUNCTIONAL MRI

1.4.4.1 Diffusion weighted imaging (DWI)

The keystone in prostate cancer MRI is diffusion weighted imaging. The technique can be used to differentiate benign from malignant tissue, monitor treatment response in patients receiving hormonal or radiation therapy and detect recurrent disease. The sequence is based on a T2w sequence, with additional strong gradient pulses allowing measurement of microscopic random motion of intra- and extracellular water molecules. In pure water the diffusivity is unrestricted so that a single water molecule can travel farther than a water molecule bound in tissues. The gradient pulses will cause larger signal reduction in water molecules that have moved far and less signal reduction in those molecules that are restricted in their movement. The rationale behind restriction of water molecule movement is the increased cellularity in tumour tissue as well as increased extra-cellular matrix encountered in e.g. fibrosis [64], but the full correlating mechanism between diffusion and the physiological properties of the tissues is not fully understood [65] (Figure 7).

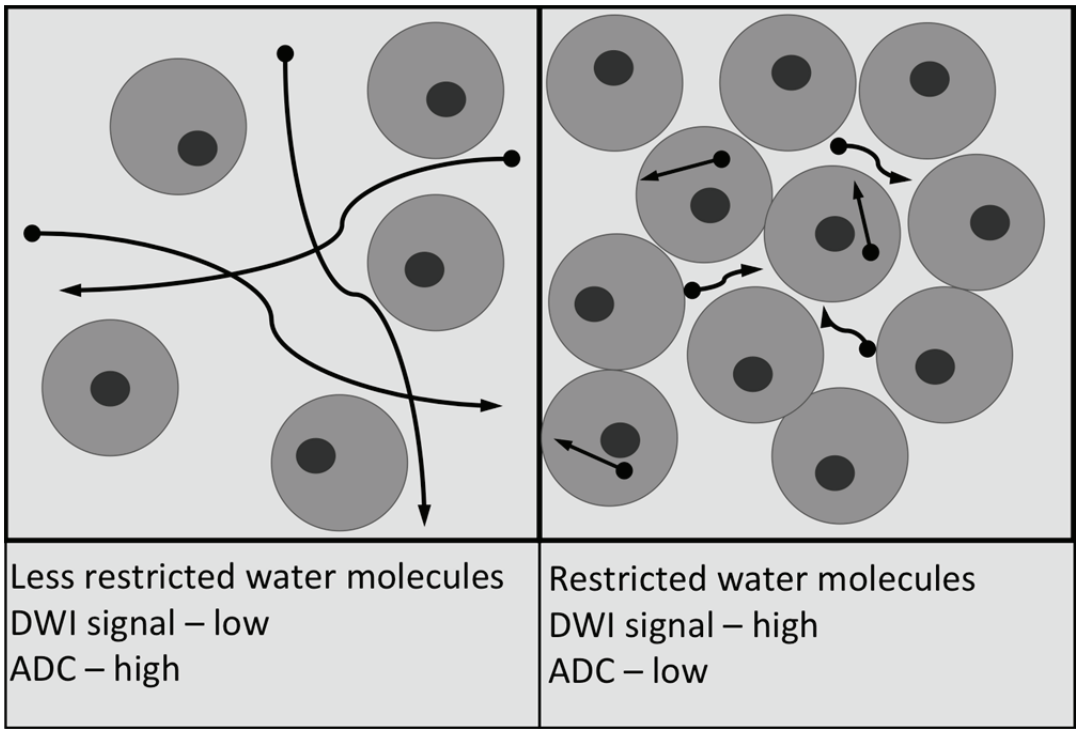

Figure 7. The movement of water molecules (curved and straight arrows) in tissues with wider extra-cellular space (Less restricted water molecules) compared to tissues with high cellular density and narrow extra-cellular space (Restricted water molecules).

The strength, length of time applied and temporal spacing of the gradient pulses will alter the b-value i.e. the degree of diffusion weighting (Figure 8). The stronger the gradient

in combination with a longer duration of the gradient applied gives a higher b-value. The higher b-value used, the higher the sensitivity of the sequence to water restriction, but at the same time with decreasing signal-to-noise ratio (SNR). The reduced SNR impairs image quality and can to some extent be overcome by repeating the sequence several times, i.e. acquire several averages.

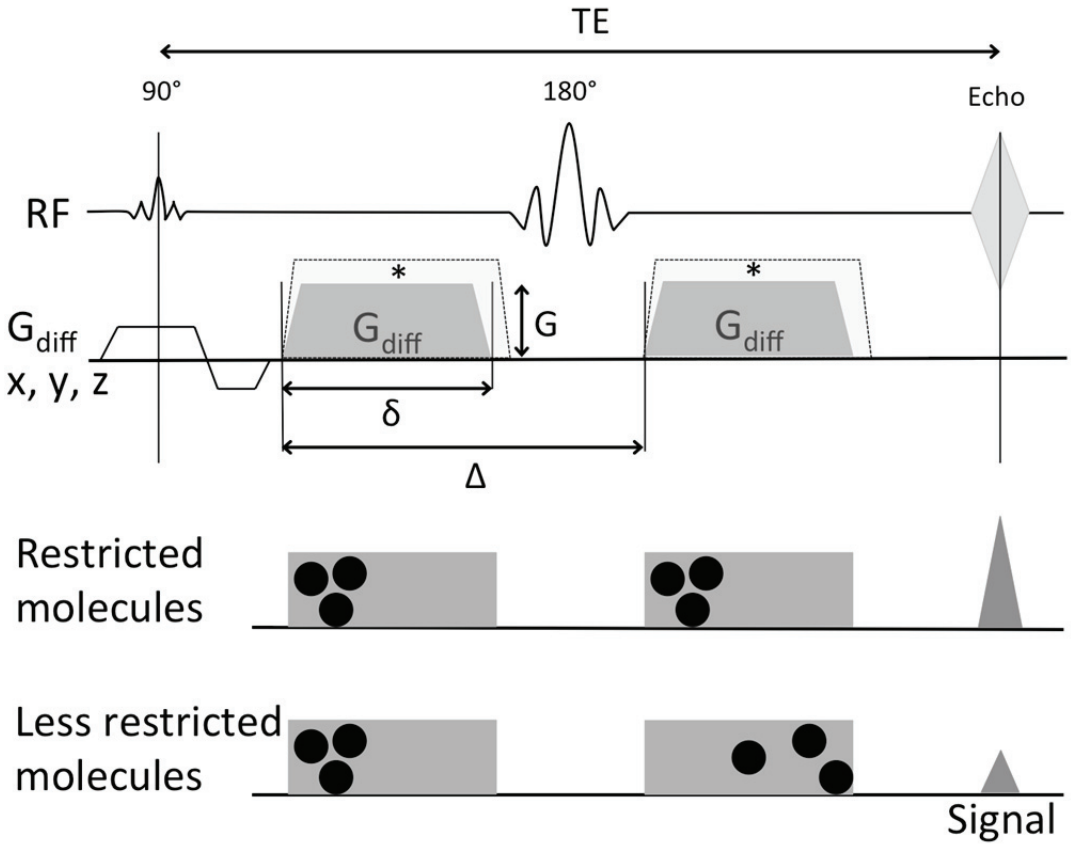

Figure 8. The diffusion weighted sequence measuring the diffusion of water. The diffusion gradients are applied in three orthogonal directions x, y, z. The duration (δ) of the gradient, the time between applied gradients (Δ) and the strength of the gradients (G) can be altered to acquire diffusion weighting at different b-values (*). Restricted water molecules are less affected by the two gradient pulses (G_{diff}) and minor signal loss occurs. Less restricted water molecules will have moved and therefore not be entirely rephased by the second gradient pulse and will therefore lose much more signal.

At each b-value, in standard DWI, diffusion is measured in three orthogonal directions to get a combined, non-directional diffusion for each voxel of the tissues, i.e. trace images. A tumour with high cellular density, where water diffusion is restricted, will in high b-value images appear bright (Figure 9), while more freely moving water as in benign tissues with lower cellularity will appear darker [66]. In prostate MRI usually a low (0-200 s/mm^2), an intermediate high (200-500 s/mm^2) and a high b-value (800-1000 s/mm^2) is used to

calculate the apparent diffusion coefficient (ADC) . The ADC is the slope of the logarithmic signal decay in each voxel calculated from different b-values and from this higher b-value images than those acquired can be computed. This has been proven useful since acquired high b-value images >1500 s/mm^2 are usually hampered by low SNR and artefacts are less apparent in the computed images [67,68]. The lowest b-value used when calculating the ADC should be separated from b=0 since it contains both micro-capillary perfusion and diffusion information giving a "falsely" steeper signal decay than when using a b-value separated from "zero" and thereby affecting the ADC [69]. In ADC-maps, voxels with restricted diffusion will appear dark and each pixel will have a corresponding ADC-value measured in mm^2/s (Figure 9). There is an inverse relationship between the ADC-value and the tumour Gleason grade, resulting in a lower ADC-value at a higher Gleason grade [70,71]. However, there is an overlap of ADC-values of malignant tissues and benign conditions, such as post biopsy inflammation and prostatitis.

DWI is most important for tumour detection in the peripheral zone, whereas T2w imaging is the key sequence in the transition zone, where DWI interpretation is hampered by low ADC values from the high cellular density of adenomatous nodules interspersed by fibrosis.

The DWI technique is sensitive to motion, e.g. bowel movement that will induce motion artefacts. Therefore an antispasmodic agent to reduce bowel movement is given just prior to the examination. Artifactual distortion may be seen at DWI by the presence of stool or air in the rectum and can partly be overcome by administering a minimal bowel enema to the patient in the hours prior to the examination.

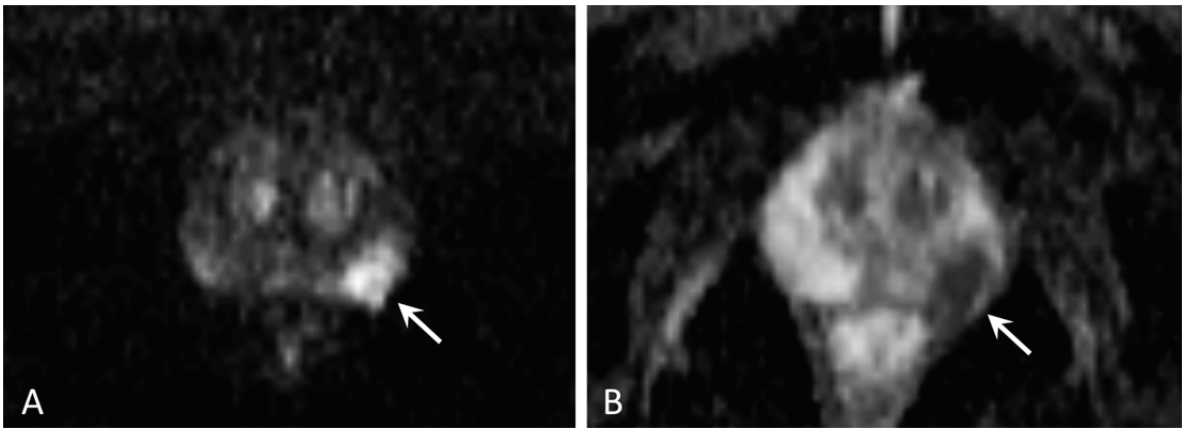

Figure 9. A: High b-value diffusion weighted trace image (b=1500) with a tumour dorsolateral in the left peripheral zone (arrow). B: Corresponding tumour appearing dark on the ADC-map. The tumour is the same as in the T2w image in Figure 3.

1.4.4.2 Dynamic contrast enhanced MRI (DCE-MRI)

In the first version of Prostate Imaging-Reporting And Data System (PI-RADS) DCE-MRI had a high impact on the final tumour suspicion score [72] but in the second version has a more modest influence. The use of contrast enhancement in multi-parametric prostate MRI is a contentious issue [73,74] and its added value is possibly refuted in two meta-analyses although one contained a limited number of studies with direct comparison between DCE and DWI [75] and the other pooled data from several studies reporting on one or more imaging sequences including DCE-MRI [76].

Vascular angiogenesis is the sprouting of new blood vessels from existing ones and neo-angiogenesis is the formation of vessels de novo. Neo-angiogenesis occurs in prostate cancer as well as other solid tumours to support tumour growth. The newly formed vessels are often more abundant in malignant than in normal tissue. The vessels have leaky endothelium with arterio-venous blood shunts giving a relatively high blood volume in cancerous tissue compared to normal. In DCE-MRI a gadolinium based contrast agent is given intra-venously. Gadolinium shortens the T1-value rendering a high signal where contrast is abundant. A baseline T1-map is first acquired calculating the T1-value of the tissues prior to administration of contrast media to be able to calculate the relationship between signal intensity and the concentration of contrast agent in the tissues. T1w imaging with short sampling time creates a volumetric image of the whole prostate in a few seconds. This is repeated for 3-5 minutes to follow the behaviour of the contrast over time. Time-concentration curves are created for each voxel and these can either be quantitative or qualitative. In the quantitative model the transfer constant of plasma, with the contrast agent as visualising mediator, from the vasculature to the extracellular space (K^{trans}) and the other way around (K_{ep}) is measured in relation to the extra vascular extracellular space (EES=v_e) [77] (Figure 10, next page). In the qualitative model the wash-in and washout of contrast in the tissues is either visually determined or by signal intensity derived curves.

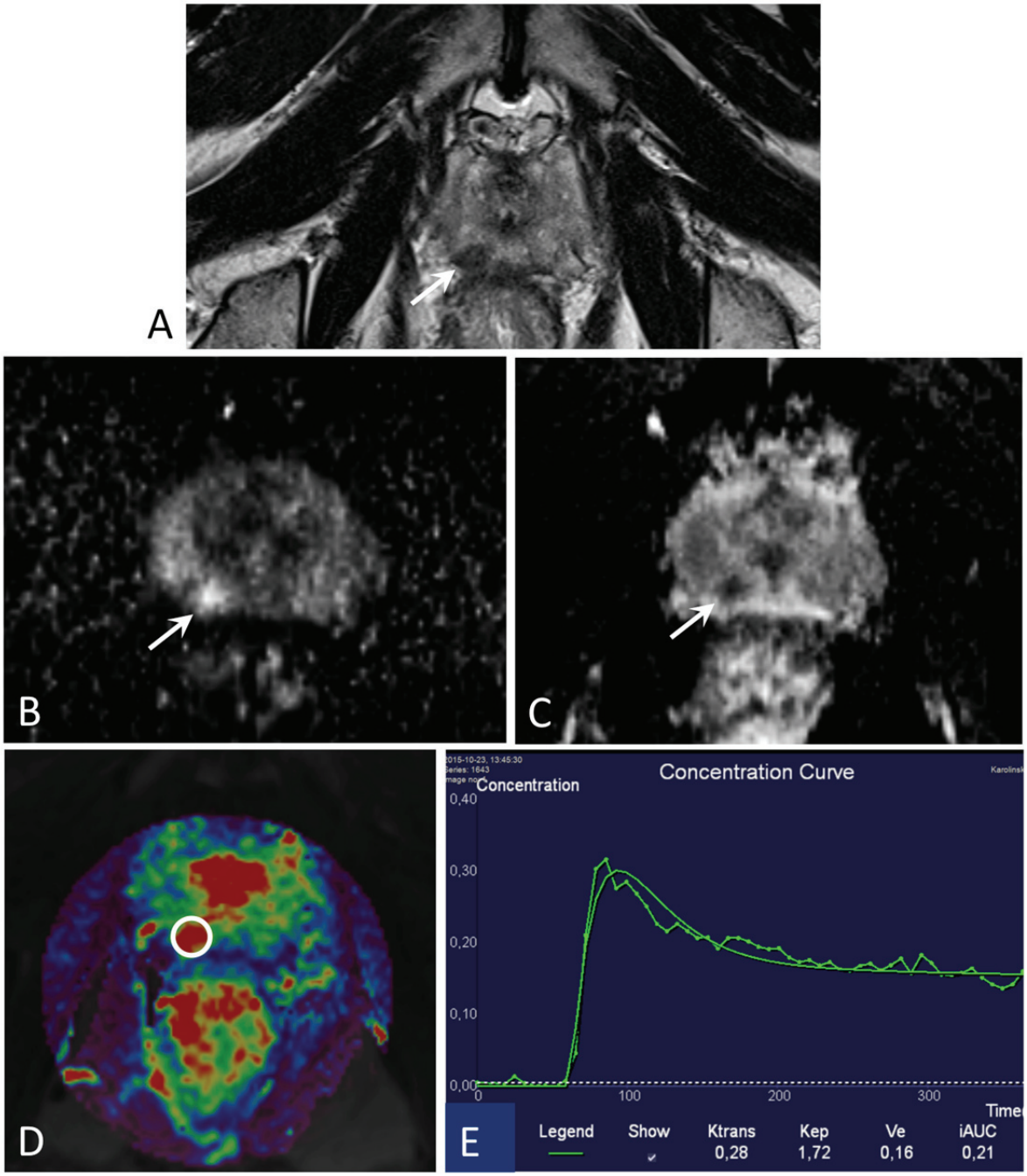

Figure 10. T2w axial image with a low signalling tumour dorsolateral in the peripheral zone on the right side (arrow) (A). Diffusion weighted images with the same tumour as in "A" (arrows) showing a dark area with restricted diffusion in the ADC-map (B) and bright in the trace image of calculated b=1500 (C). K^{trans} map with region of interest (white circle) (D) and graphic presentation of the contrast dynamics over time with fast inflow of contrast (E) for the corresponding area encircled in D.

1.4.5 Prostate Imaging-Reporting and Data System (PI-RADS)

PI-RADS is an extensive document on how to perform optimal magnetic resonance imaging in prostate cancer, which includes recommendations for patient preparations, image

acquisition, interpretation and reporting of findings. The document is intended for optimization of tumour detection in men with suspected prostate cancer in the pre- or post biopsy setting [74].

Background: In 2012 following a consensus meeting based on a survey conducted in 2009 [78] the European Society of Urogenital Radiology (ESUR) published the first PI-RADS [72]. The system is based on scientific evidence of the prerequisites for optimal tumour detection as well as local staging. The PI-RADS document includes recommendations regarding MRI pulse sequences as part of a multi parametric MRI protocol with imaging specifications, including how assessment and reporting should be carried out. Tumour suspicion is scored 1-5 (1=Clinically significant disease is highly unlikely to be present, 2=Clinically significant cancer is unlikely to be present, 3=Clinically significant cancer is equivocal, 4=Clinically significant cancer is likely to be present, 5=Clinically significant cancer is highly likely to be present). Each pulse sequence is evaluated individually to form a final score. The PI-RADS version 2 was published in 2015 based on an expert joint committee published on the homepage of the American College of Radiology [62]. This document revised some of the recommendations from the first version. The new version pays less attention to spectroscopy, due to the technical challenges inherent in the pulse sequence. In assessment of the peripheral zone DWI was given the highest influence on the score and T2w imaging in transition zone. DCE got less influence on the final score with just a positive or negative enhancement score. DCE will increase the score in the peripheral zone from 3 to 4 if enhancement is early or contemporaneous. In the transition zone a PI-RADS 3 lesion based on T2w imaging is upgraded to 4 if DWI receives a score of 5. The scoring system is rigorous but the judgement of each sequence is subjective, so there will always be some inter-reader variability. The system has been validated showing only moderate correlation both regarding tumour yield in the different scoring categories [79] and in scoring between readers [80,81]. Despite the shortcomings of the PI-RADS scoring algorithm, individual training and constant follow up of the pathological findings from targeted biopsies and prostatectomy specimen should be carried out, to build confidence in the assessments.

Local staging has a less prominent role in version 2. In a large meta-analysis including original articles concerning local staging the sensitivity and specificity for EPE was 57% and 91% respectively, confirming the difficulties in using MRI as a staging tool in its current form [82].

1.4.6 TARGETED PROSTATE BIOPSIES

An emerging, and more precise biopsy technique to diagnose prostate cancer, is known as targeted biopsies. This approach has in several studies shown to achieve targeting of more significant tumours [83,84] and better index tumour detection [85,86] while using fewer biopsy cores [87,88] as compared to systematic biopsies.

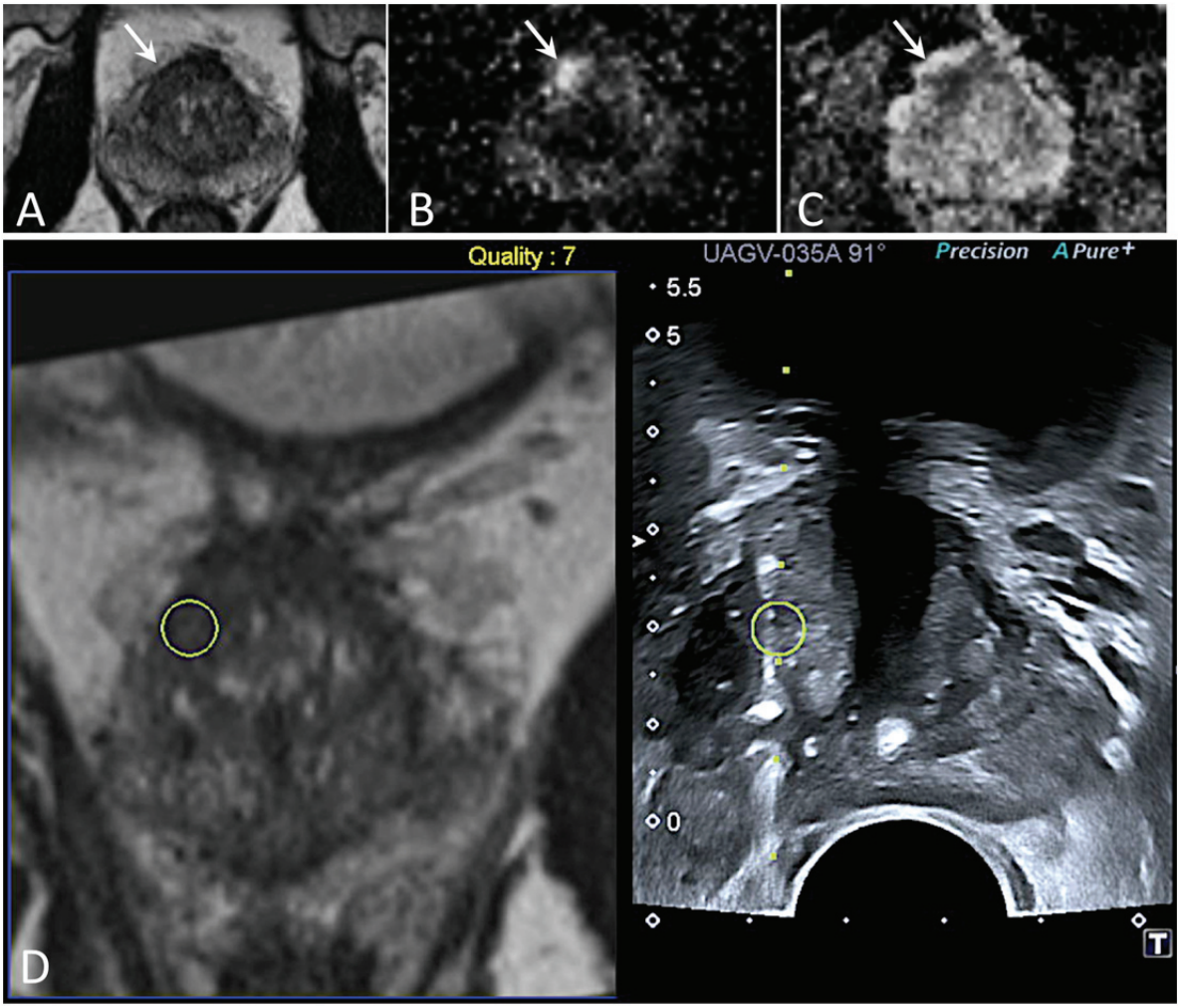

Figure 11. Case with MRI/Ultrasound fusion guided biopsy. T2w imaging with lenticular shaped, tumour suspicious lesion anterior in the transition zone on the right side (PI-RADS 4) (arrow) (A), with restricted diffusion on calculated b=1500 trace image (arrow) (B) and on ADC-map (C). In D the side-by-side fusion of the T2w image (left) and ultrasound image (right) with the target encircled in green. The biopsy needle is visual along the dotted line in the ultrasound image. The Gleason score from targeted biopsies revealed a 4+3=7 tumour that on postoperative specimen turned out as 3+4=7. Note the compression of the prostate projecting the green circle in the ultrasound image posterior to the true target, due to the rigid type of software used.

After assessment of MRI, using the information from functional and morphological sequences, the tumour suspicious areas are graded in accordance with PI-RADS [89]. The

biopsies are subsequently targeted towards the tumour suspicious area (usually PI-RADS 3-5) either directly in the MRI gantry (in-bore) [90] or by fusing the MRI images with the ultrasound images (MRI/US fusion) [91] (Figure 11). If those techniques are not available cognitive fusion is an option where the TRUS biopsies are directed toward the tumour suspicious location on MRI using anatomical landmarks [83]. Fusion guided biopsies are very useful in men with a previous negative systematic biopsy and remaining suspicion of prostate cancer [92] or prior to the second biopsy round before entering an active surveillance program [93,94].

1.5 TEAM CONFERENCES

Multi-disciplinary team (MDT) conferences have become the preferred system of communication of health care in oncological patients [95]. The system is based on both technical and non-technical factors. Technical factors include patient related information (preoperative variables, co-morbidities, psychosocial aspects and patients' choice), expert reviews of radiological and pathological findings, recording of the decision from the MDT and technical support with videoconference equipment, all of which will affect decision making [95]. Non-technical factors are team member attendance, leadership, discussions and consensus as a team and finally conveying the decision to the patient [95]. Two crucial aspects are dynamics within the team for fruitful and open discussions and that the patient's expectations are taken into account. In many guidelines pre-treatment MDT is recommended for optimal patient care and has been shown to improve oncological outcome in rectal cancer compared to no MDT [96].

1.6 SURGERY

The first radical prostatectomy as treatment for prostate cancer was first described by Hugh Hampton Young in 1905 [97]. He used a perineal approach and it was not until 1945 that Terence Millin described a retropubic procedure in the Lancet [98]. This achievement was applauded by the surgical community and in an anonymous editorial was compared to other great advances such as those of Lister and Bilroth, among others. In 1979 Reiner and Walsh introduced the ligation and control of the dorsal venous complex in order to reduce bleeding complications, earlier a great cause of morbidity and mortality at radical prostatectomy [99]. The introduction of nerve sparing retropubic radical prostatectomy by Walsh in 1982 provided the opportunity to preserve sexual function [100].

The main issue in prostate cancer surgery is the balance between oncological and functional outcome. A good oncological outcome is negative surgical margins and no lymphnode metastases whenever lymph-node resection is carried out. A poor oncological outcome is positive surgical margins (PSM) and/or lymph-node metastases. PSM is leaving cancerous tissue behind. These are most often minute (≤ 3 mm in length) and usually do not introduce the risk of disease recurrence, whereas cases of extensive (≥ 3 mm) or multifocal PSMs lead to a higher frequency of biochemical recurrence (BCR), especially in high grade tumours [101-103]. Functional outcome measures are sexual potency and urinary continence. Many definitions on urinary continence exist but mainly pad/leakage free is considered the optimal outcome. A pad is a small absorbent disposable diaper used in urinary incontinence. In erectile function the International Index of Erectile Function (IIEF-5) is the standard assessment tool [104]. An IIEF-5 score over 21 means no erectile dysfunction. The risk of PSM increases in surgery when a nerve preserving surgical strategy is chosen or when the tumour grows outside of the prostatic confinement. In a nerve sparing operation the surgical plane is either intra- or interfascial (Figure 12 A-B) close to the capsule, especially at the dorsolateral aspect of the prostate where the important nerves for erectile function and also urinary continence run. Whenever the tumour is suspected to grow outside the confinement of the prostate a non-nerve sparing (extrafascial) procedure is chosen, in order to reduce the risk of PSM, but at the cost of decreasing the chance of retained erectile function (Figure 12 A, C-D).

Urinary continence is also dependent on the urethral length and the surgeon therefore tries to save as much of the lower sphincter as possible by cutting the urethra as close to the apex as possible. By doing so the risk of PSM is increased if the tumour is located at the apex. Another surgical consideration is bladder neck preserving surgery or not, depending on tumour location. Tumours in the anterior fibromuscular stroma (AFS) at the base may invade the bladder neck as well as tumours in the transition zone at the base.

In high-risk patients a lymph-node dissection is always considered for staging purposes, taking the patient's comorbidities into account. Due to the fact that up to 10% [105] and even as high as 51% [106] of patients experience lymphoceles and to the increased in risk of postoperative deep venous thrombosis and lung embolism after lymph node dissection, patient selection must be meticulous [107].

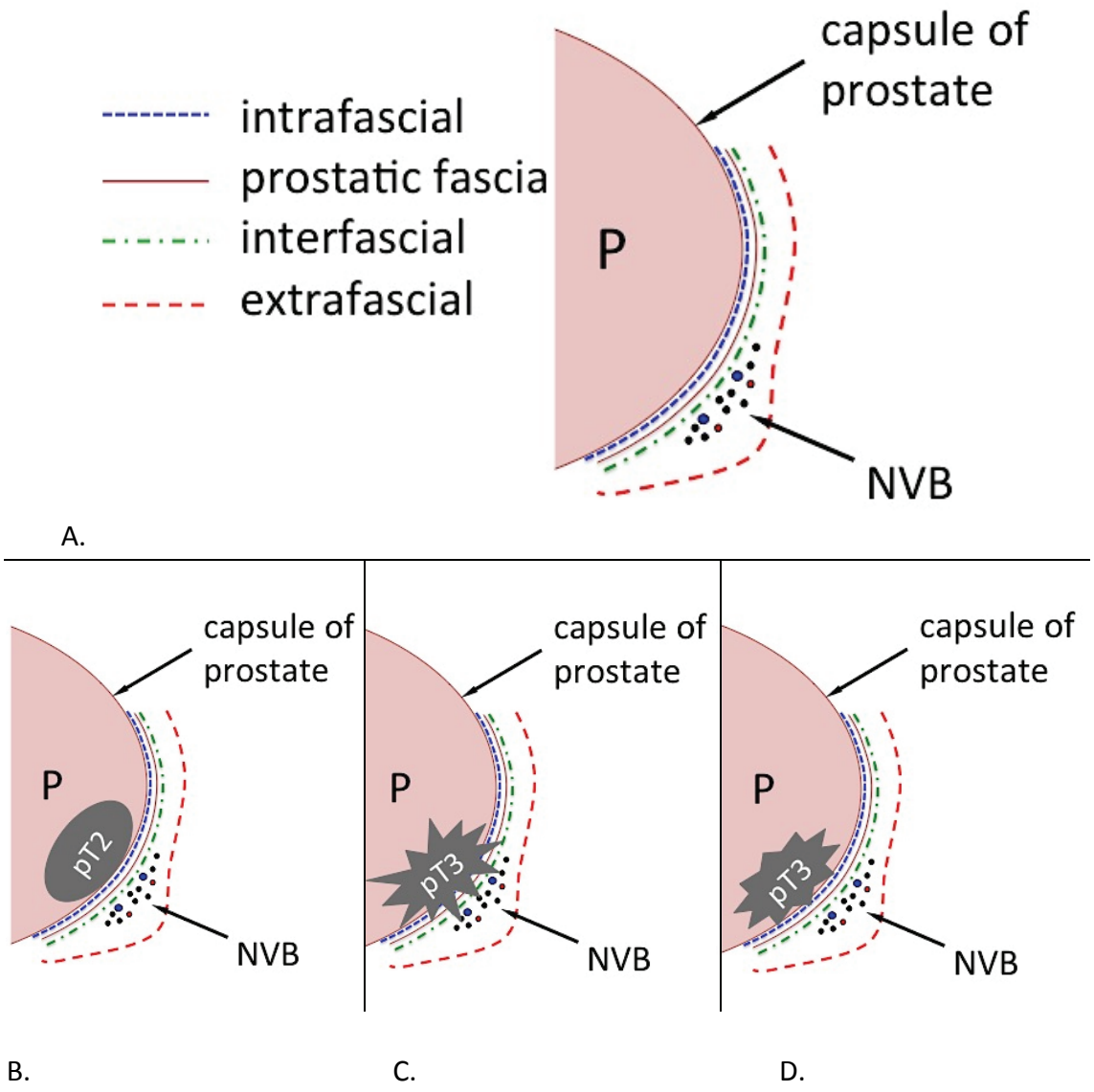

Figure 12 A-D. Surgical planes in prostate cancer surgery (dotted lines) (A). In organ confined disease (pT2) an intra- or interfascial procedure can be used, saving the neurovascular bundles (NVB) thus increasing the chance of retained erectile function and urinary continence (B). In overt extra prostatic tumour growth (EPE) (C) or minute EPE (D) a more radical approach must be taken, usually a non-nerve sparing procedure (extrafascial) to obtain a good oncological outcome.

A lymph node dissection should always be performed as extended pelvic lymph node dissection (ePLND). Extended PLND includes the fibro-fatty tissues bordered anteriorly by the external iliac arteries and posteriorly by the internal iliac arteries up to the iliac bifurcation, laterally by the pelvic wall and medially by the perivesical fat [108]. Whether ePLND is performed only for staging purposes or if it has beneficial effect on oncological outcome is debated and in lack of randomized studies the effect is still unknown.

Surgery is at present performed as open retropubic prostatectomy (ORP) or laparoscopic surgery with or without robotic assistance. The debate on which surgical technique provides the best outcome regarding oncological and functional results is intensively debated in the urological community. The advantage of open surgery is the proprioception not available in laparoscopic instrumentation. Laparoscopic surgery has the favour of magnification of the surgical field. In robotic assisted radical prostatectomy (RARP) hospitalisation is often shorter, perioperative bleeding reduced and reoperation less frequent than in open surgery [109,110]. Regarding urinary continence no difference between techniques used has been noted [111,112] though earlier recovery was seen in the RARP group in bilateral nerve sparing [113]. One study with matched pairs using historical data for ORP showed better functional outcome overall in favour for RARP, but the significance of such a study is questionable [114]. In the LAPPRO study a modest but significant difference was detected in erectile function in favour for RARP over ORP [111]. The positive surgical margin rate was in a large observational cohort study shown to be reduced but only for organ-confined disease [115], whereas it was found to be equal in the randomized study by Yaxley et al. [110] and in the LAPPRO study [111]. One major objection to the randomized study was the difference in surgical experience where the ORP surgeon had performed > 1500 procedures at the start of the study while the RARP surgeon only had performed 200 procedures. Both oncological and functional outcome is highly influenced by the experience and skill of the individual surgeon. In a large systematic review the average rate of PSMs in contemporary RARP series was 15% (range: 6.5-32%) [116] and the learning curve for prostate cancer surgeons in reduction of PSMs steadily improves up to 1600 prostatectomies [117]. Regarding functional outcome significantly better results in postoperative urinary continence was seen for more experienced surgeons but no difference was seen for erectile function [118]. Surgical complications were also reduced in high volume compared to low volume centres where a surgeon on average performs a higher number of procedures [119].

1.7 PATHOLOGY

1.7.1 Gleason scoring of needle biopsy

The Gleason system is histological grading based on different morphological tumour patterns and was introduced in the late 1960s by Donald F Gleason and co-workers and has been used for almost 50 years. In a publication by Gleason in 1974 he included the prognostic value of the different grades proving its usefulness [120]. The system has evolved

over the years with refinement of the attribution of different patterns to respective grade. The Gleason patterns are graded 1 to 5, with 1 being benign adenosis and 5 being the most dedifferentiated pattern. The sum of the two most common patterns, where the primary Gleason pattern is the most abundant pattern plus the secondary pattern makes up the Gleason score. If Gleason pattern 3 is most abundant and pattern 4 is the second most common pattern the score will become 3+4=7. Pathology reports of today only include Gleason pattern 3 to 5, while pattern 1 and 2 are not graded. Cases with pattern 3, 4 and 5 should not be graded 3+4=7 with tertiary grade 5 but instead as 3+5=8 to address the highest grade, since many clinicians uses tables such as Partin's table [121] to calculate risk of EPE, seminal vesicle invasion and lymph node involvement where only two grades are included [122]. Needle biopsies should be taken in a systematic fashion with each biopsy core placed in a separate vial and marked with location from where it was taken, according to the recommended nomenclature for biopsy location from our National Guidelines (Figure 13).

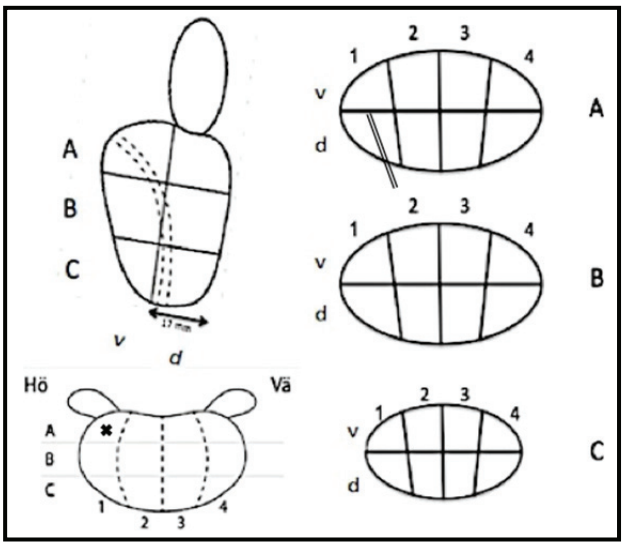

Figure 13. Biopsy template according to the Swedish National Guidelines including axial slices for reporting on tumour location at magnetic resonance imaging (right column). A lateral biopsy at the base on the right side is designated 1Ad (x in the coronal image, and double line on axial image A). If the biopsy is sent in a separate vial to the pathology department and tumour is confirmed at histology then tumour location is known, important for treatment purposes.

1.7.2 Histology of whole mount prostate specimen

After surgery the whole prostate is transported in 10% formal saline [123]. The left and right side is coloured in different colours. The specimen is weighed and measured in three

dimensions. After that the specimen is submerged in 10% buffered formaldehyde for about 24 hours, a process that can be enhanced by injecting formalin into the specimen. The specimen is then cut for embedding in the transversal plane, perpendicular to the dorsal aspect of the prostate in 3-4 mm thick slices. The most basal and apical slices are further cut in the sagittal plane. After embedding the slices are cut into thin slices of a few µm thickness and mounted on glass slides, preferably as whole mounts. The thin slices are stained with hematoxylin and eosin sometimes immunohistochemistry is used to resolve ambiguities. The pathologist reviews every slice under a microscope to determine Gleason grade and sum of observed tumours, size of tumours, the presence of extraprostatic extension, seminal vesicle invasion and positive surgical margins (PSM). In cases where PLND has been performed the presence of lymph node metastasis is reported.
There is some inter-observer variability regarding EPE and surgical margins (SM), even among expert pathologists, especially where the prostate lacks a definable capsule [124]. In a review by van der Kwast of over 500 cases from the EORTC trial an agreement of 57.5% for EPE (κ=0.33) and 69.4% for SM (κ=0.45) was shown compared to local pathology, confirmed by correlation to biochemical progression-free survival [125]. In the LAPPRO study a central review of 289 cases by two reference pathologists revealed downgrading of 3+4 in 45.8%, of 4+3 in 44.2% and of 8-10 in 50% of the cases compared to local pathologists [126]. Central review changed an EPE status to organ-confined in 32% of the cases compared to local pathologists.

The International Society of Urological Pathology (ISUP) released their latest consensus statement on Gleason grading in 2014 [20]. The document introduces a new grading system based on the Gleason system but providing prognosis groups rather than histological patterns alone. The tumours are divided in ISUP-grade groups 1-5 as follows:

- Grade Group 1 (Gleason score ≤ 6)
- Grade Group 2 (Gleason score 3+4=7)
- Grade Group 3 (Gleason score 4+3=7)
- Grade Group 4 (Gleason score 4+4=8, 3+5=8 and 5+3=8)
- Grade Group 5 (Gleason score 9-10)

2 AIM OF THESIS

2.1 GENERAL AIM

The aim of this doctoral thesis has been to explore ways to improve preoperative local tumour staging in prostate cancer. The target area has been imaging, using MRI in this perspective, but the use of predictive models in foreseeing tumour growth outside the prostatic capsule has also been explored.

2.2 PAPER I

Observational study analysing oncological and functional outcomes 12 months after treatment of very low-risk prostate cancer with radical prostatectomy in men who could have been candidates for active surveillance.

2.3 PAPER II

The aim was to build an externally validated prediction model (nomogram) predicting extraprostatic tumour growth in men with clinically organ-confined disease from a prospectively gathered cohort of men who had undergone radical prostatectomy.

2.4 PAPER III

To investigate the additional value of adding a three-dimensional T2-weighted sequence with multi-planar reconstructions, including radial reconstruction, in local staging of patients receiving a preoperative prostate MRI.

2.5 PAPER IV

The objective in this observational cohort study was to compare the degree of nerve sparing and rate of positive surgical margins in men receiving a preoperative MRI and discussed at an interdisciplinary team conference, to men who were not examined with MRI.

3 PATIENTS AND METHODS

3.1 PAPER I

The Swedish health care system is almost entirely tax funded and patients are dependent on the health care provider in their county. The prospective multi-centre Laparoscopic Prostatectomy Robot Open (LAPPRO) trial [127] includes patients that between September 1st 2008 and November 7th 2011 received a prostate cancer diagnosis and were planned to undergo radical prostatectomy at 14 different surgical centres, reflecting both high and low volume hospitals in prostate cancer surgery. The LAPPRO trial includes pre- and postoperative data at 6-12 weeks, 12 and 24 months after surgery, as well as pre- and postoperative patient questionnaires at 3, 12 and 24 months. All patients fulfilling the very low-risk criteria according to the Swedish National guidelines (T1c, PSA concentration < 10 ng/mL, PSA density < 0.15 ng/mL/cm^3 and Gleason sum 6 in up to four positive biopsy cores, with a total biopsy cancer length of ≤ 8 mm) were included. From the database of the LAPPRO trial 338 of totally 4003 patients met the inclusion criteria. Outcome data considered adverse pathology and patient-reported functional outcomes at 12 months. Adverse pathology included pT3 status and/or Gleason score ≥ 7, positive surgical margins and a PSA > 0.1 ng/mL at 6 to 12 weeks postoperatively.

Patient reported outcome reflected urinary continence and erectile function according to the 2nd question in the International Index of erectile Function-5 (IIEF-5). The use of < 1 pad/24 h was considered continent and erectile function as “Erection hard enough for penetration more than half of the times after sexual stimulation” at 12 months postoperatively. Frequency of trifecta i.e. patients with no biochemical recurrence, urinary continence and with erectile function according to the above definition was assessed. Outcome for different surgical approaches i.e. bilateral or unilateral or non-nerve sparing technique was also assessed.

Statistical analysis

Frequencies and proportions for the different measured outcomes stratified into men below and above 60 years of age at surgery were calculated. Fisher’s exact test assessed statistical differences between age groups and all testing was done as two-sided at a 5% significance level. Fisher’s exact test is used to detect significant differences between two groups with categorical data or when having few observations. Significance testing can

either be done as hypothesis testing using p-values or as estimations using confidence intervals (CI), the result is the same but estimations are more informative since you receive the range of likely values within the CI of 95% and information on sample size. A large sample size under normal circumstances gives a narrow CI while a wide CI indicates a smaller sample, information not provided when using hypothesis testing receiving a p-value. Significance testing can be used whenever we want to draw a conclusion if a difference between groups really exists or not. When using hypothesis testing a p-value of 0.05 is considered significant, meaning that we accept a 5% risk of receiving a false difference between groups. To test whether our group estimates are separated we can create confidence intervals, usually with a range of 95%, i.e. the received mean of our test for each group contains the true mean with 95% probability and if the confidence intervals of the two groups don't overlap there is a significant difference.

3.2 PAPER II

From the LAPPRO study database (described in study 1) we extracted all men with clinically organ-confined disease i.e. patients with DRE T1c-T2. Information on pathological T-stage was used to create the prediction model. The cohort for external validation was extracted from the largest clinic in the LAPPRO study, with patients outside the timeframe of the inclusion period of the LAPPRO study. To build the prediction model we considered previously reported variables like PSA, biopsy Gleason score and mm of cancer in the biopsies, but also tested for other variables that could be relevant for the outcome pT3 (non-organ confined disease) such as prostate volume and BMI. The prediction model was validated internally, internally-externally and externally (described below).

Statistical analysis

In univariable logistic regression each single considered variable (independent variable) is tested to predict the outcome (dependent variable), in our case pT3, presented as odds ratio (OR) with 95% confidence intervals (CI).

To address the problem with missing values often encountered in clinical studies due to non-compliance in filling out questionnaires by patients or missed reporting by doctors in a busy daily routine, we used imputations to complete the data set. Missing values were replaced by a value using a regression model from all the other potential available variables [128]. In the process of imputation we created 100 new complete data sets to reduce the risk

of bias as compared to having created only one imputation set. On the 100 new imputed data sets we performed multivariable logistic regression modelling for the outcome pT3. In the multivariable logistic regression analysis all the considered variables were used in the modelling, thereby eliminating the confounding by the different included variables. The effect of each variable is "unconfounded" in the multivariable regression analysis by the others [129]. The multivariable regression analysis was repeated for all the 100 imputed data sets, one at a time, to select the model variables by using automated backwards elimination. The remaining variables for each of the 100 sets that were in majority were then globally selected to build the model. The globally selected variables were subsequently used to build the final model.

Validation of the model was carried out using internal ten-fold cross-validation (i), external-internal (ii) and external validation (iii). (i) In ten-fold cross-validation the patient data set is randomly divided into ten sets with equal amount of patients. Nine of the sets are then used to create a model with the globally selected variables and the tenth set is used to validate the model. This is repeated ten times so that each set has been used to validate the model. (ii) In internal-external cross-validation each of the 14 centres were tested against a model created by the remaining centres. (iii) The model was further validated using an external cohort derived from the largest centre in the study. The ability of the model to discriminate pT3 status was assessed with receiver operating characteristics (ROC) with area under the curve (AUC) (Figure 14). ROC is a line-graph that illustrates the probability of a true positive result (sensitivity, y-axis) against the probability of a false positive result (specificity, x-axis). The sensitivity and the specificity of the model to predict non-organ confined disease (pT3) from organ-confined disease (pT2) at different probability levels are plotted into the graph. The area under that curve is called AUC and a perfect discriminant tool has an AUC = 1. An AUC of 0.7 is considered fair and an AUC of 0.5 no better than flipping a coin.

As a sensitivity analysis we included "centre" as a variable in our model to assess potential differences in pathological staging and/or other included variables between different centres. The assessment also included testing for interactions between "centre" and the other variables, i.e. if the other variables potentiated the effect of "centre". If "centre" were neutral in the analysis, i.e. no difference between centres in assessment of the included variables, it would not show significance to the outcome pT3.

From the model a prediction tool called nomogram was created (Figure 15). The tool can be used to preoperatively assess the risk of an individual having extraprostatic tumour growth. Each included variable in the nomogram for a single patient is plotted into the respective variable-line and a vertical line is drawn from that point to the top Point scale to receive a point for that variable. This is continued with all variables, giving a point for each variable. The points are then summoned and placed on the Total point scale after which a vertical line is drawn downwards to the predicted probability line (probability of having pT3). A high probability of EPE approaches 1. Depending on the decided probability cut-off, a specific sensitivity/specificity level of risk of having pT3 is chosen.

3.3 PAPER III

Great efforts have been made in improving sensitivity of local staging of prostate cancer using MRI. In this retrospective study we assessed the staging performance of two radiologists reading two different sets of preoperative MRI images of 100 consecutive men who had undergone radical prostatectomy. The first set included two-dimensional (2D) T2 weighted images and the second set included two and three-dimensional (3D) T2 weighted images with multi-planar reconstructions of the 3-D images and a radial reconstruction. Each set also contained DWI and T1 weighted images. Index tumour detection and assessment of extraprostatic disease was done using a 5-grade scale where 1 indicated either “no tumour” or “no suspicion of EPE” and 5 indicated either “tumour is highly likely to be present” or “measurable extraprostatic disease is present”. The tumours were plotted in the previously described template (Figure 9). The sets were evaluated with a period of at least 2 months apart to reduce the risk of recall bias. Reports from pathological evaluation of radical prostate specimen were used as gold standard.

Statistical analysis

Sensitivity of detecting the index tumour was established by comparing the tumour location from the reports by the two radiologists with the pathology reports. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for EPE were calculated for each radiologist and for each set. The sensitivity and specificity for EPE for each grade on the 5-grade scale was calculated and plotted into an ROC curve with an AUC. ROC curves for the two readers for the two different sets were created.
The correlation between the two readers when assessing EPE at the two different reading modes was calculated using Cohen’s kappa (κ). Cohen’s kappa assesses the inter-rater

agreement for each case resulting in a value for all patients ranging between 0 and 1. Cohen's kappa does not take into account whether the assessment as compared to pathology is accurate or not. The interpretation of Cohen's kappa is performed as follows; < 0.20 = poor agreement; 0.21−0.40=fair agreement; 0.41−0.60=moderate agreement; 0.61−0.80=good agreement; 0.81−1.0=very good agreement.

3.4 PAPER IV

The inter-disciplinary team conference was introduced in October 2013. The team is comprised of one radiologist and the team of prostate surgeons and convenes on a weekly basis. Patients having performed a preoperative MRI were discussed and a consensus reached on surgical approach, taking preoperative characteristics, tumour location, risk of EPE and patients' own wishes into account. To evaluate the outcome from introducing such an intervention we needed a comparison group. A historical comparison usually inherits unforeseen bias and was ruled out early on. For comparison a group of men operated on without a preoperative MRI at Karolinska University Hospital during the same time frame was chosen. Most patients in that group had less aggressive preoperative tumour characteristics. Adjustments for preoperative characteristics had to be carried out to address that issue and was performed as described below.

Between October 2013 and June 2015, 1027 patients had prostate cancer surgery at Karolinska University Hospital. Six hundred and seventeen (617) had a preoperative MRI, performed at 25 different MRI departments, of which 573 were discussed at the inter-disciplinary team conference and those were assigned to the MRI group. The non-MRI group consisted of 410 patients and method of operation in this group was chosen according to each surgeon's own judgement.

At the team conference the patient's preoperative characteristics, i.e. level of PSA, number of positive biopsy cores, mm of cancer in the biopsies, Gleason score and general health was presented. Thereafter findings on MRI, i.e. tumour locations, risk of EPE, seminal vesicle invasion (SVI), lower sphincter and bladder neck invasion as well as any suspicion of lymph node and bone marrow metastasis was presented. After gathering all findings a consensus in the urology team on surgical approach was taken.

Two radiologists with 3 years of experience in prostate MRI at the start reviewed most of the cases. Ten surgeons performed the RARPs and surgeons with an experience of over 100 previous RARPs operated 81% of the cases.

Statistical analysis

Sensitivity and specificity of clinical and MRI staging compared to prostate whole-mount histology was calculated, summarized and presented as ROC curves.
We used log linear regression analysis to calculate relative risk (RR) ratios with 95% confidence intervals (CI) for the association between MRI and positive surgical margins (PSM). To obtain comparable groups (MRI vs. non-MRI) due to the differences in preoperative tumour characteristics we made adjustments using stabilized inverse probability weights (SIPWs). We first estimated the propensities of their MRI status (dependent variable), i.e. receiving or not receiving MRI, using logistic regression with the preoperative variables PSA, Gleason score, mm cancer and clinical T-stage as predictors (independent variables). The data of each patient was then weighted by their SIPW, i.e. the product of the overall probability of their respective MRI status and the inverse estimated propensity of being assigned to their actual MRI status. A patient in the non-MRI group with aggressive tumour characteristics would then get a high score, as would a patient in the MRI group with more benign tumour characteristics. By doing so the groups were “pulled towards” each other to be more alike and thereby comparable. Along each patient with their respective weights the pathological outcome i.e. pT-stage and PSMs is also attached. High SIPWs were truncated so that a patient could only be counted a maximum of 4 times. All statistical testing was done two-sided at a significance level of 5%. All patients with missing data were excluded from the analysis.

4 RESULTS

4.1 PAPER I

Adverse pathological outcome with upgrading to pT3 and/or Gleason score ≥ 7 was seen in 34% (115/333) of all the patients. No patient turned out with Gleason ≥ 8. PSM was seen in 16% of the cases and PSA > 0.1 ng/mL at 6-12 weeks postoperatively in 2.1% (7/329). At 12 months 2.4% (8/334) had biochemical recurrence (BCR).

Table 2. Functional outcome stratified by age group. (IIEF= International Index of Erectile Function, NS=Nerve Sparing, Q=Question)

Characteristic	Age 39-59 n/N (%)	Age 60-74 n/N (%)	p
Surgical approach			
Bilateral	102/124 (82)	140/213 (66)	
Unilateral	18/124 (15)	36/213 (17)	<0.001
None	4/124 (3)	37/213 (17)	
Erectile function 12 months postoperatively; preoperative IIEF > 21 + bilateral NS:			
IIEF 2nd Q: ≥ about half the time	34/74 (46)	48/98 (50)	0.759
IIEF > 21	16/59 (27)	17/62 (27)	1.000
Urinary continence 12 months postoperatively; -preoperative one pad or less/24 h + bilateral NS			
Change of pad less than once per 24 h	75/81 (93)	106/125 (85)	0.126
-preoperative pad-free/leakage-free + bilateral NS			
Pad free and leakage-free	36/71 (51)	59/107 (55)	0.646
Trifecta at 12 months			
Yes	34/87 (39)	50/134 (37)	0.887
No	53/87 (61)	84/134 (63)	

Of men with preoperative status <1 pad changed per 24 h, 84.2% remained so 12 months after surgery. Of preoperatively continent men, 52% were fully continent 12 months after surgery. In men with preoperative "Erection hard enough for penetration more than half of the times after sexual stimulation" 44% remained so at 12 months postoperatively. Only 27% (41/150) had full erectile function 12 months after surgery (IIEF > 21) among men

with IIEF > 21 preoperatively. There was no significant difference between age groups regarding functional outcomes (Table 2, previous page).

4.2 PAPER II

From the LAPPRO database 3386 men fulfilled our inclusion criteria. Of these men with clinically organ-confined disease 26.8% had non-organ confined disease at pathology. In the validation cohort the corresponding figure was 22.6%. The selected variables in the multivariable regression analysis was age, ln [PSA], ln [millimetre cancer/biopsy core] (ln [mmCa/biopsy]), biopsy Gleason score, ln [prostate volume] and body mass index (BMI). The variable with the highest AUC of 0.669 (95% CI 0.647–0.688) was ln [mmCa/biopsy core]. When applying the full model on all patients an AUC of 0.741 was received (Figure 10). At ten-fold cross validation (internal validation) the AUC was 0.738. The internal-external validation revealed great heterogeneity between different centres in the study with AUCs ranging from 0.476-0.892. Upon validation using the external cohort the AUC was 0.699.

When we included “centre” as a variable it showed significance to the outcome (p<0.001).

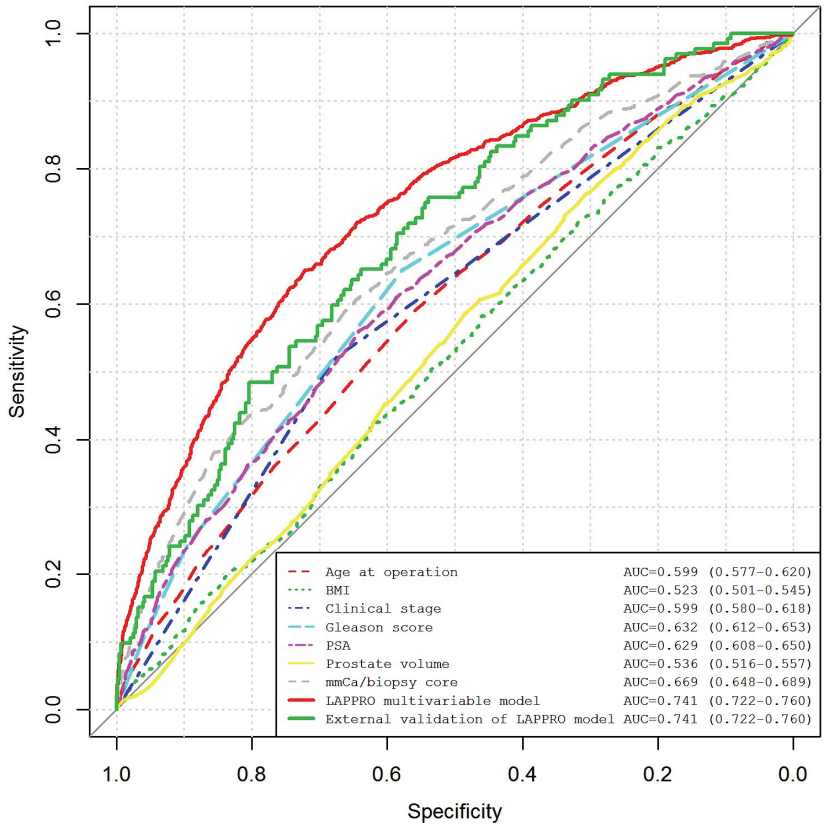

Figure 14. Receiver operating characteristic (ROC) with area under the curve (AUC) for the included variables and the full multivariable model as well as the external validation cohort.

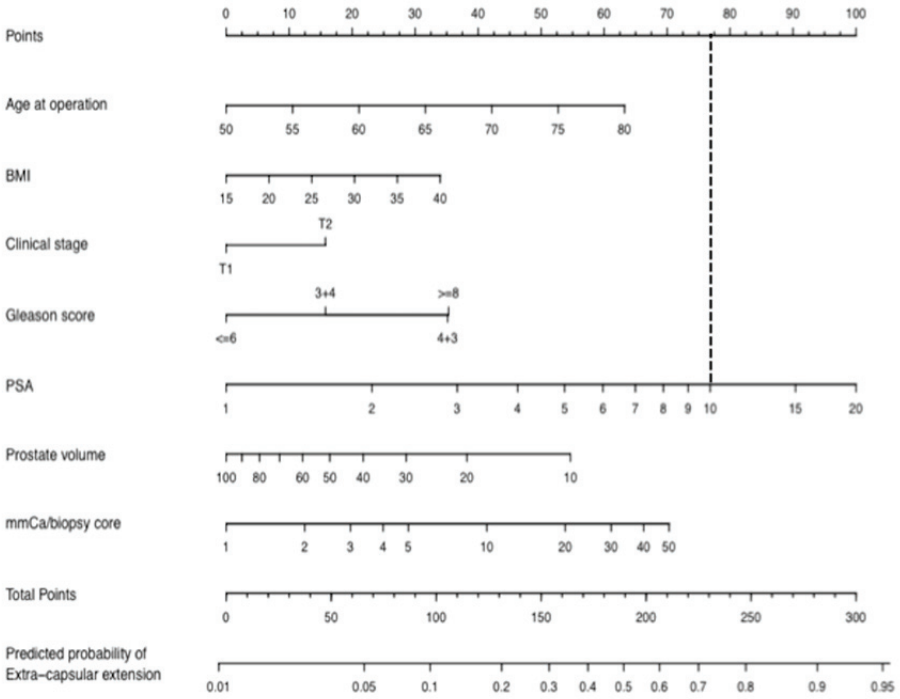

Figure 15. The prediction model presented as a nomogram. The included variables on the left each have a scale. The values for an individual patient for each variable are plotted and from that point a vertical line is drawn to the upper hand Point scale (see dashed line from PSA 10 ng/mL receiving 77 points, as an example). The received points for each variable is summoned and by placing the sum on the Total Points scale and from there drawing a vertical line down to the Predicted probability line the probability of having extra capsular extension is obtained.

4.3 PAPER III

Of the 100 included patients 6 were excluded due to technically inadequate examinations. In the remaining cohort of 94 patients 39 (41%) were pT3 and 55 (59%) were pT2. When assessing the 2D image set the two radiologists identified 80% vs. 83% of the index tumours and upon adding the 3D set 83% vs. 78% respectively. By choosing the cut-off on the 5-point grading scale for assessment of EPE ≤ 2 for organ confined disease and ≥3 for non-organ confined disease the sensitivity, specificity, PPV and NPV for EPE evaluating the 2D set was 77%, 48%, 56% and 70% versus 74%, 64%, 58% and 78% respectively for the two readers. Corresponding figures when adding the 3D sequence yielded 77%, 43%, 52% and 69% versus 69%, 59%, 60% and 68% respectively for the two readers. The inter-rater correlation according to Cohen's kappa (κ) using the 2D set was 0.42 (moderate agreement) and when adding the 3D set 0.17 (poor agreement).

4.4 PAPER IV

MRI detected 80.8% of the index tumours with an AUC of 0.74 for discrimination pT3 from pT2 when compared to pathology of the prostate specimens. MRI assessment for EPE generally had a high sensitivity of 80% with a low specificity of 57% thereby prioritizing oncological before functional outcome, since a described risk of EPE would make the surgeon more reluctant to perform a nerve sparing procedure.

Positive surgical margins (PSMs) were generally high in both groups but with an adjusted RR of 0.73 [95% CI 0.59-0.91] of PSMs in the MRI group. On the other hand more non-nerve sparing procedures were seen in the MRI group with a RR of 1.86 [95% CI 0.59-0.91] compared to the non-MRI group after adjustments.

5 DISCUSSION AND CONCLUSIONS

The papers in this thesis have been undertaken with the attempt to improve local staging in prostate. The objective of correct local staging is to avoid overtreatment in men with organ-confined disease so that they will retain erectile function and urinary continence as well as avoiding under-treatment in men with non-organ confined disease with risk of positive surgical margins and disease recurrence.

In *Paper 1* we explored the outcomes for a group of patients that according to current diagnostic standards are designated "very low-risk" but in fact contains cases with a higher risk category when evaluated post surgery at pathology. As many as 34% of the patients turned out with adverse pathology i.e. Gleason score ≥ 7 and/or pT3, illustrating the shortcomings of systematic biopsies and digital rectal exam (DRE) in predicting correct local stage. In a series of 300 patients Gleason upgrading from biopsy Gleason score ≤ 6 to specimen Gleason score 3+4=7 was seen in 47% of the cases [130]. A pre-biopsy MRI with fusion-guided biopsies would lead to better targeting of significant tumours [84] and the MRI could to some extent reduce the number of unexpected pT3 tumours [82], thereby potentially lowering the proportion of positive surgical margins of 16% further. The poor outcome regarding postoperative continence and erectile function reflects the risks following prostate cancer surgery. This should be an important point of discussion when counselling patients with very low-risk cancer where active surveillance is the proper treatment option. The high frequency of patients in this study with adverse pathology postoperatively stresses the need for MRI with subsequent targeted biopsies prior to engagement in an active surveillance program.

In *Paper 2* we attempted to build a preoperative prediction tool (nomogram) to be used in clinical practice to predict the risk of having non-organ confined disease in patients with clinically organ-confined tumours. The internal-external validation of the nomogram revealed large heterogeneity between centres with a prediction performance with AUCs ranging from 0.476 to 0.892. The main reason to be found was the difference between centres in assessing pT-stage and to some extent Gleason scoring [125,126]. Documents on how to assess and report biopsy and postoperative specimen pathology exist [123,131,132], but the final report is dependent on the knowledge and expertise of the individual pathologist. This could be one main reason for the poor outcomes of external validations of prediction

models created elsewhere [133,134], sometimes explained by genetic differences between the populations where the prediction model was created and the validation cohort [133]. This stresses the importance of validating the pathology data in large trials [125] and to validate any nomogram used in clinical practice [135].

In *Paper 3* an attempt was made to improve local staging by adding a three-dimensional (3D) T2w sequence to the recommended two-dimensional (2D) T2w images. The 3D images were reconstructed in a radial manner to intercept the capsule at a 90° angle to overcome the problem of partial volume effect at the capsule seen at the curved portions of the prostate in traditional 2D T2w images, making the assessment of EPE difficult. This study could not show any improvement in staging performance using the 3D sequence. The lower spatial resolution in the 3D images compared to the higher spatial resolution of 2D pulse sequences in their acquired plane, proved to be a disadvantage in making the distinction between organ and non-organ confined tumours. The time to acquisition of the 3D images is longer compared to 2D images, which also could be explanatory, since it can introduce movement artefacts giving an inexact rendering of the true anatomy.
Using a retrospective study design could generate hypotheses for future studies, but have the downside of creating an artificial setting not reflecting a real clinical situation where assessments made would make a difference for a single patient and the outcome of such studies could therefore be misleading. Further work is needed to make the staging performance more accurate using MRI. Functional imaging with improved diffusion weighted protocols might be an adjunctive technique to morphological imaging.

In *Paper 4* we assessed the combined effect of MRI and a preoperative inter-disciplinary team conference on the frequency of positive surgical margins after robot-assisted laparoscopic prostatectomy and the degree of nerve sparing. We compared the outcome of the MRI group with a group of patients who were operated on during the same time period without having had a preoperative MRI. The surgical margins were significantly reduced in the MRI group but at the expense of more cases receiving a non-nerve sparing surgery. This is due to the known poor sensitivity of MRI in detecting EPE. We chose to have a high sensitivity at the EPE assessment by including the indirect sign, 'length of tumour abutment to the capsule' ≥ 12 mm as risk of EPE, with a trade-off for fewer nerve sparing procedures, prioritizing the oncological before the functional outcome. The sensitivity and low specificity could partly be explained by the varying quality of the MRI examinations

coming from 25 different departments with differing methodology. The take-home message from this paper is that MRI contributes to reduce PSMs, lowering the risk of disease recurrence, but at the expense of more radical surgery and risk of a worse functional outcome, resulting in reduced quality-of-life for the patient. A limitation of the study is the lack of information on functional outcome, which did not enable us to fully explore these issues. A large randomized study is needed to fully address these questions.

In conclusion; not disregarding the fact that prostate cancer under some circumstances is a deadly disease, even more men are living with the disease with different degrees of functional impairment. Future work has to focus on standardization of all aspects in the chain of diagnostics and of treatment procedures of prostate cancer.

6 FUTURE ASPECTS

This thesis reveals several issues that in the future need to be explored to improve patient outcome in prostate cancer care, both in regard to oncological and functional recovery, reducing morbidity and increasing quality of life. Depending on the patient's wishes on what matters (oncological vs. functional outcome) preoperative counselling is of outmost importance, since an optimal result regarding both aspects is possible in organ-confined disease only.

Described below are studies not part of this thesis but future work part of the on-going quest to improve prostate cancer care.

PSA screening has been shown to reduce mortality rates but at the same time increasing the overdetection of indolent cancers, raising the question of where the balance between benefit and harm lies [136]. In the future there is a need for better algorithms in selecting the right patients at risk of harbouring significant tumours that require treatment. The STHLM 3 study using different plasma protein biomarkers, genetic polymorphisms and clinical information could be such a tool and has shown beneficial result in reducing the number of men in need for biopsies without a reduced number of Gleason ≥ 7 tumours compared to PSA alone [137]. Moreover it reduced the number of "insignificant" tumours (Gleason 6) by 17% and detected 19% of the significant tumours in the PSA range of 1-2.99 ng/mL, below the cut-off used for going forth with biopsies when benign causes have been ruled out. Still 54% of the tumours detected in STHLM 3 were of low grade Gleason 6. An on-going study is evaluating the benefits of the STHLM 3 algorithm in conjunction with a

pre-biopsy MRI and subsequent targeted biopsies aiming at reducing the number of insignificant tumours further. Patients will in the first exploratory phase of the study also have systematic biopsies taken. If a high negative predictive value of MRI, with the bi-parametric screening MRI protocol included in the study, can be achieved, then men without tumour suspicious lesions on MRI do not have to be biopsied.

Prognostic information using biomarkers differentiating ductal from acinar cancer, retained in the biopsies apart from the Gleason score, has so far been over-looked and could indicate the need of further imaging workup in patients with high risk of generalized disease [138]. Imaging workup could include an extended MRI protocol using whole body diffusion weighted imaging [139], PET-CT or PET-MRI with new tracers such as prostate specific membrane antigen (PSMA) as a biomarker [140].

Multi-disciplinary teamwork is essential to further improve treatment and patient outcome. The team should include representatives from radiology, pathology, urology, oncology and contact nurses and uro-therapists to take all aspects of the patient and his disease into account prior to treatment. A clinical study will soon be started to evaluate a prostate cancer specific platform for gathering of all clinical data on the patient as well as patient questionnaires. The platform gathers information from many different sources and will be able to push data to different registries, to overcome the excessive double reporting that is an unnecessary workload. The platform will be a foundation for the MDT to facilitate the presentation of all relevant information as well as the topographic presentation of tumour location. The rationale is to make the MDTs more effective, doctors' work-life smoother and to ultimately provide an improvement of the patient's experience of health care.

To further assess the use of a preoperative MRI a randomized study in patients with intermediate risk cancers, allocating patients to either a preoperative MRI or no MRI has been commenced by our team. We want to evaluate its value in directing towards an optimal surgical plan. As primary endpoint the rate of positive surgical margins in the two groups will be compared. The secondary endpoints will be functional outcome including urinary continence and erectile function as well as biochemical recurrence one year after surgery.

The on-going debate concerning the treatment-of-choice in high-risk patients has not been concluded. The recently published ProtecT study revealed no significant difference between patients receiving surgery or radiotherapy in patients with localized prostate cancer regarding mortality, disease progression and metastasis ten years after treatment [141]. Whether there is a difference between these treatment modalities on cause-specific survival, metastasis free survival and quality of life in high-risk patients, with pT3 status is not known. This is studied in the Scandinavian Prostate Cancer Group (SPCG) study 15 (SPCG-15) where patients with locally advanced disease are randomized to either surgery + radiotherapy if necessary or radiotherapy + androgen deprivation treatment (ADT). MRI is recommended as a local staging tool in the study.

Active surveillance (AS) is a treatment option advocated in patients diagnosed with very-low risk or low risk cancer (Gleason < 7 and a PSA below 10 ng/mL). Active treatment is deferred and the patient is carefully monitored with PSA levels and digital rectal exam, until curative treatment is initiated at signs of disease progression or at the patient's wish. MRI has shown to be a promising tool to rule out significant disease that needs treatment prior to enrolment in an AS program, but its use in monitoring patients on AS has not been fully investigated and there are no definite criteria on how evaluation should be carried out or what "triggers" for disease progression to use [94]. This will be studied in the SPCG-17 where patients with both low and intermediate risk (Gleason 7 with no more than 30% cancer cores or 10 mm cancer) cancers will be included. The reason to include patients with biopsy Gleason 7 is the change in Gleason grading by the ISUP in 2005 [122], implicating that a patient with entirely 98% Gleason grade 3 and 2% grade 4 component in the needle biopsy was given a 3+4=7 score as compared to previous grading where the grading would have been 3+3=6. The study includes MRI for all patients every second year and patients are randomized into two different "trigger" groups for change from AS to treatment with curative intent. One trigger group is followed according to current practice and one with fixed triggers such as MRI progression i.e. increase in tumour size, increase in PI-RADS score with/without signs of EPE or pathological progression. The end-points are cumulative prostate cancer specific survival with prolonged stay within AS and better quality-of-life for both the patient and the doctor when using standardized triggers for treatment intervention.

Great efforts to improve diffusion weighted imaging (DWI) in detecting prostate cancer are made. As part of a closed MRI study, not yet analysed, on 29 patients diagnosed with prostate cancer who underwent a preoperative investigation, 6 different DWI techniques were tested in a multi-parametric protocol. One technique that shows promising results is microscopic fractional anisotropy, which analyses the cellular eccentricity and orientation within the tissues using both linear and spherical tensor diffusion techniques. It is shown that microscopic fractional anisotropy is higher in tumour tissue compared to normal tissue. Making direct comparison with pathology will further assess this. The goal is to find a diffusion technique that better distinguishes normal tissue from malignant than the standard DWI used today.

To conclude, MRI will in the future play an increasingly important role in the detection of tumours and treatment planning regardless whether it is active surveillance, surgery, radiotherapy or focal treatment. Being the largest cancer group the need for dedicated radiologists is rising with an urgent need for education and training in prostate MRI reading.

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