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Panu Tonttila

MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING FOR THE DETECTION AND CHARACTERISATION OF PROSTATE CANCER

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
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MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL

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PANU TONTTILA

MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING FOR THE DETECTION AND CHARACTERISATION OF PROSTATE CANCER

Academic Dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 1 of Oulu University Hospital (Kajaanintie 50), on 8 May 2020, at 12 noon

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Supervised by
Docent Markku H. Vaarala

Reviewed by
Docent Irina Rinta-Kiikka
Docent Harri Visapää

Opponent
Professor Kimmo Taari

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University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the fifth leading cause of cancer death among the male population worldwide, according to the GLOBOCAN 2018 database (Bray et al., 2018). Current methods to diagnose and characterise prostate cancer with prostate-specific antigen (PSA) measurement, standard random sextant biopsies (SB), and clinical data have established deficiencies. Multiparametric magnetic resonance imaging (MP-MRI) is a promising tool to address these shortcomings.

In the first study of this thesis, we randomized 130 biopsy-naive men with a suspicion of PCa based on abnormal PSA value to pre-biopsy MP-MRI and control groups. Targeted biopsies (TB) from suspicious MP-MRI lesions, if found, were performed in the MRI group in addition to SB. TB did not significantly improve PCa detection rate. In 9/10 patients with a solitary anterior lesion in MP-MRI, clinically significant cancer was diagnosed with TB, while only three cancers, all clinically insignificant, were found with SB.

In study II, the prostatectomy histology of 162 men with preoperative prostate MRI was re-evaluated and compared to original MRI readings. The aim was to estimate the predictive value of MRI lesion maximal diameter to adverse pathological staging. MRI index lesion diameter ≥ 15 mm was an independent risk factor for extraprostatic extension (EPE), positive surgical margins (PSM), and seminal vesicle invasion (SVI). Lesion diameter ≥ 20 mm was a significant risk factor for lymph node metastasis (LNM).

Study III estimated the diagnostic value of MRI for prostate cancer histological subtypes of invasive cribriform Gleason pattern 4 (CA) and intraductal prostate cancer (IDC), which have recently been demonstrated to be adverse pathological features. Prostatectomy histology and MRI images of 124 consecutive men were re-evaluated. MRI identified 90.5% (95% CI 82.8–95.6%) of tumours including any CA/IDC. All 21 tumours with predominantly CA/IDC histology (≥ 50%) were identified with MRI.

In conclusion, the diagnostic value of MRI was limited in a pre-biopsy setting, but it has since been improved through enhanced imaging, reporting, and biopsy protocols. MRI is a promising tool for grading and staging PCa, but it needs to be further studied in prospective trials before implementing in daily clinical use for these indications.

Keywords: cribriform prostate cancer, diagnosis, intraductal prostate cancer, magnetic resonance imaging, neoplasm grading, neoplasm staging, pathology, radical prostatectomy, targeted biopsy

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Tiivistelmä

Eturauhassyöpä on 2018 julkaistun GLOBOCAN tietokannan mukaan ilmaantuvuudeltaan toiseksi yleisin ja kuolinsyynä viidenneksi yleisin miesten syöpä maailmassa. Eturauhassyövän diagnosointi ja syövän luonteen arviointi PSA-veritestin, peräsuolen kautta ultraääniohjauksessa otettujen neulakudosnäytteiden ja kliinisen tutkimuksen perusteella on todettu puutteelliseksi. Eturauhasen monimuuttujainen magneettikuvaus (MK) on osoittautunut lupaavaksi menetelmäksi puutteiden korjaamiseksi.

Väitöskirjatyön ensimmäisessä osatyössä poikkeavan PSA-arvon vuoksi ensimmäistä kertaa eturauhasen neulanäytteisiin ohjatut 130 miestä satunnaistettiin kahteen ryhmään. MK-ryhmän miehille suoritettiin eturauhasen MK ja sen jälkeen otettiin rutiininäytteet ja mahdollisista MK-poikkeavuuksista kohdennetut neulakudosnäytteet. Kontrolliryhmän miehiltä otetiin vain rutiininäytteet. Tulosten mukaan kohdennetut näytteet eivät lisänneet todettujen syöpien lukumäärää tilastollisesti merkittävästi. Kliinisesti merkityksellinen syöpä löytyi kohdennetuista näytteistä 9/10 mieheltä, joilla todettiin yksittäinen eturauhasen etuosassa sijaitseva MK-poikkeavuus. Rutiininäytteissä vain kolmelta heistä löytyi syöpä, joista jokainen oli kliinisesti merkityksetön.

Toisessa osatyössä sama patologi tutki taannehtivasti MK:ssa ennen eturauhasen poistoa käyneiden 162 syöpäpotilaan eturauhasen kudosnäytteet. Löydöksiä verrattiin alkuperäisiin MK-lausuntoihin. Tavoitteena oli selvittää epäilyttävimmän MK-muutoksen suurimman läpimitan ennustearvoa syövän paikallis- ja imusolmukelevinneisyyteen. MK-muutoksen läpimitta ≥ 15 mm oli itsenäinen ja tilastollisesti merkittävä riskitekijä kapselin läpikasvulle, positiiviselle leikkausmarginaalille ja syövän etenemiselle siemenrakkuloihin. ≥ 20 mm läpimitta oli tilastollisesti merkittävä riskitekijä imusolmuke-etäpesäkkeiden löytymiselle.

Kolmannessa osatyössä selvitettiin vastikään huonompaan ennusteeseen liitettyjen tiehyensisäisen eturauhassyövän (IDC) ja Gleasonin luokka 4 seulamaisen, verkkomaisesti rakentuvan alatyypin (CA) erottumista MK:ssa. 124 syövän takia leikatun miehen eturauhasnäytteet ja magneettikuvat arvioitiin uudelleen. 90.5 % (95 % CI 82.8–95.6 %) kaikista vähänkin CA/IDC syöpätyyppiä sisältävistä kasvaimista erottui magneettikuvissa. Sensitiivisyys oli hyvä riippumatta CA/IDC esiintyvyyden %-osuudesta kasvaimissa. Kaikki 21 valtaosin CA/IDC kasvutapaa (≥ 50 %) edustavat kasvaimet erottuivat MK:ssa.

MK:n hyöty diagnostiikalle ennen ensimmäisiä neulanäytteitä oli rajallinen, mutta on sittemmin parantunut kuvaus-, raportointi-, ja näytteenottotekniikoiden kehityttyä. MK on lupaava tekniikka eturauhassyövän levinneisyyden ja pahanlaatuisuuden arvioimiseen. Päivittäinen kliininen käyttöönotto edellyttää kuitenkin eteneviä lisätutkimuksia.

Asiasanat: diagnoosi, kasvainten pahanlaatuisuusluokittelu, kohdennettu biopsia, magneettikuvaus, patologia, prostatektomia, syövän levinneisyysluokitus, tiehyensisäinen eturauhassyöpä, verkkomaisesti rakentuva eturauhasyöpä

Dedicated to Liisa, Juho, Anni, and Olli

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I am grateful to my pathologist colleagues Anne Ahtikoski, MD, PhD, Docent Pasi Hirvikoski, and Docent Saila Kauppila for the high-quality histopathological analyses needed for this study. I had the opportunity to get acquainted with their demanding work, which has a different point of view from mine. During the project, I had an opportunity to concretely see a glimpse of the challenges of pathological diagnostics.

I wish to thank my retired colleagues Professor Pekka Hellström, Professor Olavi Lukkarinen, and Docent Aare Mehik for guidance in my earlier career to become an urologist and to rouse my interest in scientific work, even if it took a while to grow from spark to fire.

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Oulu February 2020 *Panu Tonttila*

Abbreviations

AI	Artificial intelligence
ADC	Apparent diffusion coefficient
AUA	American Urological Association
AUC	Area under the curve
AS	Active surveillance
BCR	Biochemical recurrence
BPH	Benign prostatic hyperplasia
BP-MRI	Biparametric MRI
CA	Invasive cribriform Gleason pattern 4 prostate cancer
CCL	Capsule contact length
CDR	Cancer detection rate
CI	Confidence interval
csPCa	Clinically significant prostate cancer
cT	Clinical T-class
CT	Computed tomography
DCE	Dynamic contrast enhancement
DNA	Deoxyribonucleic acid
DRE	Digital rectal examination
DWI	Diffusion-weighted imaging
EAU	European Association of Urology
EORTC	European Organisation for Research and Treatment of Cancer
EPE	Extraprostatic extension
ERSPC	The European Randomized Study of Screening for Prostate Cancer
ESUR	European Society of Urogenital Radiology
GG	Grade group
IDC	Intraductal prostate cancer
ISUP	International Society of Urological Pathology
LNM	Lymph node metastasis
LUTS	Lower urinary tract symptoms
4M	The Met Prostaat MRI Meer Mans study
MK	Magneettikuvaus
MP	Multiparametric
MRI	Magnetic resonance imaging

MRSI	Magnetic resonance spectroscopic imaging
MSKCC	Memorial Sloan Kettering Cancer Center
NCCN	National Comprehensive Cancer Network
NOC	Non organ confined
OR	Odds ratio
PCa	Prostate cancer
PET	Positron emission tomography
PI-RADS v.	Prostate Imaging and Reporting Data System version
PLCO	The Prostate, Lung, Colorectal and Ovarian cancer screening trial
PRECISION	MRI-targeted or standard biopsy for prostate-cancer diagnosis
PROMIS	Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer
PSA	Prostate-specific antigen
PSAd	Prostate-specific antigen density
PSA f/t	Free to total PSA ratio
PSM	Positive surgical margin
PSMA PET/CT	Prostate-specific membrane antigen positron emission tomography/computed tomography
RF	Radiofrequency
RNA	Ribonucleic acid
RP	Radical prostatectomy
SB	Standard random biopsies of the prostate
SPCG-4	The Scandinavian Prostate Cancer Group Study Number 4
STHLM3	Stockholm3-test
SVI	Seminal vesicle infiltration
T	Tesla
T2w	T2-weighted imaging
TNM-classification	Tumour-Node-Metastasis-classification
TB	Targeted biopsies of the prostate
TPMB	Transperineal template guided mapping biopsies
TR	Transrectal
TRUS	Transrectal ultrasound
US	Ultrasound
USA	United States of America

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Tonttila, P., Lantto, J., Pääkkö, E., Piippo, U., Kauppila, S., Lammentausta, E., Ohtonen, P., & Vaarala, M. H. (2016). Prebiopsy multiparametric magnetic resonance imaging for prostate cancer diagnosis in biopsy-naive men with suspected prostate cancer based on elevated prostate-spesific antigen values: Results from a randomized prospective blinded controlled trial. *European Urology, 69*(3), 419–425. https://doi.org/10.1016/j.eururo.2015.05.024

II Tonttila, P., Kuisma, M., Pääkkö, E., Hirvikoski, P., & Vaarala, M. H. (2018). Lesion size on prostate magnetic resonance imaging predicts adverse radical prostatectomy pathology. *Scandinavian Journal of Urology, 52*(2), 111–115. https://doi.org/10.1080/21681805.2017.1414872

III Tonttila, P., Ahtikoski, A., Kuisma, M., Pääkkö, E., Hirvikoski, P., & Vaarala, M. H. (2019). Multiparametric MRI prior to radical prostatectomy identifies intraductal and cribriform growth patterns in prostate cancer. *BJU Int*, *124*(6), 992-998. https://doi.org/10.1111/bju.14812.

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1 Introduction

Among the male population, PCa is the most frequently diagnosed cancer in 105 of 185 countries of the world and the leading cause of cancer death in 46 countries, especially in Sub-Saharan Africa and the Caribbean (Bray et al., 2018). Major recognized etiological factors are age, African descent, and genetic predisposition, meaning that the main risk factors are unavoidable and the incidence is growing since the worldwide average life span is extending (Attard et al., 2016).

Incidence among populations is highly dependent on the coverage of PSA-based screening. Globally, the national trends in incidence and mortality from the early 1980s to 2016 show conflicting trends because of stage shift, attribution bias of the cause of death when PSA test became available, and improved treatments of both local and advanced cancer (Culp, Soerjomataram, Efstathiou, Bray, & Jemal, 2019; DeSantis et al., 2019; Feuer, Merrill, & Hankey, 1999). In autopsy studies, the prevalence of PCa increases from 5% at the age < 30 years to 59% by age > 79 years (Bell, Del Mar, Wright, Dickinson, & Glasziou, 2015).

PCa incidence in 2017 in Finland was 5 446 and 912 men died of it, 496 at the age ≥ 80. Age-specific mortality has been decreasing since period 1992–1996, but the number of PCa deaths is still increasing due to increasing life expectancy (Finnish cancer registry: Cancer statistics 2017.).

Most histological prostate cancers cause problems only if they are diagnosed. PSA-based screening of asymptomatic populations for PCa, to diagnose it while in local stage for curative treatment, may result in a small potential benefit in some men, but may result in the potential harms of overdiagnosis and overtreatment for many men. Furthermore, sensitivity and accuracy of characterization of diagnosed cancer with current transrectal random biopsies and clinical data is deficient.

The European Randomized Study of Screening for Prostate Cancer (ERSPC), with 16 years of follow-up, pointed out that population-based screening with PSA and transrectal ultrasound (TRUS)-guided biopsy protocol, one PCa death can be averted with 18 prostate cancer diagnoses (Hugosson et al., 2019).

The pressing concern is to stratify the risk of cancer and other prognostic issues of an individual man to select the best diagnostic and treatment options. Only recently, new imaging methods such as MRI and prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT), along with increasing knowledge of genetic risk factors, have made it more likely

that in the near future we will be able to reliably select the best treatment individually and hopefully avoid overdiagnosis and overtreatment.

The objective of this thesis was to investigate if we can improve diagnostics, preoperative staging, and grading of PCa with MRI. At our hospital, the inadequate diagnostic value of standard prostate biopsies was evident with the increasing rate of positive transperineal mapping biopsies after negative standard biopsies. After a while, preoperative staging MRI was introduced and the benefit of MRI in staging had to be evaluated. Finally, as active surveillance is more and more important as a treatment option, we wanted to study if MRI can be used in risk stratification of PCa, especially in estimating the risk of intermediate risk cancer.

2 Review of the literature

2.1 Background

Histologically, PCa was first described by surgeon J Adams in 1853 (Adams, 1853). It wasn't until the early 1900s, when surgical treatment of urinary obstruction became available, that PCa and benign hyperplasia could be differentiated. Even though surgical treatments and radiotherapy have been developed for PCa since then, for decades, the disease was mostly diagnosed at an advanced stage and curative treatment was not possible. For advanced disease, a major step forward in the treatment was castration and estrogens, an approach that was invented by Nobel Prize laureate Charles B. Huggins in 1941 (Huggins & Hodges, 1941).

Advances in early diagnosis using PSA measurement from blood samples were published between 1979–1987 (Kuriyama et al., 1981; Papsidero, Wang, Valenzuela, Murphy, & Chu, 1980; Stamey et al., 1987; Wang, Valenzuela, Murphy, & Chu, 1979). PSA was approved by the Food and Drug Administration of the United States in 1986 to monitor men with diagnosed PCa and in 1994 for PCa screening.

Until the late 1980s, histological diagnosis was usually based on the specimens from subcapsular prostatectomy, transurethral resection of the prostate, and fine-needle aspiration of a suspicious prostate. A TRUS-guided biopty-gun sample from an abnormal lesion was found to be superior to digitally targeted biopsies in 1988 (Ragde, Aldape, & Bagley, 1988). Soon after, the sextant random-biopsy protocol was shown to be superior to TRUS-targeted biopsies for men with palpably abnormal prostates (Hodge, McNeal, Terris, & Stamey, 1989). With PSA testing and a practical outpatient random sextant biopsy technique available, there was soon a surge of early-stage cancers to be treated with curative intent.

Just before the widespread expansion of PSA screening, a radical operative treatment with acceptable risks and functional results was developed by Walsh, Lepor and Eggleston (1983). External beam radiotherapy with curative intent was developed in the 1960s (George, Carlton, Dykhuizen, & Dillon, 1965). The modern brachytherapy method with TRUS-guided iodine-125 seeds was published by Holm, Juul, Pedersen, Hansen and Stroyer (1983). Radiotherapy was developed further with high-dose external beam radiotherapy and brachytherapy methods with computed tomography (CT)-based and MRI-based treatment plans in the early 1990s (Mangar et al., 2005).

Due to the enormous effort required for screening and early treatment, it was evident that randomised trials were needed to determine the pros and cons of PSA-based screening of mostly symptomless PCa. After ethical discussions concerning the acceptability of screening trials, a large ERSPC trial 1993–2005, and the Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO) 1993–2001 in Europe and the United States of America (USA), respectively, were conducted (Adami, Baron, & Rothman, 1994; Andriole et al., 2012; Schroder et al., 2014). The PLCO trial suffered from opportunistic PSA-screening contamination of the control arm and did not show any mortality benefit after 13 years of follow-up. On the other hand, ERSPC with less contamination and now with 16 years of follow-up time indicates that the absolute reduction of PCa mortality increases with longer follow-up, so that in the intention to treat analysis, the risk ratio was 0.80 (95% CI 0.72–0.90) (Hugosson et al., 2019). A constant effect on mortality by radical prostatectomy compared to watchful waiting was established in a pooled analysis of three randomized trials (Kilpelainen, Jarvinen, & Tikkinen, 2019).

Due to excessive overdiagnosis and overtreatment, various organizations have recommended against routine screening and instead proposed shared decision making of screening for men in risk groups starting at age > 45 and for the others 50–69 years old with a life expectancy > 10–15 years (Bjurlin et al., 2019; Mottet, van den Bergh, Briers et al., 2019). Before screening, men should be informed of the potential benefit of screening but also of the risks and harms of false positive results, diagnostic procedures, and curative treatment options, knowing that the benefits might not be seen until 10 years after treatment.

2.2 From clinical suspicion to the diagnosis

PCa in early stages does not have specific symptoms. Lower urinary tract symptoms (LUTS) are exceedingly common among middle-aged men, and observational studies suggest that men with LUTS symptoms do not have increased risk of advanced PCa. A PSA test for a man with LUTS symptoms but no other risk factors should be based on informed choice (Ostero, Jakupsstovu, & Brodersen, 2018). Apart from accidental diagnoses from metastases or prostate tissue received from surgical procedures, the diagnosis of PCa is based on needle biopsies performed either because of abnormal PSA or digital rectal examination (DRE).

The positive predictive value of DRE is weak, sensitivity is poor, and interobserver variability is substantial (Catalona et al., 2017; Naji et al., 2018). During the ERSPC study, the positive predictive value of DRE was only 4–11%

with PSA values between 0–2.9 ng/ml (Schroder et al., 1998). Furthermore, 15–25% of the cancers are located anteriorly in the transition zone, further making DRE unreliable. Nevertheless, in large studies, abnormal DRE had a positive predictive value between 4–14% with PSA values 0–2.9 ng/ml and is an indication to biopsy (Carvalhal, Smith, Mager, Ramos, & Catalona, 1999).

TRUS is not reliable in detecting PCa, but it is an essential part of the sextant biopsy protocol, which has been further developed to include optimal 10–12 biopsies (Bjurlin & Taneja, 2014; Eskicorapci et al., 2004). Transperineal biopsy-route does not improve diagnostics, but the infection risk is lower (Stefanova et al., 2019; Xue et al., 2017). However, in a re-biopsy setting, transperineal template-guided mapping biopsies (TPMB) yielded a 38% cancer detection rate with increased detection of significant but also insignificant cancers (Moran, Braccioforte, & Conterato, 2006; Taira et al., 2010). New ultrasound modalities such as sonoelastography, contrast-enhanced ultrasound (US), and high-resolution micro-US are still under further investigation to be implemented in daily practice (Eure, Fanney, Lin, Wodlinger, & Ghai, 2019; Lughezzani et al., 2019; van Hove et al., 2014).

2.3 Histology

The prostate consists of epithelial and stromal cells. Epithelial cells are the origin of prostatic acinar adenocarcinoma comprising approximately 90–95% of cancers. Most common non-acinar primary carcinomas of the prostate include urothelial, ductal, and neuroendocrine carcinoma (Xin, 2013; Humphrey, 2012).

Isolated primary urothelial carcinoma accounts for 1–4% of cancers (Esrig et al., 1996; Walsh et al., 1983). At primary diagnosis, < 2% of cancers of the prostate have neuroendocrine differentiation, but discovering solitary neuroendocrine cells is a common finding. About half of neuroendocrine prostate cancers are admixed with prostatic acinar adenocarcinoma. About 50% of contemporary small cell carcinomas arise during PCa treatments and progression as many of the other neuroendocrine-subtypes (Epstein et al., 2014).

Ductal carcinoma of the prostate is a subtype of prostatic adenocarcinoma usually intimately admixed with acinar adenocarcinoma. Tumour cells have typical cytological features. Clinical stage and grade are usually high (Morgan, Welty, Vakar-Lopez, Lin, & Wright, 2010). Very rare malignancies of the prostate are

squamous cell carcinoma, primary lymphoma, and metastases (Arva & Das, 2011; Bostwick, Iczkowski, Amin, Discigil, & Osborne, 1998).

IDC is a neoplastic proliferation with prominent cytological atypia located inside prostatic ducts and acini. It distends the lumen of ducts and acini.

Acinar prostate cancer consists of well-differentiated Gleason patterns 1-3, intermediately differentiated Gleason pattern 4, and poorly differentiated Gleason pattern 5 subtypes. Gleason pattern 3 is composed of well-lineated glands infiltrating between benign glands and without basal cell layer (if immunohistochemistry is used). Glandular differentiation is decreasing in higher grades. Gleason pattern 4 is further divided to poorly formed, fused, glomeruloid, and cribriform subtypes, often in a mixture with each other and with pattern 3 and 5. Pattern 5 includes solid sheets, single tumour cells, cords of tumour cells, and glands with comedonecrosis. Cytologically, nuclei are enlarged with prominent nucleoli. Multifocality is a common feature of PCa, yet it seems not to affect prognosis (Moch, Humphrey, Ulbright, & Reuter, 2016; Wise, Stamey, McNeal, & Clayton, 2002).

Figure 1 illustrates a representative histological picture of PCa including minor amounts of Gleason pattern 3 (green arrow), Gleason pattern 4 fused type (red arrow), and Gleason pattern 4 cribriform architecture (blue arrow) subtypes. Gleason score based on this view would be 4 + 3 = 7 and grade group 3.

2.4 Grading

Tumour aggressiveness is determined by a pathologist using grading systems. The current system of PCa grading is based on Gleason grading (Gleason & Mellinger, 1974) and further refined by the International Society of Urologic Pathology (ISUP) 2005 and the 2014 consensus conferences (Epstein, Allsbrook, Amin, Egevad, & ISUP Grading Committee, 2005; Epstein, Egevad et al., 2016). It helps to predict tumour behaviour. Contemporary Gleason grading does not assign Gleason scores 2-5 to cancer on biopsy material and scores 2-5 are seldom used in other specimens either (Moch et al., 2016).

Table 1 demonstrates how Gleason patterns are used to construct Gleason scores and grade groups.

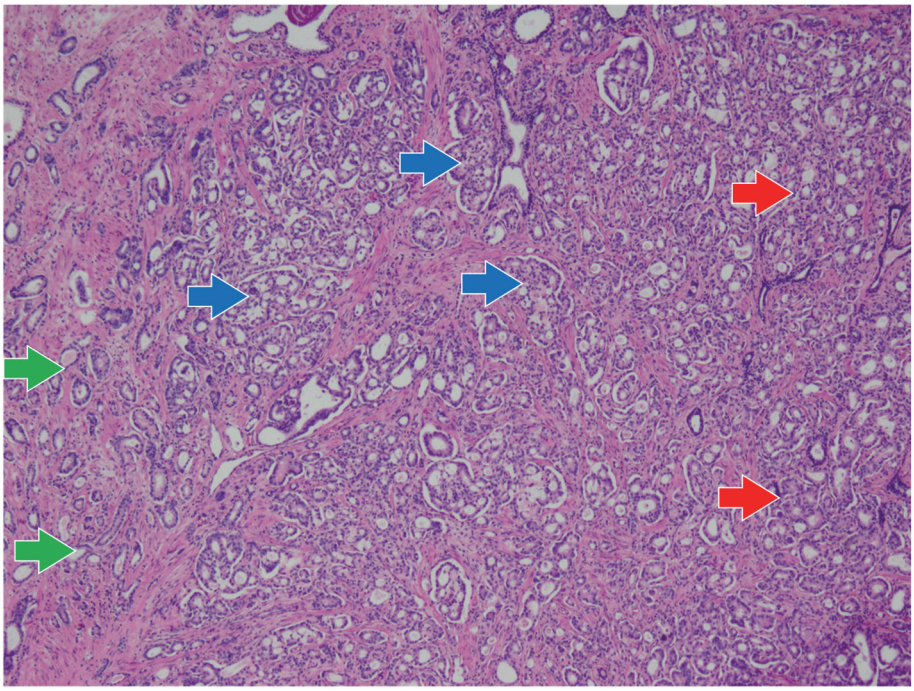

Fig. 1. Representative picture of prostate cancer.

Table 1. Combinations of Gleason patterns and corresponding Gleason scores and grade groups.

Gleason pattern sum	Gleason score	Grade Group
3 + 3	6	1
3 + 4	7	2
4 + 3	7	3
4 + 4, 3 + 5, 5 + 3	8	4
4 + 5, 5 + 4, 5 + 5	9, 10	5

The ISUP grading system includes five groups with different biochemical recurrence (BCR) risks and is based on a multi-institutional study of 20 845 men treated by radical prostatectomy (RP) and 5 501 by radiotherapy between 2005 and 2014. Grade groups (GG) for prostatectomy histology are formed by combining the two most common Gleason patterns of 3, 4, and 5. Any amount of Gleason pattern 4 in prostatectomy histology raises the grading to GG2. In other grade groups, a minor tertiary high-grade pattern < 5% does not change the GG, but is reported.

Biopsy GG comprises the most common and highest grade, irrespective of its extent. From the original Gleason grading system pattern 3, all of the cribriform subtype have been moved to pattern 4. CA of grade 4 subtypes has the strongest association with BCR, extraprostatic extension (EPE), positive surgical margin (PSM), distant metastases, and disease-specific survival (Iczkowski et al., 2011; Kweldam et al., 2015; Sarbay, Kir, Topal, & Gumus, 2014). In biopsy material, CA is linked to higher risk of upgrading and upstaging found in prostatectomy histology (Masoomian et al., 2018). Choy et al. (2016) studied the prevalence of CA in 350 GG2–3 prostatectomy samples. The prevalence of CA was 38.7% in GG2 and 66.7% in GG3 cancers (Choy et al., 2016).

IDC is almost always associated with invasive carcinoma. In a solitary finding in biopsy material, it is proposed not to be graded with Gleason grade but informed the high probability to be connected with high-grade cancer (Epstein et al., 2016). Differential diagnosis of IDC from CA is made by immunohistochemistry, which is not routinely done. The prognostic value of each seems to be similar (Kweldam et al., 2015; Trudel et al., 2014). The prevalence of IDC in a recent study was low in low-risk cancers (2.1%), but increased to 23.1% and 36.7% in patients with moderate- and high-risk cancers (Porter et al., 2017).

Mucinous adenocarcinoma of the prostate is not more aggressive than the underlining grade pattern and is graded based on Gleason patterns.

Percent pattern 4 is recommended to be reported both from biopsy and prostatectomy histology as it gives further information on the prognosis (Deng et al., 2016; Reese et al., 2012). Recommendations are also made for grading separate tumour foci if found. Typically, there is a dominant nodule bearing the biggest volume, highest grade, and stage (Stamey, McNeal, Wise, & Clayton, 2001; Wise et al., 2002). However, in one study, 14% of the highest-grade tumours were not the largest ones, and up to 25% of non-dominant tumours were ≥ GG2 (Le et al., 2015).

Based on RP-histology grade groups 1, 2, 3, 4, and 5 had a five-year BCR risk of 4%, 12%, 37%, 52%, and 74%, respectively. Compared to the original Gleason grading system, there is clear Gleason inflation so that many of the original Gleason classification 3 + 3 are in the 3 + 4 group or GG2 in the contemporary grading system (Danneman, Drevin, Robinson, Stattin, & Egevad, 2015).

While the most common criteria for clinically significant cancer (csPCa) is GG ≥ 2, the grading system still suffers from high intra- and interobserver variability due to the subjective nature of grading Gleason patterns (Engers, 2007; Kweldam, Nieboer et al., 2016). Furthermore, several studies have indicated that

prognosis differs between Gleason pattern 4 subtypes such that CA has a significantly worse outcome (Dong et al., 2013; Kweldam et al., 2015; McKenney et al., 2016).

2.5 Staging

Tumour stage refers to the spread of cancer in and beyond the prostate. The most common staging system is the Tumor, Node, Metastasis (TNM) classification (Brierley et al., 2017). Table 2 summarises the clinical TNM classification of prostate cancer.

During the planning for the best individual treatment, the clinical stage (cT) is estimated and it reflects to the DRE finding only. It is used as a prognostic tool in conjunction with PSA, biopsy GG, and possible imaging and biomarker examinations. Present data does not support histopathological T2 subclassification of final prostatectomy pathology, and it has been excluded from the TNM classification (Brierley et al., 2017). DRE and TRUS have low accuracy in T-staging (Grossfeld et al., 2001; Mullerad et al., 2005). TRUS does not improve the results of clinical T-staging (Smith et al., 1997). Now that MRI is becoming more and more widespread, suggestions to include it in clinical staging has emerged (Caglic, Kovac, & Barrett, 2019). European Association of Urology (EAU) Guidelines 2019 indicate that, especially when combined with clinical and quantitative MRI data, MRI may improve local staging (Mottet et al., 2019).

Metastatic and lymph-node staging by CT scan and bone scintigraphy is suggested by EAU guidelines for high-risk patients. The sensitivity and specificity of bone scintigraphy is not optimal, 59% and 89%, respectively (Shen, Deng, Hu, & Jia, 2014). For lymph node metastases, MRI and CT have a sensitivity of only < 40% (Hovels et al., 2008). In retrospective studies, PSMA-PET has been superior to traditional imaging to diagnose regional and distant metastases, but maturation of prospective studies is needed before implementing PSMA-PET in the primary diagnostic pathway (Koschel, Murphy, Hofman, & Wong, 2019). In a recent meta-analysis comparing bone scintigraphy, whole body MRI, PSMA-PET, choline-PET, and natriumfluoride-PET/CT in detecting bone metastases, PSMA-PET had the highest per patient sensitivity and specificity followed by natriumfluoride-PET/CT and MRI (Zhou et al., 2019).

Table 2. Pathologic TNM staging of prostate cancer.

Stage	Descripition
Primary tumour (T)	
TX	The primary tumour cannot be evaluated
T0	No evidence of a tumour in the prostate
T1	Clinically inapparent tumour that is not palpable
T1a	Tumour incidental histologic finding ≤ 5% of tissue resected
T1b	Tumour incidental histologic finding > 5% of tissue resected
T1c	The tumour was identified by needle biopsy (due to PSA)
T2	The tumour is palpable and confined within prostate
T2a	The tumour involves one half of 1 side of the prostate
T2b	The tumour has grown beyond one half, but not in the other lobe
T2c	The tumours have grown into both lobes
T3	The tumour has grown through the prostate but is not fixed
T3a	The tumour has grown through the prostate, but not into the seminal vesicles
T3b	The tumour has grown into the seminal vesicles
T4	The tumour has fixed to or is growing into nearby tissues other than seminal vesicles
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	Nearby lymph nodes don't contain cancer
N1	The cancer has spread into the nearby lymph nodes
Metastasis (M)	
M0	The cancer hasn't spread to other parts of the body.
M1	The cancer has spread outside the pelvis
M1a	Distant lymph node metastases outside the pelvis
M1b	The cancer has spread to bone(s)
M1c	The cancer has spread to distant organs

2.6 Risk classification

The first challenge is to estimate the individual's risk for csPCa before proceeding to biopsies to avoid diagnosis of insignificant prostate cancers. PSA, DRE, family history, age, and general health status are the main factors available. After prostate cancer diagnosis, the major therapeutic challenge is to distinguish indolent cancers from aggressive ones. The problem with standard-biopsy-based risk stratification by Gleason grading has been the significant up- and downgrading, and upstaging verified by prostatectomy histology. In several studies, the upgrading rate from Gleason score ≤ 6 has been $\approx$ 35–36% and downgrading from Gleason score $7 \approx 10\%$. In a study by Epstein et al. (2012), the downgrading incidence for

Gleason score 8 and 9–10 was 51.3% and 31.1%, respectively (Epstein, Feng, Trock, & Pierorazio, 2012). Reasons for this are sampling errors, tangentially sectioned glands in limited biopsy material, and interreader variability. During the opportunistic/systematic PSA-screening era, most of the cancers diagnosed with biopsy belonged to the low and intermediate Gleason score 6 and 7 risk groups (Cooperberg, Lubeck, Meng, Mehta, & Carroll, 2004).

Risk assessment tools have been constructed to overcome this shortcoming. The most common is D´Amico classification, which is the basis of contemporary EAU risk grouping. Based on serum PSA, clinical stage, and biopsy Gleason score, low-, intermediate-, and high-risk groups are created (D'Amico et al., 1998). The system does not separate Gleason 3 + 4 from 4 + 3 identified to have unequal prognosis (Epstein, Zelefsky et al., 2016). Furthermore, MRI and TB are not included in the model. There is a quest for evidence-based risk classification taking into account MRI, TB, and new biomarker data (Kane, Eggener, Shindel, & Andriole, 2017; Serrano & Anscher, 2016). Subclassification of low- and intermediate-risk groups has been performed by AUA and National Comprehensive Cancer Network (NCCN) in the USA, but there are some differences between them (National comprehensive cancer network [NCCN] guidelines version 4/2019. prostate cancer.2019; Sanda et al., 2018). Tables 3 and 4 summarises the risk groups of EAU and AUA guidelines.

Table 3. EAU pre-treatment risk classification model.

Low risk	Intermediate risk	High risk
PSA[1] < 10	PSA 10–20	PSA > 20
+ GG[2]1	+ GG2 OR GG3	OR GG ≥ 4
+ cT[3]1–cT2a	OR cT2b	OR cT2c

[1] prostate-specific antigen, [2] grade group, [3] clinical T-stage

Table 4. AUA pre-treatment risk classification model.

Very low risk	Low risk	Favorable intermediate risk	Unfavorable intermediate risk	High risk
PSA[1] < 10	PSA < 10	GG1	GG2 with	PSA > 20
+ GG[2]1	+ GG1	+ PSA 10–< 20	EITHER	OR
+ cT[3]1-cT2a	+ cT1	OR GG2	PSA 10 –< 20	GG ≥ 4 OR
+ PSAd[4] < 0.15	OR cT2a	+ PSA< 10	OR cT2b-c	cT≥ 3
+ no core with > 50%			OR GG3 + PSA < 20	
+ < 34% cores involved				

[1] prostate-specific antigen, [2] grade group, [3] clinical T-stage, [4] PSA density

In a pre-biopsy-setting, several risk calculators have been developed to predict the individual risk of csPCa. In 14 articles providing evidence from The Prostate Cancer Prevention Trial (Thompson, Leach, & Ankerst, 2014) and ERSPC (Kranse, Roobol, & Schroder, 2008), risk calculators improved the discriminating power of PSA alone to estimate the risk. The median area under curve (AUC) with prostate cancer prevention trial, ERSPC, and PSA was 0.72 (range 0.51–0.88), 0.74 (0.69–0.78), 0.68 (0.59–0.82), respectively. These risk calculators have been further developed to include newly discovered risk factors (histology, biomarkers, MRI) but probably have deficiencies as they were developed during the time of extensive PSA screening (Ankerst et al., 2018). Further, to optimate the results of these risk calculators, they should be geographically validated (Verbeek, Nieboer, Steyerberg, & Roobol, 2019).

Not only age but individual general health and co-morbidity are often the most important prognostic issues before proceeding to diagnostic procedures and while discussing treatment options with the patient. Several risk calculators are suggested by EAU and NCCN 2019 guidelines to estimate the vulnerability, frailty, and predicted 10- to 15-year survival. Palliation is suggested for men with irreversible poor health status.

2.7 Clinically significant prostate cancer

The first and most widely used criteria for clinical significance for sextant biopsy and radical prostatectomy histology was published in 1994 in a study by Epstein et al. (Epstein, Walsh, Carmichael, & Brendler, 1994). The Epstein criteria for clinically insignificant cancer in prostate biopsies were GG1, one or two cores positive of cancer, < 50% cancer of any core, and a prostate-specific antigen density of < 0.15 ng/ml. Insignificant tumours in prostatectomy histology were classified as those with index tumour volume < 0.5 cm^3, GG < 2, and no extracapsular extension. These stringent criteria have been challenged as a consequence of more liberal active surveillance protocols, TPMB, new biomarkers, and MRI with targeted biopsies. Traditional criteria, based on cancer core length and proportion of positive cores are not valid in the era of targeted biopsies (Robertson et al., 2014). Furthermore, prognostic significance of tumour volume has not been established, even if it might have significance among high-risk patients (Castiglione et al., 2017; Ito et al., 2019; Kikuchi, Scardino, Wheeler, Slawin, & Ohori, 2004).

Studies from ERSPC data indicate that GG2 cancers without CA/IDC-architecture might have the same prognosis as GG1 cancer (Kweldam, Kummerlin et al., 2016).

With long-term follow-up data from the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) and biopsy + MRI data from the PROMIS study, the clinical significance of GG2 cancer has further been questioned (Norris, Simpson et al., 2019). Naturally, the problem with the SPCG-4 study performed decades ago is the apparent grade migration and grade inflation as a consequence of PSA testing, advanced biopsy-protocols, and changes in histological grading guidelines. To diminish this bias, SPCG-material prostatectomy histology was re-evaluated in 2006, separating GG2 and GG3. PCa-related mortality for men with GG2 was not statistically different from men with GG1 neither in univariate nor multivariate Cox Regression analyses whilst those with overall GG3 had adjusted relative risk of 5.73, 95% CI 1.59–20.67 (Bill-Axelson et al., 2018).

A need for a new threshold for csPCa is widely accepted (Matoso & Epstein, 2019; Ploussard et al., 2011).

2.8 Biomarkers of prostate cancer

2.8.1 Traditional biomarkers

Prostatic acid phosphatase was already the major tumour marker of PCa during studies by Huggins in the early 1940s, usually indicating an advanced disease. After introduction of PSA, the use of prostatic acid phosphatase was virtually negligible (Burnett, Chan, Brendler, & Walsh, 1992).

Prostate-specific antigen: From the late 1980s onward, PSA has been the mainstay of PCa diagnostics, staging, grading, and follow-up after treatment. PSA is a glycoprotein enzyme and a member of kallikrein-related peptidase produced by prostate epithelium and secreted in the ejaculate and in minor quantities in blood circulation depending on the histology and size of prostate (Stamey et al., 2001). PSA is an organ-specific but not cancer-specific biomarker. Elevated values are associated to cancer, benign prostatic hyperplasia (BPH), infection, and any prostate manipulation (for example, DRE, catheterization, urinary retention). Low values do not exclude high-grade PCa.

PSA kinetics and derivatives have been developed to increase the information PSA measurement gives in certain circumstances. PSA velocity and PSA doubling

time do not seem to give added value to PSA alone in clinical decision making in early-staged PCa or diagnosis of PCa, but may have a prognostic role (Heidenreich, 2008; Vickers, Savage, O'Brien, & Lilja, 2009). PSAd has been associated to tumour volume and Gleason grade (Epstein et al., 1994; Nakanishi et al., 2007). For free/total PSA ratio (PSA f/t), highly variable sensitivity and specificity results have been published. It should only be used combined with other diagnostic tools. Furthermore, the measurements may be affected by both pre-analytical and clinical factors (Huang, Li, Huang, Song, & Wang, 2018). EAU guidelines in 2019 suggest it to be of limited value, if the novel serum tests are available. However, PSA and PSA f/t are both widely available and inexpensive.

2.8.2 Next generation biomarkers

Prostate Health Index (PHI) and 4Kscore are serum biomarkers based on combinations of PSA isoforms and/or related proteins combined to clinical information. They improve identification and detection of an aggressive disease. These tests have outperformed PSA f/t in prospective trials (Bryant et al., 2015; Catalona et al., 2011).

The Stockholm3 (STHLM 3) blood model combines plasma protein biomarkers (PSA, free PSA, intact PSA, human kallikrein 2 [hK2], gene coding for β-microseminoprotein [MSMB], macrophage inhibitory cytokine [MIC1]), genetic polymorphism (232 single nucleotide polymorphism [SNP]), and clinical variables (DRE data, previous biopsy data, age, family, history) to estimate the risk of csPCa and the need for biopsy (Gronberg et al., 2015).

Prostate cancer antigen 3 (PCA-3) is a urine test taken after prostate massage. It is a non-coding ribonucleic acid (RNA) biomarker and the measured score is dependent on existence and volume of cancer but independent of prostate volume. It might be used to guide biopsy decisions before biopsy and after negative biopsy (Schilling et al., 2010).

Liquid biopsy: Further tests based on RNA biomarkers and genomic alterations are under investigation. Liquid biopsy is a promising new technique to provide information for diagnostics, risk stratification, follow-up, and treatment planning by the aid of studying circulating cancer cells, deoxyribonucleic acid (DNA), and RNA (Hua, Chen, & He, 2019; Ku, Gleave, & Beltran, 2019; Barentsz et al., 2012).

ConfirmMDx assesses methylation levels of a multigene panel from histologically benign biopsy tissue analysing the risk of missed cancer and the need

for re-biopsy. The basis is an epigenetic field effect near the cancer foci displaying DNA-methylation changes (Van Neste et al., 2016).

OncotypeDX analyses expression of 12 cancer-associated genes to predict the probability of cancer aggressiveness of early-stage PCa from tissue samples (Cullen et al., 2015).

Prolaris Molecular Score estimates the risk of progression by measuring expression of 31 cell cycle progression and 15 housekeeping genes from biopsy samples (Cuzick et al., 2011).

Decipher analyses 22 RNA markers from prostatectomy or biopsy material to predict risk of metastatic disease during the next 5–10 years after prostatectomy (Spratt et al., 2017).

Several markers have been indicated to improve risk stratification of adverse pathology and even mortality in retrospective studies. The cost of many of these commercial analyses is substantial. Prospective studies showing decreased morbidity, mortality, or the ability to point out true clinical insignificance are still missing (Cooperberg et al., 2019; Fine, LaPolla, Epstein, Loeb, & Dani, 2019).

2.9 MP-MRI of the prostate

2.9.1 Background

Clinical MRI imaging is based on strong magnetic fields usually of 1.5 Tesla (T) or 3T generated by superconducting magnets. Electromagnetic pulses of radiofrequency region (RF pulses) are used to excite nuclear spin of hydrogen atoms in a strong magnetic field. During relaxation of excitation state, a radio frequency signal is emitted. Signals of relaxation are detected with a receiving coil array. Spatial encoding of measured signals is produced by pulsed gradient field. In the human body, water and fat include abundant amounts of hydrogen atoms. T1- and T2-weighted (T2w) images are created by varying the sequence of delivering and collecting RF pulses.

Diffusion weighted imaging (DWI) is physically based on different mobility of water molecules in different tissues. Image contrast is modulated with different "motion probing" gradient pulses. The apparent displacement of water molecules between two diffusion-sensitizing gradients can be measured. Different b-values are used to probe different degrees of mobility and apparent diffusion coefficient (ADC) maps are calculated using images with several different b-values. Dynamic

contrast enhancement (DCE) images are produced with series of T1w images during intravascular circulation and passive diffusion to extracellular space of intravenously injected gadolinium contrast with relatively small molecular size.

Multiparametric MRI constitutes from anatomic T1w and T2w images combined to functional imaging (DWI-imaging and possible DCE-imaging).

After several steps in the study of nuclear magnetic resonance, Paul Lauterburn developed the technique to generate the first nuclear magnetic cross-sectional image of a living mouse 1974. He was awarded the Nobel prize with Peter Mansfield almost 30 years later when the fundamental importance of their work for medicine was evident. The first MRI scanners were built at the University of Aberdeen and used for clinical purposes for the first time in 1980. The first documentation of the use for prostate imaging as a staging tool of cancer with the prototype machine was published in 1982 (Steyn & Smith, 1982). The diagnostic accuracy improved with further development of MRI scanning from anatomic T1w and T2w to MP-MRI with functional parameters as DWI, DCE, and magnetic resonance spectroscopy imaging (MRSI).

MRI imaging is safe as it does not use ionizing radiation. In particular, the image contrast of soft tissues is good compared to CT. The time needed for one study has been much longer compared to CT but with the present imaging methods, this difference has been decreasing. Severe claustrophobia, restlessness (motion artefacts), many implanted electronic devices, and ferromagnetic material in the body might be contraindications to perform MRI.

2.9.2 General considerations

With a rapidly expanding use of this new promising imaging-method for PCa, the need for global standardization was obvious. Prostate Imaging and Reporting Data System version 1 (PI-RADS v.1) was published in 2012 by the European Society of Urogenital Radiology (ESUR) for global standardization of prostate MRI (Barentsz et al., 2012). As limitations were noticed and technical progress continued, PI-RADS v.2 was published in 2015 (Weinreb et al., 2016) and further updated in 2019 to version 2.1, especially to improve simplicity and inter-reader variability (Turkbey et al., 2019).

PI-RADS v.2 presents several prerequisites that have to be fulfilled to have a good quality prostate MRI examination. Minimum technical parameters for prostate MRI are established. The hardware needs to be 3T or up-to-date 1.5T scanner. For older 1.5T scanners, an endorectal coil is suggested. A 3T scanner is

preferred as the signal to noise ratio with a 3T scanner is higher, meaning improved image quality. On the other hand, the risk of artefacts is higher and a 1.5T scanner is preferable if the patient has metallic implants such as hip prostheses. At least 16-channel surface coils are suggested by current recommendations. Use of endorectal coils is optional. The advantage of endorectal coils might be better staging accuracy but with a risk of more artefacts. The coil is uncomfortable and increases costs.

To improve tumour detection, PI-RADS v.2 sets new criteria for DWI imaging with the high b-value ($\geq$ 1 400 s/mm^2) acquired or calculated from lower values (50–1 000 s/mm^2). The software needs to be adjusted specifically for prostate MRI scans and for individual patients by experienced personnel. Only suggestions to diminish artefacts caused by bowel motility, rectal gas, and feces are given. Post-biopsy changes (haemorrhage, inflammation) may compromise reading of the prostate MRI, even for months at least for staging purposes. Postponing MRI for at least six weeks after biopsy is recommended if clinically safe. The radiologist should be informed of the biopsy date and key clinical data to obviate false-positive interpretations (Weinreb et al., 2016).

For reporting prostate MRI readings, a 41-sector PI-RADS v.2.1 Sector Map is provided to improve communication with the urologist and pathologist about the localisation and size of the target.

As with any MRI examination, the safety instructions have to be strict for safe examinations. There has to be a protocol to ascertain possible ferromagnetic materials and electric implants such as pacemakers in the patient. Furthermore, the radiologist has to be educated to interpret and report prostate MRI using present guidelines, and the individual volume of interpretations should be adequate. Finally, there should be close collaboration with the urologist to maintain continuous quality control.

2.9.3 MRI-sequences

T1w imaging is mainly used for excluding haemorrhage in prostate and seminal vesicles. Haemorrhage can lead to false-positive interpretation of T2 images (Rosenkrantz & Taneja, 2014). T1w images can also be used in the metastatic evaluation of lymph nodes and bones.

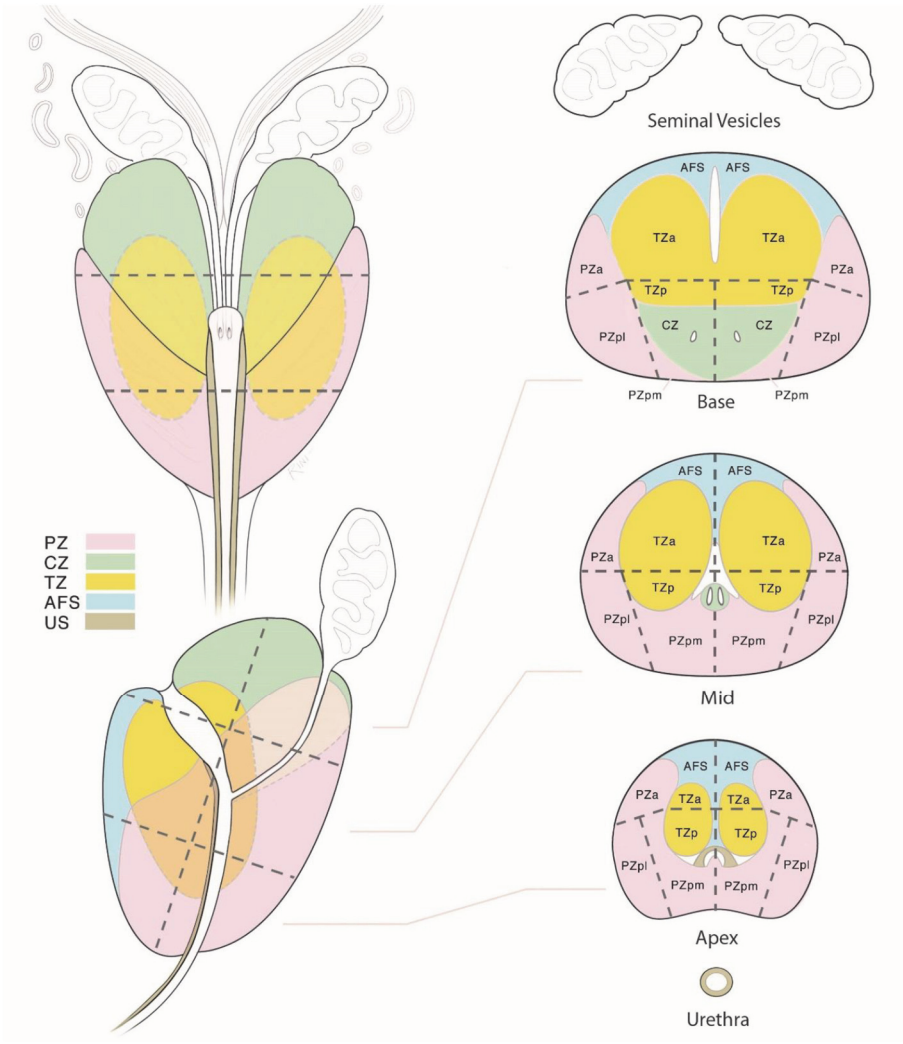

Fig. 2. PI-RADS v.2.1 Sector Map. Prostate Imaging Reporting and Data System (PI-RADS) by American College of Radiology. AFS = anterior fibromuscular stroma; CZ = central zone; PZ = peripheral zone; TZ = transition zone; US = urethral sphincter; a = anterior; l = lateral; m = medial; p = posterior. http://creativecommons.org/licenses/by-nc-nd/4.0/

T2w imaging provides information of zonal anatomy as described by McNeal in 1981 (McNeal, 1981). It is the basis for detecting, localizing, and staging of cancer. The normal peripheral zone is hyperintense due to the relatively high water content.

The central zone and transition zone have intermediate to low signal. The signal of the central zone is more homogenously low. Among patients with marked prostatic hyperplasia, the area with heterogenous signal of transition zone occupies most of the prostate. The anterior fibromuscular stroma shows as bilateral symmetric hypointense rim. Cancer tissue with higher cellularity and lower water content appears hypo-intense. About 20% of cancers appear in the transition zone. T2w-images are the primary modality to evaluate the transition zone. Areas different from other hyperplasia nodules having obscure margins, lenticular shape, or invasive appearance should be scored with PI-RADS score. SVI leads to lower signal intensity (Weinreb et al., 2016).

DWI is the other main imaging parameter of prostate MRI. DWI is used as a diagnostic tool, but suggestions of its usefulness as a marker of tumour aggressiveness have been done. Cancer appears hyperintense in high b-value images and hypointense in ADC maps. DWI is the primary method to estimate peripheral zone where 70% of cancers arise. DWI is further used to analyse suspicious areas of T2w imaging elsewhere in the prostate.

DCE has a minor role compared to T2w and DWI imaging in PI-RADS v.2.1. However, DCE is essential in estimating suspicious local recurrence (Turkbey et al., 2019). DCE is positive if the focal contrast enhancement is earlier in a T2w or DWI imaging suspicious lesion than in the surrounding normal area. DCE may help to estimate the character of equivocal and anatomically challenging lesions and while artefacts disturb reading of T2w and DWI images.

Biparametric MRI (BP-MRI) with no DCE imaging has been suggested to save costs and avoid risk of gadolinium-contrast agents. Several, mostly single-centre, studies have shown equivocal results with MP-MRI. However, the PI-RADS Steering Committee suggests more studies to be done to establish this also in daily clinical praxis. In any case, MP-MRI is preferred in situations like prior prostate interventions (including 5-alpha reductase and testosterone therapies), hip implants, high-risk patients (such as genetic predisposition by family history or biomarkers), a persistent suspicion after BP-MRI, during active surveillance or after previous negative biopsy (Turkbey et al., 2019). The use of BP-MRI might be the primary tool among radiologists most experienced in prostate MRI (Gupta, Mehta, Turkbey, & Verma, 2019).

MRSI is a functional imaging mode measuring concentrations of citrate, creatine, and choline known to be altered in cancer tissue. It is technically

challenging and time consuming. It is no longer part of PI-RADS v.2 imaging parameters.

2.9.4 Reporting of MRI: PI-RADS

Before the PI-RADS system, variable reporting schemes were used. Likert scoring was based on subjective four- to five-step suspicion scoring by the radiologist. Structured reporting with criteria to assign specific score of suspicion is the foundation of the PI-RADS system. A five-point scale was created. Table 5 describes PI-RADS v.2.1 assessment categories. CsPCa is defined here as the presence of any of the following: GG ≥ 2 and/or volume of the cancer ≥ 0.5 cm^3 and/or cancer with extraprostatic extension.

Table 5. PI-RADS v.2.1 assessment categories.

Category	Description
PI-RADS 1:	Clinically significant cancer is highly unlikely
PI-RADS 2:	Clinically significant cancer is unlikely to be present
PI-RADS 3:	The presence of clinically significant cancer is equivocal
PI-RADS 4:	Clinically significant cancer is likely to be present
PI-RADS 5:	Clinically significant cancer is highly likely to be present.
PI-RADS X:	Component of examination technically inadequate or not performed

Scoring is done by combination of T2w and DWI imaging with DCE images as aid in solitary cases, but not any other clinical data. The risk of cancer and clinically significant cancer increases with higher scores. No ideal detection rate has been set. In three recent, large multicentre trials, the detection rate of ≥ GG2 cancers from PI-RADS 3 lesions was 12–18% (Kasivisvanathan et al., 2018; Rouviere et al., 2019; van der Leest et al., 2019). In a review of 8 252 men, the detection rates of any cancer at first biopsy from the index lesion with PI-RADS score 3, 4, and 5 was 39%, 62%, and 92%. Of these cancers, 54%, 63%, and 76% were clinically significant, respectively (Schoots, 2018).

Maximum diameter of < 15 mm and ≥ 15 mm separates PI-RADS 4 and 5 (excluding cases with extra-prostatic extension to be counted as PI-RADS 5). A PI-RADS 3 lesion should not be upgraded based on size criteria if the characteristics of the lesion do not fulfil PI-RADS 4–5 criteria.

PI-RADS v.2.1 gives guidelines to systematically measure prostate volume with consistent methods. MRI-based volume measurement is more accurate than

TRUS measurement and is increasingly used for risk stratifications especially in a prebiopsy setting (Bhat et al., 2019; Christie & Sharpley, 2019; Distler et al., 2017).

Figure 3 illustrates prostate MP-MRI images of a 68-year-old man with a rising PSA to 9.6 (f/t 9.4%) after six years use of dutasteride, clinical stage was T2c. With MP-MRI, two PI-RADS v.2 score 4 targets were found. Index lesion with a maximum diameter of 11 mm is located peripherally in the left dorsal mid-area and is clearly visible in all imaging parameters. (A: T2w; B: ADC; C: DWI with b = 1500 s/mm²; D: DCE). Histologically, a 12 mm GG5 tumour with 95% of CA/IDC was found. A focal EPE was noticed, but no PSM. A secondary MRI lesion is located in the right apex and measured only 6 mm. It was only visible in DWI images (E: ADC; F: DWI with b = 1500 s/mm²). Histology was a 12 mm GG2 tumour with 90% of Gleason pattern 3 and no CA/IDC. A third tumour with 5 mm diameter in right anterior transition zone was not identified with MRI. Histology was GG2 (50% Gleason pattern 3).

2.10 Prostate MRI and detecting of prostate cancer

2.10.1 The accuracy of MRI in detecting prostate cancer

After meta-analysis of 16 studies published by Schoots in 2015, MRI was largely implemented in guidelines for detection of PCa after negative biopsies but not in a pre-biopsy setting. After previous negative biopsy among patients with MRI target, the detection rate of csPCa with MRI-TB was higher than in SB group (relative sensitivity 1.54, 95% CI 1.05–2.57). The detection rate of insignificant cancer was lower (relative sensitivity 0.51, 95% CI 0.25–1.04). In a pre-biopsy setting, the total cancer detection rate in MRI group was similar and there was only a small difference in the detection rate of csPCa (relative sensitivity 1.10, 95% CI 1.00–1.22). MRI was suggested to be performed after initial negative biopsy (Schoots et al., 2015). Since then, four large multicentre studies addressing the question of the value of MRI before first biopsies have been published during 2017–2019.

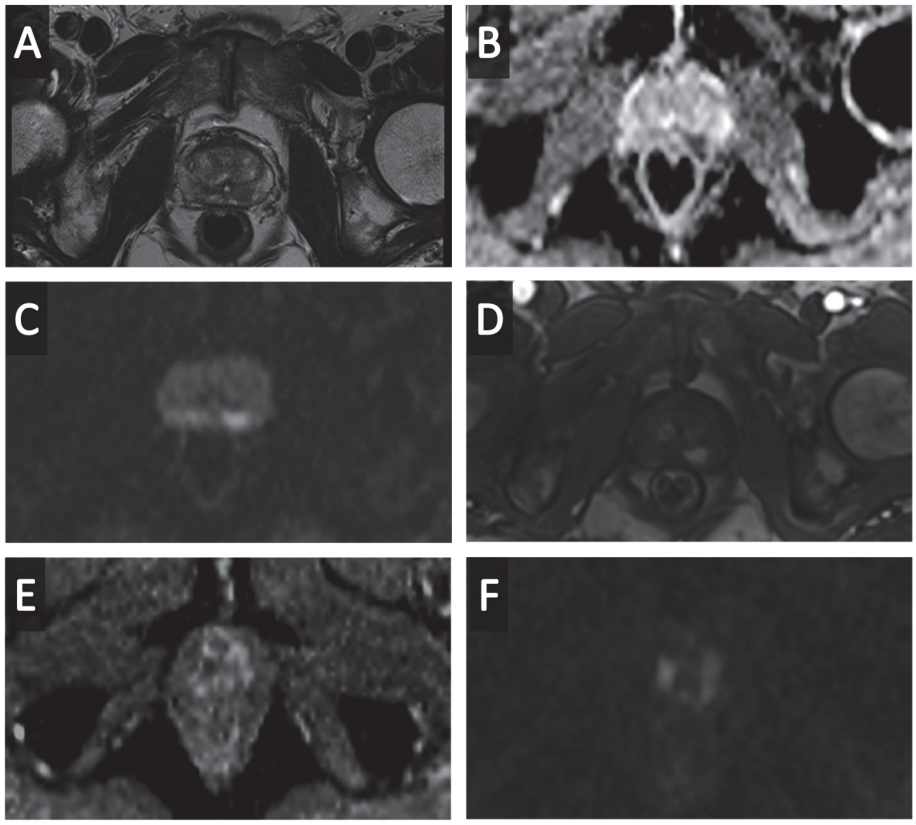

Fig. 3. illustrates representative MP-MRI findings from a man with T3a GG5 prostate cancer with three separate tumour foci in prostatectomy histology.

Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS) was explored in a multicentre study published in 2017 (n = 576) concluding that with prebiopsy 1.5T MRI following only TB from suspicious lesions, 27% of primary biopsies could be avoided and up to 18% more significant cancers found (Ahmed et al., 2017). The sensitivities of MRI and TRUS biopsy were 93% (95% CI 88–96%) and 48% (95% CI 42–55%). The specificity of MRI was 41% (95% CI 36–46%). In this study, the primary classification of clinical significance was GG3 or cancer core length ≥ 6 mm in TPMB. The study protocol and conclusions raises several questions. Only 56/230 (24.3%) of cancers were categorized as significant based on TPMB Gleason score, most by size criteria (≥ 6 mm). Tumours with contemporary GG1 grading have excellent prognosis irrespective of size (Matoso & Epstein, 2019). The sensitivity of TPMB for finding

significant cancer is at best 90–95% compared to prostatectomy histology (Crawford et al., 2013; Lecornet, Ahmed, Moore, & Emberton, 2010). No targeted biopsies were performed. Missing the target is quite common depending on the experience, skill, and characteristics of the target (Gold et al., 2019). For ethical reasons, TRUS biopsies were performed after TPMB during the same session so that swelling and haemorrhage probably made impossible TRUS targeting to possible suspicious lesions, making TRUS biopsy probably less accurate. Comparisons were made patient-based and no comparisons between locations of MRI lesions and cancer foci were made. Of note, with GG2 as the limit of clinical significance, per patient-based sensitivity of MRI was lower, 88%.

The MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis (PRECISION) study was a multicentre randomized study comparing TB and SB in a pre-biopsy setting. No biopsies were performed from MRI-negative men in the MRI group (71/252, 28%) and only targeted biopsies from PI-RADS ≥ 3 lesions were taken. In the standard-biopsy group, 10–12 cores were biopsied from 235 men. A maximum of 4 targeted biopsies per lesion from a maximum of 4 lesions were performed. Included men had suspicious PSA ≤ 20 or DRE $\leq$ cT2 with no prior biopsies or history of PCa and were suitable for biopsy and MRI. Follow-up was very short, until biopsy results and further treatment planning, but follow-up is planned to done in future studies. Clinical significance was set to a single biopsy core representing GG2. CsPCa was detected in 95 (38%) and 64 (26%) men, respectively. MRI with or without targeted biopsy was superior (adjusted difference 12 percentage points, 95% CI 4–20, $p = 0.005$). Clinically insignificant cancer was diagnosed from 23 (9%) and 55 (22%) of the men from MRI and standard-biopsy group, respectively (adjusted difference -13 percentage points, 95% CI -19 to -7, $p < 0.001$). The primary weakness of this study is the short follow-up combined with the absence of reference standard (no prostatectomy histology). In contemporary clinical praxis, MRI (and TB if needed) are performed after finding of insignificant cancer anyway. Would there still be an advantage in the detection rate of significant cancer? The centres were quite experienced with median 100 TB/year per urologist and 300 MRI-readings/radiologist. Furthermore, the 3T scanner and software-assisted biopsy was mostly used (Kasivisvanathan et al., 2018).

The Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST) trial recruited 275 biopsy-naïve men at 16 centres with PSA < 20 ng/ml and stage $\leq$ cT2. 12-core SB

combined to optional 2 cores from hypoechoic lesions was followed by TB from maximum of 2 targets, 3 cores per target. Likert score ≥ 3/5 was TB indication. Three definitions for clinical significance were used (≥ GG2; ≥ GG2 or MCCL of ≥ 6 mm; ≥ GG3). There was no significant difference between SB and TB in the detection rate of ≥ GG2 cancer (2.4 percentage points higher with TB). TB missed 5.2% of SB detected cancers. TB detected less insignificant cancers. Both techniques combined showed substantial added value. TB detected significantly more GG ≥ 3 cancers than SB. Compared to the PRECISION trial, fewer targeted cores were taken (3.2 vs 3.8) and missed targets might explain some of the difference in results. No follow-up data or reference standard is available for this study (Rouviere et al., 2019).

The Met Prostaat MRI Meer Mans (4M) study published 2019 is a large multicentre study from 4 highly experienced centres with in-bore targeted biopsies (van der Leest et al., 2019). Both radiological (before biopsy) and pathological central review was performed. MRI was performed with a 3T scanner. A minimum of 1-year follow-up was provided. 626 biopsy-naïve men with PSA ≥ 3 and no previous PCa or medications affecting PSA were recruited. Each PI-RADS v.2 3–5 lesions were biopsied in bore, 2–4 cores per lesion. Preferably during the same day, the standard biopsies were performed blinded from the MRI result. SB were performed according to guidelines. ≥ GG2 was set as a criteria for csPCa. TB and SB found 159 (25%) and 146 (23%) clinically significant cancers, respectively, with no difference in sensitivity. 88 (14%) and 155 (25%) of clinically insignificant cancers were diagnosed with TB and SB, respectively. With pre-biopsy MRI and TB, 49% of biopsies could have been avoided with a risk of missing 10/309 (3%) of significant cancers increasing to 4% during the 1-year follow-up time and further biopsies. Substantially less insignificant cancers would be detected. Comparing upgrading of TB and SB to RP pathology in 131 men, there was upgrading in 21% and 25%, respectively. The amount of uncertain (PI-RADS 3) cases in 4M trial was only 6% compared to 28% and 21% in recent PROMIS and PRECISION studies (Ahmed et al., 2017; Kasivisvanathan et al., 2018; van der Leest et al., 2019). 4M study results point out the best accessible diagnostic result to be achieved in optimal circumstances not currently achievable in most centres diagnosing PCa.

In a recent systematic review and meta-analysis, Goldberg et al. (2019) analysed the diagnostic value of pre-biopsy MRI for any csPCa (GG ≥ 2) and high-grade PCa among 29 studies (13 845 patients) comparing SB and TB either alone or in combination with SB in a population with MRI target. They found that with TB + /-SB, the likelihood of diagnosis of any cancer increased by 15%. Patients

with TB were more likely to be diagnosed with csPCa or high-grade cancer. Finally, exclusion of SB was associated with fewer insignificant cancers while not meaningfully affecting the rates of csPCa/high-grade cancers (Goldberg et al., 2019).

Another recent systematic review and meta-analysis compared TB and SB among 68 studies with 14 709 men included. The detection ratio was in favour of TB (detection ratio 1.16, 95% CI 1.09–1.24, $p < 0.0001$). No significant difference was found between biopsy-naïve and previous negative biopsy populations. Fewer clinically insignificant cancers were detected with TB (detection ratio 0.66, 95% CI 0.57–0.76, $p < 0.0001$) (Kasivisvanathan et al., 2019).

A Cochrane review published in 2019 concludes that MRI with TB only (no biopsy if no MRI target) compared to SB improves the detection rate of csPCa (≥ GG2). Pooled detection ratios are 1.05 (95% CI 0.95–1.16) for biopsy-naïve and 1.44 (95% CI 1.19–1.75, 10 studies) in prior-negative biopsy setting (Drost et al., 2019).

2.10.2 The need for standard biopsies during targeted biopsies

The need to perform SB in case with a target in MRI is still a matter of controversy (Dell'Oglio et al., 2019). The false negative rate of MRI has been reported to be 4–20% in several studies (Rouviere et al., 2019; van der Leest et al., 2019). The advantages of relying only on TB are decreased amount of biopsies performed and insignificant cancers diagnosed. This has to be weighted against ≥ 4% missed clinically significant cancers even in the most experienced clinics. Furthermore, the risk of missing multifocal high-grade cancer foci, especially with a PI-RADS 5 lesion is high (Stabile et al., 2018). This has to be taken into account while planning operation and if focal therapy is suggested. To avoid SB without compromising quality of care, the diagnostic chain should be of excellent quality, from equipment and software to individual skill of the radiologist and urologist with continuous education and mutual collaboration.

2.10.3 Targeted biopsies

Three approaches to perform TB are available. Cognitive biopsies with TRUS guidance after visually reviewing MRI images and possible MRI sector-map. MRI-TRUS fusion is an MRI image fusion with ultrasound using special equipment and

software. In-bore biopsies are performed during MRI scanning with limited sequences for localisation of a target found previously with diagnostic MRI. The availability of in-bore biopsies is limited and MRI-TRUS fusion biopsies require special equipment with considerable expenses at the beginning. All techniques are available both with transrectal and transperineal biopsy route. All are operator-dependent and there is a learning curve consisting of at least about 100 cases before plateauing (Meng et al., 2018).

In a recent multi-centre randomised controlled trial including 665 men with PI-RADS 3–5 target, the detection rates of these three techniques were equal. 234 (35%) of these men had prior negative standard biopsy. In this study, MRI-TRUS fusion biopsies were performed transperineally (BiopSee, Medcom, Darmstadt, Germany). The median number of cores per suspicious region was higher in cognitive biopsy group (4, IQR 3–5) than in MRI-TRUS fusion biopsy group (3, 3–3) and in-bore group (2, 2–3). Further, the sample size was small (77–79 per group). The authors refer to several earlier studies with a conclusion that the method for targeted biopsies should be selected based on local experience, availability, and cost (Wegelin et al., 2019). Another study using transperineal route both for cognitive and MRI-TRUS fusion biopsy comparing both techniques on each patient did not find any difference between detection rates. Three cores with both techniques were taken. Together, 93 clinically significant cancers were found, and each strategy identified 80/93 (86%). The authors suggest both techniques to be combined for the best result (Hamid et al., 2019).

In one systematic review, transperineal TB performed better than transrectal TB, especially detecting more anteriorly located cancers (Tu et al., 2019). The pooled diagnostic sensitivity of the transperineal route (86%, 95% CI 77–96) was better than the transrectal route (73%, 95% CI 62–88%). Transrectal approach missed more csPCa located at the anterior zone of the prostate (20 vs. 3).

Another question to be answered is the minimum number of TB needed per target. One retrospective study pointed out that increasing TB from one to three to five increased detection rate of csPCa from 26% to 33% and 35%, respectively (Zhang et al., 2019). Another retrospective study using the transperineal route concluded that increasing TB cores from two to four, and to 10–20 core saturation targeting including sectors adjacent to target increased the detection rate of ≥ GG2 cancer from 31%, to 34% and 42%, respectively. The reference standard was combined SB + TB with a detection rate of 45%. However, a four-core method performed excellently with PI-RADS 5 lesions with prostates ≤ 45 ml (Hansen et al., 2019). One retrospective study concluded that two cores per target compared

to five cores with bracketing the biopsy area resulted in missing of 27% of GG ≥ 2 cancers (Lu et al., 2019). An important observation by Press et al. (2019) was that targeting possible hypoechoic lesion in ultrasound nearby the MRI fusion target independently predicted the likelihood of ≥ GG2 cancer and the detection rate improved (Press, Rosenkrantz, Huang, & Taneja, 2019). Further prospective studies estimating optimal number of cores probably based on the target characteristics are awaited. Combining MRI-TRUS fusion biopsies to cognitive biopsies with targeting to suspicious areas might currently be the optimal strategy (Norris, Kinnaird et al., 2019; Press et al., 2019).

As a consequence of negative TB, several issues have to be considered. Is the MRI finding false positive? The risk increases with lower PI-RADS scores but exists with PI-RADS 5. The experience of the reader of images, possible artefacts, benign histology as inflammation, and high-grade prostatic intraepithelial neoplasia has to be taken into account. During the biopsy procedure, software registration errors and targeting errors are possible. In the PICTURE trial, about half of the missed cancers resulted from targeting errors and the other half from MRI detection errors (Simmons et al., 2018). Insertion of TRUS probe causes deformation of the prostate and the needle might deflect a few mm during biopsy. After risk stratification based on PSAd, PI-RADS score etc., re-biopsy or clinical monitoring has to be done (Gold et al., 2019).

2.10.4 MRI-negative cancers

Rosenkranz, Mendrinos, Babb, and Taneja (2012) studied RP histology from 87 tumours and 49 patients. Comparing 49 detected and 42 missed tumours, the detected tumours were larger (maximal size ≥ 1 cm), GG was > 1, and solid tumour growth was discovered (Rosenkrantz et al., 2012). Le et al. (2015) showed that in addition to size and grade, the index tumour status was an independent predictor of MRI visibility. About 80% of index tumours and 72% of tumours > 1 cm or ≥ GG2 were detected (Le et al., 2015). Wibulpolprasert et al. (2019) compared MRI and following prostatectomy histology from 415 men with 863 PCa foci in a population with 47.3% GG1 prostatectomy histology. 83.3% of index-lesions > 1 cm and ≥ GG2 were detected (Wibulpolprasert et al., 2019). Another study analysed the locations where MRI misses the most significant cancers. A retrospective study without prostatectomy histology pointed out that tumours in the dorsolateral and apical regions are most often missed by MRI (Schouten et al., 2017).

In a retrospective analysis, Johnson et al. (2019) studied 1 213 pathologically confirmed tumour foci in 588 prostates in a high-volume high-experience clinic. MRI detected 65% of ≥ GG2 tumour foci and nearly 80% of tumours ≥ GG4. MRI missed ≥ GG2 tumour foci in 34% of men overall and in 45% of men with multifocal lesions. It is worth noticing that 25% of missed solitary foci were ≥ GG3. 61.1% of missed lesions were ≤ 1 cm, and the size of tumour was the strongest predictor of MRI visibility. As index lesion typically is the largest and highest grade, smaller lesion had the highest grade in 11% of prostates. Lesion-based false-positive rate of MRI was 19% (Johnson et al., 2019).

2.11 MRI in staging of prostate cancer

2.11.1 Background

The purpose of optimal local staging would be reliable localisation of the tumour and its margins compared to the prostatic capsule, surrounding organs, and neurovascular bundles. Further, it should indicate the location and size of possible EPE and SVI. EPE and SVI are associated with greater risk of LNM and all three are associated with BCR, metastatic disease, and cancer-specific survival in this order of increased risk (Eggener et al., 2011; Swanson, Riggs, & Hermans, 2007). Prediction of EPE and LNM is crucial for surgical planning, especially concerning neurovascular bundles, and the need for lymphadenectomy. Postoperative pathologic staging is most accurate, but even it has pitfalls. In EORTC trial 22 911 inter-pathologist agreement of seminal vesicle invasion was high (94%) but much worse when estimating margin status (69.4%) and EPE (57.5%) (van der Kwast et al., 2006). The amount of pathological EPE (focal vs nonfocal) affects BCR risk but not PCa mortality in 9-year follow-up. In this analysis, 39.7% of pT3a patients were GG1 in prostatectomy pathology analysis. Criteria to grade EPE amount is lacking (Jeong et al., 2015). Pathological staging of lymph node tissue is not only dependant on the extent of lymphadenectomy but also the extent of pathologic examination (Prendeville et al., 2019). In sentinel node and PSMA-PET studies where even lymph nodes with a median diameter of 2 mm were identified, metastatic lymph nodes outside the routine dissection area were not uncommon (Hinsenveld et al., 2019; Joniau et al., 2013).

MRI is not implemented in current guidelines of operative planning before prostatectomy. Prospective multi-institutional studies are required to create a

standardized risk stratification tool, probably including clinical data and both qualitative and quantitative MRI-data to predict the risk of EPE, SVI, and LNM.

2.11.2 MRI and T-Staging

MP-MRI is the most accurate imaging method for local staging of PCa (Mottet et al., 2019). In a meta-analysis from 2016 with 75 studies and 9 796 patients and prostatectomy as a reference standard, the sensitivity was modest, 0.57 and 0.58 for ECE and SVI, respectively. Specificity was much better, 0.91 and 0.96, respectively. Studies included used qualitative analysis of EPE. Sub-analysis indicated that sensitivity improved with functional imaging parameters (DWI, DCE) and with 3T versus 1.5 MRI (de Rooij, Hamoen, Witjes, Barentsz, & Rovers, 2016).

Staging of PCa with MRI in clear T3–4 situation, when there is evident tumour invasion into the neurovascular bundle, internal sphincter, bladder neck, or seminal vesicle is quite straightforward. The clinical benefit in avoiding positive margins during prostatectomy will probably be more often gained in situations where there is focal EPE and the resolution of MRI is inadequate. The sensitivity and specificity of standard reading for EPE is poor (Tay, Gupta, Brown, Silverman, & Polascik, 2016). Tay et al. examined 120 men with 3T MRI and prostatectomy histology as reference standard. With standard academic hospital read, the accuracy was 58.7% compared to specialised read by radiologist dedicated to prostate MRI of 82.6%. Standard read of MRI was not statistically better than a model with clinical parameters only.

PI-RADS v.2 suggests assessing known imaging features associated with SVI and EPE listed below (https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2.pdf).

Extraprostatic extension:

- asymmetry or invasion of neurovascular bundles
- a bulging prostatic contour
- irregulated or spiculated margin
- obliteration of rectoprostatic angle between prostate base and seminal vesicle
- tumour-capsule interface > 10 mm
- breach of the capsule with direct tumour extension or bladder wall invasion

Seminal vesicle invasion:

- focal or diffuse low T2w signal intensity and/or abnormal contrast enhancement within or along seminal vesicle
- restricted diffusion
- obliteration of the angle between prostate and seminal vesicle
- direct tumour extension from the prostate into and around seminal vesicle

With PI-RADS v.2, morphologic criteria sensitivity of 60%–81% and specificity of 75%–78% for T3a stage have been reported (Boesen et al., 2015; Schieda et al., 2015). Nevertheless, given the interobserver variability among pathologists and reports of limited prognostic value of focal EPE, further data needs to be gathered on this issue (Jeong et al., 2015; van der Kwast, T H et al., 2006). For the surgeon, suspicion grade of focal EPE and its location would be important.

To improve poor sensitivity and interobserver variability, quantitative analyses have been studied as they are not so operator dependent. The amount of MRI lesion in contact with prostate capsule (CCL) ≥ 20 mm was superior to conventional MRI criteria to predict EPE in a study by Baco et al. (2015). CCL measurement has good inter-reader agreement and is a strong predictor of EPE, but imaging and reading protocols have to be standardised before general guidelines can be given of reliable thresholds (Caglic et al., 2019). Several studies estimating the value of ADC in predicting EPE are published. A meta-analysis concluded that ADC is an independent predictor of EPE. A pooled sensitivity of ADC was 80.5% and specificity 69.1%. At present, no general cut-off value of ADC can be stated as it is hardware and software setting dependent (Bai, Sun, Li, & Zhang, 2019). Present interest in artificial intelligence (AI) with computerized analyses is addressed in a study where the radiomics signature of T2w images outperformed radiologists' visual assessment (based on sole T2w data) of EPE status in sensitivity (Ma et al., 2019).

In a recent prospective study (n = 553), qualitative, quantitative, and clinical risk assessment tools were combined. An MRI-based grading system generating three grades of MRI risk was created. Grades were based on findings of curvilinear contact length > 15 mm (Quantitative, Grade 1), capsular bulge, or irregularity (Qualitative, Grade 1), both preceding together (Grade 2), and visibly frank EPE in MRI images (Grade 3). Combining the grade with clinical data (PSA, Gleason score), AUC of 0.81 was achieved (Mehralivand et al., 2019).

In the first randomised study (n = 438) investigating if MRI reduces the rate of PSM at radical prostatectomy, PSM rate was similar in both groups even if location

of PSM was the index tumour in 89% of cases. Interpreting their negative result, Rud et al. (2015) suggest that communication between radiologist and operating urologist only by schematic drawings is insufficient. In a subgroup with cT1, there was a possible benefit of decreased PSM in MRI group. MRI changed the operative plan to a more radical one in 29% of cases. The authors speculate that the probable subgroup effect was based on the knowledge by the surgeon about the location and size of the lesion (independent of the radiologist's assessment of probable EPE) as MRI is weak in T-staging (Rud et al., 2015).

An observational cohort study with 557 men with preoperative MRI and 410 without MRI suggests that MRI and a preoperative meeting with the radiologist and operating urologist reduces PSM and at the same time the use of nerve-sparing technique. In this study, the risk factors between groups were adjusted only retrospectively (Jaderling et al., 2019). It seems, that the strategy to use only sector map drawings or readings in written form for transmitting the information is insufficient (Greer et al., 2018; Westhoff et al., 2019).

The accuracy of MRI to estimate true tumour volume seems to be good for GG $\geq$ 2 and higher PI-RADS score tumours with a tendency of underestimation depending on imaging parameters (Bratan et al., 2015). Accuracy depends on the PI-RADS score, tumour size, and GG. Furthermore, some parts of tumours are not visible in MRI as a consequence of heterogeneity of histology and intermediate density in T2w and DWI images (van Houdt et al., 2019).

2.11.3 MRI and lymph node staging

PI-RADS v.2 recommends prostate MRI to include additional sequences for pelvic nodal staging. In a meta-analysis, pooled sensitivity and specificity of MRI in lymph node staging was 0.39 (95% CI 0.22–0.56) and 0.82 (95% CI 0.79–0.83), respectively (Hovels et al., 2008). The size criteria for suspicious lymph nodes in this meta-analysis varied (0.5–2.0 cm) but is usually recommended to be > 0.8 cm in the short axis in the pelvis and > 1 cm outside pelvis. Reactive hyperplasia might cause false positive findings. LNM of PCa tend to be small. The reference standard for LNM used has been lymphadenectomy which is not 100% sensitive even in extended mode.

Using ultra-small super paramagnetic iron oxide particles as lymph node contrast media to improve detection of LNM in MRI has been studied for quite a

long time with some promising results published. The technique in not in routine use currently (Zarzour, Galgano, McConathy, Thomas, & Rais-Bahrami, 2017).

In daily clinical praxis, Partin tables and various nomograms are the basis to estimate the risk of LNMs and the need for lymphadenectomy if prostatectomy is planned to be done. In a retrospective analysis of 497 cases, Gandaglia et al. (2019) developed a new nomogram including TB and MRI in addition to the Briganti 2012 or the Memorial Sloan Kettering Cancer Center (MSKCC) nomograms (Briganti et al., 2012; Memorial Sloan Kettering Cancer Center, n.d.). This novel nomogram including MP-MRI and MRI-targeted biopsy data improved the Briganti and the MSKCC nomograms such that 60% of lymphadenectomies would have been avoided missing only 1.6% of LNM (Gandaglia et al., 2019).

2.12 MRI and grading of prostate cancer

Originally, prostate MRI was performed for staging and with further technical development to improve detecting of PCa. Lately, the possibility to aid grading of cancer has been evolved. Visibility in MRI, lesion size, and functional imaging characteristics have been studied for this purpose. Furthermore, for grading before treatment decisions, TB seems to perform better than SB to predict true cancer grade.

More accurate grading with TB renders new kinds of problems. Criteria for active surveillance (AS) are generated on the data received from SB. With TB, there is grade shifting when more higher-grade cancers are found. Bass et al. (2019) compared SB and TB for T1c patients and found that one in five were upgraded with TB with the same risk factors otherwise. Is AS still a possible option? They conclude that nomograms need to be validated for AS criteria (Bass et al., 2019). However, there was a selection bias in this study including only MRI positive men. Suggestions not to include MRI-visible tumours to T1c have been made (Caglic et al., 2019). In a recent meta-analysis with 10 studies and 1 215 men with both SB and TB performed, upgrading was more likely from SB pathology to final prostatectomy pathology (OR 2.47, 95% CI 1.48–4.14, $p = 0.001$). No significant difference in downstaging was discovered (Goel et al., 2019).

Johnson et al. evaluated the lesion-based cancer detection rate for preoperative MRI from 588 patients and 1 213 cancer foci. Only 19% (104/548) of all GG1 tumour foci and 59% (44/74) of solitary GG1 cancers were identified when positive MRI was set to PI-RADS v.2 ≥ 3 (Johnson et al., 2019). Bratan et al. (2013) studied

detection rates compared by two radiologists. Only 21% and 29% of GG1 cancer foci < 0.5 cm^3 were identified (Bratan et al., 2013).

PI-RADS scoring was developed for standardization and improved detection of cancer. In addition to predicting the possibility of cancer, increasing evidence is pointing out that higher PI-RADS v.2 score correlates to higher-grade cancer. Faiena et al. retrospectively analysed 326 men treated by prostatectomy, of which 164 were biopsy GG2. They conclude that after including conventional risk factors in multivariate analysis, PI-RADS v.2 score 5 was an independent predictor of upgrading regardless if biopsies were SB or TB (Faiena et al., 2019).

Many studies have estimated the value of various parameters of DWI for PCa grading purposes. A systematic review and meta-analysis published in 2018 in European Urology concludes that for peripheral zone cancers, the inverse correlation between ADC and Gleason score is moderate. Instead, in the transition zone, the correlation is only weak. Most of the studies were retrospective with quite small sample sizes, variable measurement protocols and hardware. Diffusion parameters provide information of tissue microstructure which does not always correlate to cancer grade (Surov, Meyer, & Wienke, 2019).

Further data of the grading of PCa is cumulating, but the long-term data of PI-RADS score effect on metastatic progression and mortality is still missing.

3 Aims of the present study

Only a minority of prostate cancers should be diagnosed and treated. This depends on the characteristics of the cancer and the life expectancy of the individual man. Combined with clinical data, nomograms, and biomarkers, MRI is a promising tool to achieve true personalized treatment of prostate cancer.

The specific aims of this study were to:

1. Assess the incremental value of pre-biopsy MP-MRI and cognitive targeted biopsies to standard biopsy pathway for detecting PCa and csPCa (I)
2. Assess if simple and reproducible maximal lesion diameter of MRI index lesion read by radiologists with variable experience predicts the pathological tumour and nodal staging of PCa (II)
3. Assess the detection rate of preoperative MRI for PCa foci containing CA and/or IDC and to evaluate the prognostic value of these histological subtypes recently connected to worse outcome (III)

4 Materials and methods

4.1 Study populations and characteristics

Table 6 presents the sequence parameters suggested by PI-RADS v.2.1 and the ones used during different time periods in Oulu university hospital for multiparametric MRI performed with Body and Spine Matrix Surface Coils at 3T. All imaging parameters used the same axial plane. Triplanar T2w was performed. Gadolinium-based contrast media was used with a dose of 0.1 mM/kg and the injection rate was 2.5 ml/s.

4.1.1 Study I

The patients recruited for this prospective randomized single centre study were referred to urological outpatient clinic of Oulu University Hospital as a consequence of abnormal PSA value suspicious of PCa. 130 men were eligible for the study and they were randomized. The inclusion criteria were age between 40 and 72 years, PSA < 10 ng/ml with free/total PSA ≤ 15% or total PSA < 20 ng/ml in repeated measurements (4 weeks minimum interval) with no known noncancerous factor elevating the PSA value (infection, catheterisation, bladder stones, etc.). The exclusion criteria were previous prostate biopsy or prostate surgery, abnormal digital rectal examination by the referring doctors, and known contraindication for MRI examination.

4.1.2 Study II

In this singe-centre retrospective study, we analysed MRI readings from patient records for all 162 consecutive men with prostatectomy (between January 2011 and November 2016) and preceding MRI with various imaging protocols. During the timeline the data was collected, the main indication for prostate MRI before prostatectomy was preoperative staging and detection of cancer after negative standard biopsies. Some patients included attended clinical pre-biopsy trial or MRI was performed during active surveillance. Staging MRI was first performed for high-risk cases and after January 2016 for all patients before prostatectomy.

Table 6. MP-MRI[1] sequence parameters used in Studies I-III and suggested by PI-RADS v.2.1.

Sequence	slice/gap, mm	FOV[6], cm	in-plane, mm trequency	in-plane, mm phase	TR[7], ms	TE[8], ms	b values for ADC, s/mm^2	high b value, s/mm^2	temporal resolution, s	total scan time, min
T2w[2] axial										
PI-RADS[3] v.2.1	**3 / 0**	**16–20**	**≤ 0.4**	**≤ 0.7**						
2010–2015	3 / 0.6	20	0.39	0.52						
2015–2019	3 / 0.6	20	0.39	0.52						
1.5T	3 / 0	20	0.63	0.75						
DWI[4]										
PI-RADS v.2.1	**≤ 4 / 0**	**16–22**	**≤ 2.5**		**≥ 3000**	**≤ 90**	**0–100, 800–1000**	**≥ 1400**		
2010–2015	4 / 0.8	30 x 38	2		4100	68	50, 300, 800	no		
2015–2019	4 / 1.2	29 x 38	2		4100	68	50, 380, 800	1500		
1.5T	4 / 0.8	31 x 24	1.61		6700	66	50, 400, 800	1500		
DCE[5]										
PI-RADS v.2.1	**3 / 0**		**≤ 2**		**< 100**	**< 5**			**15**	**2**
2010–2015	3.6 / 0		1.35		5.1	1.7			10	3
2015–2019	3.6 / 0		1.35		5.1	1.7			8	2

[1] Multiparametric magnetic resonance imaging, [2] T2 weighted imaging, [3] Prostate Imaging and Reporting Data System version, [4] Diffusion weighted imaging, [5] Dynamic contrast enhanced imaging, [6] Field of view, [7] Repetition time, [8] Echo time

Lymphadenectomy was performed for 64 men with high-risk cancer according to the risk analysis by the operating urologist. Pathological analyses were re-evaluated by a single pathologist. MRI readings and prostatectomy pathology were compared.

4.1.3 Study III

In this single-centre retrospective study, MRI and prostatectomy histology of 124 consecutive men with a history of preoperative 3T-MRI including high b-value (1 500 s/mm^2) DWI images were collected between August 2014 and November 2016. The most common indication for MRI was preoperative staging (79.8%) followed by diagnostic after previous biopsy (9.7%), pre-biopsy (5.6%), and part of active surveillance (4.8%). Until December 2015, preoperative MRI was performed only for high-risk patients so that GG5 cancers are overexpressed among these 35 patients (42.9%) compared to rest of the study population (18%).

4.2 Study designs, methods and outcome measures

4.2.1 Study I

The included 130 men were randomized 1:1 to pre-biopsy MRI group and standard biopsy group. In the MRI group, patients underwent MP-MRI with T1w, T2w, DCE, and DWI imaging with b-values of 50, 300, and 800 s/mm^2 using body and spine matrix surface coils. ADC maps were generated. MRI reading was performed by two experienced body-radiologists without consensus reading. MRI-findings were drawn in a 16-sector map and subjectively scored by a 4-step Likert-type score:

1. no cancer,
2. probably not cancer,
3. probably cancer
4. highly suspicious of cancer.

Minimum 30 minutes after single-dose 500 mg ciprofloxacin and preceding periprostatic lidocaine infiltration, a standard 10- (TRUS-volume < 30 ml) or 12-core (TRUS-volume ≥ 30 ml) biopsy was performed following EAU guidelines to all men by three urologists with varying experience.

Urologists were blinded to the MRI results until after standard biopsy in the MRI group, the reading and sector-map was provided by the study nurse and

cognitive targeted biopsies maximum 2 cores per lesion were performed from maximum of two lesions. All the biopsy cores were put in separate jars with number codes indicating the biopsy site.

Primary outcome of this study was cancer detection rate. Secondary outcomes were the detection rate of significant cancer and number of positive biopsies compared to negative biopsies in between SB and TB. Further, comparison between SB and TB in MRI group was performed. CsPCa was defined as Gleason score > 3 + 3, more than two positive cores, or a maximum cancer core length ≥ 3 mm. Possible complications following biopsy procedures were documented.

The sample size was estimated by assuming 60% cancer detection rate using our study protocol criteria. According to literature then available, 90% sensitivity with MRI and overall detection rate of 31% with SB was predicted. Sample size of 56 per group was calculated to be sufficient to detect 23% difference with $\alpha = 0.05$ and $\beta = 0.20$ (power: 0.80). As at least a 10% dropout rate was assumed, 65 men per group was concluded to be randomised.

4.2.2 Study II

MRI protocol included 3T scanning with T1w, T2w, and DWI sequences and surface coils. 27 DWI scans were performed with the highest b-value of 800 s/mm^2 and with 1 500 s/mm^2 thereafter. 73 preoperative scans were performed without DCE imaging. To diminish artefacts from hip prostheses, two patients of the study population were studied with a 1.5T scanner.

Several radiologists read prostate MRI and consulted one of three colleagues who were more experienced before synopsis. PI-RADS v.1 was not used and PI-RADS v.2 was implemented only after June 2016. Nevertheless, number and dimensions of suspicious lesions were reported systematically and maximal lesion diameter was measured from T2 (73.5%) or DWI images (15.4%) irrespective of plane. 18 scans (11.1%) were MRI-negative.

In this study, we wanted to estimate the results based on our normal workflow, as the reported results of MRI in detecting and staging cancer are heavily dependent on the experience of the reading. No re-reading was performed.

PI-RADS scores 4 and 5 are separated only by size criteria of the index lesion < 15 mm and ≥ 15 mm. We wanted to analyse the possible differences in pathological staging between groups with a lesion ≥ 15 mm (n = 97) and the other group with a lesion < 15 mm (n = 47) or negative MRI (n = 18).

Prostatectomy histology was evaluated or re-evaluated by a single experienced pathologist. In addition to GG, EPE, PSM, SVI, and LNM were recorded. The disease was defined non-organ-confined (NOC) if any of them appeared to be positive. Relevant clinical data such as PSA, biopsy GG, and clinical T-staging was collected from medical records and with this data, D'Amico risk groups were created (D'Amico et al., 1998).

To estimate if lesion size predicts non-organ-confined disease, a logistic regression analysis including preoperative variables was performed.

4.2.3 Study III

Patient characteristics such as age, preoperative clinical staging, PSA before prostatectomy, and MRI-based PSA density were recorded from the medical records. Postoperative follow-up data of PSA and possible other progression signs of the disease were documented. The time point when PSA first became measurable (≥ 0.1 ng/ml) was recorded as biochemical recurrence. Included in the analysis were also the 28 men with persistent measurable PSA at the first control visit 1–3 months postoperatively.

All MRI scans included 3T scanning with T1w, T2w, and DWI with high b-value of 1 500 s/mm^2. ADC maps were generated. DCE was not included in the imaging protocol for 73 preoperative cases.

MRI images were re-evaluated in consensus by two experienced radiologists blinded to the pathological data but aware of the fact that the patient had prostate cancer. Maximum target diameter of maximum of two targets identified with highest PI-RADS scores, were included and drawn to a region of interest sector map with 16 separate sectors. PI-RADS v.2 scoring, and ADC measurements of MRI lesions ≥ PI-RADS v.2 score 3 were performed. By placing a region of interest in the ADC map just inside the lesion, the mean ADC value was received and the manufacturer's software informed the minimum ADC value of the region (ADC min). The index lesion was the one with highest PI-RADS score and if two lesions had the same score, the one with widest maximal diameter.

Blinded to the MRI data, all prostatectomy pathology specimens were re-evaluated by two experienced pathologists in consensus. Prostatectomy cancer lesions were graded separately with GG, measured for largest diameter, and drawn on a sector map analogous to the MRI data (except < 5 mm GG1 lesions unless solitary findings). From every prostatectomy lesion, percentages of Gleason pattern 3, 4, and 5 were visually estimated. Furthermore, percentages CA and IDC were

estimated. CA and IDC were not separately analysed or differentiated with immunohistochemistry as the prognostic value of both has been documented to be similar. The index prostatectomy lesion was the one with highest GG and if there were several tumours with the same GG, the one with widest diameter. Secondary, tertiary, and quaternary prostatectomy lesions were arranged with the same principle.

Tumours with CA/IDC were further categorised along the localisation of this pattern inside the lesion so that tumours including ≥ 80% were registered as pure cribriform lesions. Tumours containing CA/IDC with comedonecrosis were classified as Gleason pattern 5 but were analysed within CA/IDC group.

The diagnostic value of MRI for tumours containing any CA/IDC was analysed lesion based with detection rate. Secondary, analysis of the prognostic value of CA/IDC among GG2 cancers was estimated by the risk of BCR. Further, the diagnostic value of MRI in detecting pathological index lesion was estimated.

4.3 Statistical analyses

All statistical analyses were performed with SPSS for Windows versions 21.0–25.0 (IBM Corp., Armonk, NY, USA). In all three studies, the study groups were compared with Student's t test (continuous variables) and Fisher's exact test (categorial variables). Two-tailed p-values are reported.

Study I: In the MRI group, the κ coefficient was calculated to evaluate reliability between TB and SB. To assess if TB affected cancer detection rate (CDR) after SB, McNemar or McNemar-Bowker test was calculated. A κ value < 0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and > 0.80 denotes slight, fair, moderate, substantial, and almost perfect reliability, respectively.

Study II: Summary measurements are presented as medians (interquartile range). Logistic regression model was used to assess the impact of maximal MRI lesion diameter (< 15 mm vs. ≥ 15 mm) on EPE, PSM, SVI, LNM, and NOC. PSA, biopsy GG, clinical T-class, and D'Amico risk groups were entered one at a time as adjusting factors.

Study III: Summary measurements are presented as medians (interquartile range). Kaplan-Meyer analysis was used to assess the impact of adverse histology on BCR-free survival. P-values were calculated using the log rank test. A consequence to the fact that all the patients had prostate cancer was that it was not possible to calculate specificity for MRI to detect CA/IDC.

4.4 Ethics

Studies II and III were retrospective cohort reviews, and all studies were approved by the Northern Ostrobothnia Hospital District Ethics Council and conducted in accordance with the principles of the Declaration of Helsinki.

In study I, written informed consent was provided by all patients before enrolment. The patients were informed of a possible extra visit for MRI scanning and the use of gadolinium contrast media. Kidney function and other contraindications for MRI would be clarified and no extra risk for patients was expected. For the MRI group, a maximum of four extra prostate biopsies were expected to be taken and the procedure would take a few minutes more time. This might be more uncomfortable, but the risk of more serious complications compared to standard biopsies would be minimal.

5 Results

Patient demographics and baseline clinical data of study groups in studies I, II, and III with subgroups are summarised in Table 7.

5.1 Study I

After randomisation, 12 patients in MRI group (19%) and 5 patients (7.7%) in control group were excluded as a consequence of protocol violations. 53 men in MRI group and 60 in control group were evaluable for further analysis.

The overall cancer detection rate was 64% (34/53) and 57% (34/60) in the MRI group and control group, respectively. The difference was not statistically significant (7.5% difference [95% CI -10 to 25], p = 0.5).

The detection rate of csPCa was 55% (29/33) and 45% (27/60) in the MRI group and control group, respectively. The difference was not statistically significant (9.7% difference [95% CI -8.5 to 27], p = 0.8). Figure 4 illustrates grade groups of prostate cancers detected in the MRI and control groups.

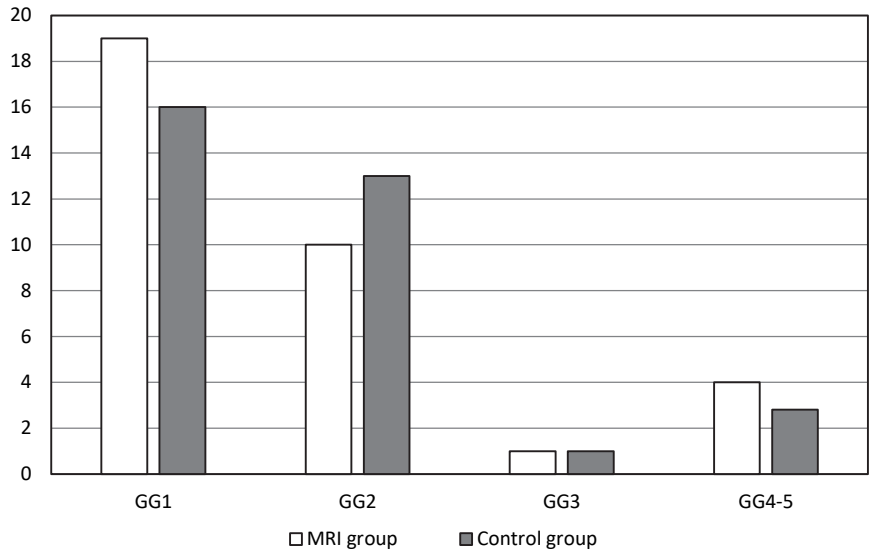

Fig. 4. Detection rate of prostate cancers within grade groups in the multiparametric magnetic resonance imaging and control groups (p = 0.5).

Table 7. Baseline characteristics of study groups (I–III).

Characteristics	Study I		Study II			Study III
	MRI group	Control group	MRI lesion < 15 mm	MRI lesion ≥ 15 mm	p-value	
Patient, n	53	60	65	97		124
Age	63 (60–66)	62 (56–67)	63 (59–67)	64 (59–69)	0.37	64 (59–69)
PSA[1] (ng/ml)	6.1 (4.2–9.9)	6.2 (4.0–10.7)	7.0 (4.8–10.0)	9.0 (6.5–16.0)	< 0.001	8.1 (5.5–13.1)
Prostate volume, ml	27.8 (23.5–36.6)	31.8 (26.1–44.3)				36.0 (30.8–44.9)
Clinical T-stage					0.020	
cT1c[2] (%)	42 (79)	37 (62)	35 (54)	35 (36)		51 (41)
cT2 (%)			25 (39)	41 (42)		52 (42)
cT3 (%)			5 (8)	21 (21)		21 (17)
Any prostate consistency abnormality in DRE[3], n (%)	11 (21)	23 (38)				
Biopsy GG (%)					0.004	
GG1			28 (43)	18 (19)		
GG2			17 (26)	24 (25)		
GG3			9 (14)	22 (23)		
GG4			5 (8)	19 (20)		
GG5			5 (8)	14 (14)		
Small cell carcinoma			1 (2)			

[1] prostate-specific antigen, [2] clinical T-stage; [3] digital rectal examination. Data for continuous variables are presented as median (interquartile range).

Within the MRI group, 81 TB and 580 SB were taken. Both TB and SB detected 27 cancers (51%). 22 (82%) and 19 (70%) of the cancers in MRI and control group were clinically significant. No statistically significant difference was discovered (McNemar-Bowker test, p = 0.67).

The mean number of TB per patient was 2.0, mean 1.8 from index lesions, and mean 1.1 from 9 secondary lesions. Five secondary lesions were not biopsied. Cancer was found in 56% (40/71) of index lesion cores, no cancers were found in secondary lesions. Among 40 MRI-positive patients with any suspicion score, TB detected cancer in 68%.

Crosstabulation of clinically significant and insignificant cancers found among 40 patients with any target in MRI is presented in Table 8. Among MRI positive patients, no cancer was upgraded by RB while two were upgraded by TB. Further, TB detected 7 cancers, 4 of which were clinically significant, while SB was negative. Three GG2 cancers were found with SB from 13 MRI-negative patients.

Table 8. Crosstabulation of clinically significant and insignificant cancers in SB and TB among men with any suspicious MRI finding (n = 40).

Histology of TB[1]	Histology of SB[2], n (%)			
	No cancer	Clinically insignificant cancer	Clinically significant cancer	Total
No cancer	10 (25)	3 (7.5)	0 (0)	13
Clinically insignificant cancer	3 (7.5)	12 (30)	0 (0)	15
Clinically significant cancer	4 (10)	2 (5)	6 (15)	12

[1] targeted biopsy, [2] standard biopsy. Clinically significant cancer is defined as ≥ GG2.

Among 10 patients with an MRI lesion located only anteriorly, TB detected 9 significant cancers whereas only three insignificant cancers were found by SB.

One patient had to be followed up 2 hours after suturing a small head wound as a consequence of collapse after biopsy procedure. No other biopsy complications were observed.

5.2 Study II

The prevalence of EPE, PSM, and SVI among 162 patients was 53.1% (86/162), 22.8% (37/162), and 17.9% (29/162), respectively. Among 64 men with

lymphadenectomy performed, 14 (21.9%) had LNM, only one with a lesion size < 15 mm. Table 9 presents adverse pathological findings among different MRI lesion size groups.

Table 9. Adverse pathology findings in different MRI lesion size groups.

MRI[1] lesion size	EPE[2] (%) (n = 162)	PSM[3] (%) (n = 162)	SVI[4] (%) (n = 162)	LMN[5] (%) (n = 64)
< 15 mm (n = 65)	16 (24.6)	4 (6.2)	3 (4.6)	1/13 (7.7)
≥ 15 mm (n = 97)	70 (72.2)	33 (34.0)	26 (26.8)	13/51 (25.5)
< 20 mm (n = 100)				2/26 (7.7)
≥ 20 mm (n = 62)				12/38 (31.6)

[1] magnetic resonance imaging, [2] extraprostatic extension, [3] positive surgical margin, [4] seminal vesicle infiltration, [5] lymph node metastasis

In univariate analysis, the odds ratio (OR) for EPE, PSM, SVI, and NOC was 7.6–7.9 among patients with an index lesion diameter ≥ 15 mm compared to group with no lesion or lesion < 15 mm.

The high risk remained when adjusted to common preoperative risk factors as D'Amico risk groups, preoperative PSA, clinical T-class, and biopsy GG in multivariate logistic regression analysis. No PSM patients belonged to D'Amico low-risk group and multivariate analysis of this subgroup was not possible. The multivariate analysis of the risk for EPE and SVI in different MRI lesion size, and D'Amico risk groups are presented in Table 10. The complete information from this analysis can be seen in the original article.

To clarify, if the MRI negative cases (n = 18) would account for the difference between groups, we evaluated only MRI positive patients (n = 144). In this analysis of D'Amico risk groups and lesion size groups for NOC disease, lesion diameter ≥ 15 mm and D'Amico high-risk group were independent predictors of NOC disease with an OR 6.44 (95% CI 2.98–13.90, $p < 0.001$) and an OR 20.2 (95% CI 5.15–79.18, $p < 0.001$), respectively.

Among men with an index lesion diameter ≥ 15 mm, 25.5% (13/51) were found to have LNM whereas only one (7.7%) in the group with lesion size < 15 mm had LNM. However, the difference was not statistically significant (OR 4.10, 95% CI 0.49–34.72, $p = 0.195$). We tested also the size limit of ≥ 20 mm and with this limit, the difference was statistically significant ($p = 0.02$). Nevertheless, no data is available for the 98 men with no lymphadenectomy performed. When comparing biopsy and prostatectomy GG, a tendency towards more upgrading and less downgrading of patients with an index lesion ≥ 15 mm was noted.

Table 10. Logistic regression analysis in 162 men for extraprostatic extension (EPE), and seminal vesicle invasion (SVI).

Adverse pathology characteristic / Covariate	OR	95% CI	p-value
EPE			
Size[1] < 15 mm	1 (ref)		
Size ≥ 15 mm	6.4	2.8–14.3	< 0.001
D'Amico low-risk group	1 (ref)		
D'Amico intermediate-risk group	3.2	0.8–12.7	0.10
D'Amico high-risk group	18.0	4.4–74.2	< 0.001
SVI			
Size < 15 mm	1 (ref)		
Size ≥ 15 mm	5.6	1.6–20.3	0.008
D'Amico low-risk group	1 (ref)		
D'Amico intermediate-risk group	1.6	0.2–14.3	0.69
D'Amico high-risk group	5.3	0.6–44.5	0.13

[1] MRI lesion diameter

5.3 Study III

Of the 124 prostates studied, 70 (56%) had a solitary tumour. From 42 (34%), 10 (8%) and 2 (2%) prostates 2, 3, and 4 tumour foci were registered. Altogether, 192 cancer foci were included in the analysis.

CA/IDC was identified in 71% (89/124) of the prostates and in 49.5% (95/192) of all registered tumour foci. Distribution of CA and IDC among index- and non-index prostatectomy lesions and among different prostatectomy grade groups is illustrated in Figure 5.

Table 11 shows the number of MRI positive and MRI negative tumour foci with or without any CA/IDC. MRI identified 86/95 of all the tumour foci with any CA/IDC with a sensitivity of 90.5% (95% CI 82.8–95.6%). MRI identified all 21 tumours with predominantly (≥ 50%) CA/IDC. Four and six of the tumours with pure CA/IDC were classified as PI-RADS v.2 Score 4 and 5, respectively. Only 10.1% (9/89) of the GG ≥ 2 tumours with any CA/IDC were MRI negative while 62.9% (61/97) of tumours without CA/IDC were MRI negative.

MRI identified 63.5% (122/192) of all prostatectomy pathology lesions. MRI correctly identified as index lesion 85.5% (106/124) of the prostatectomy index lesions. Lesions correctly identified by MRI as index lesions were larger (median 23.0 mm, IQR 16–28 mm) than unidentified ones (10.5 mm, 10–13). MRI

identified as index lesion 9 prostatectomy secondary lesions and correctly as secondary lesions further 6 prostatectomy secondary lesions.

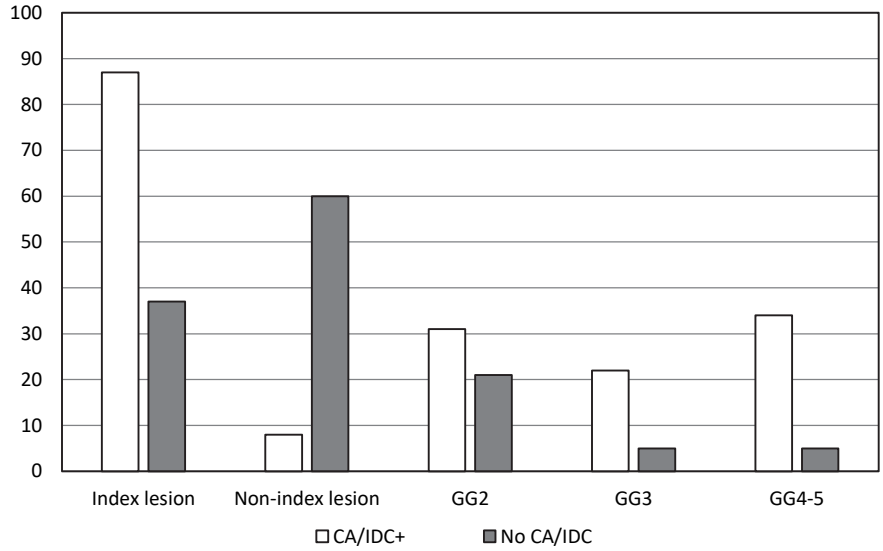

Fig. 5. Distribution of cribriform architecture and intraductal prostate cancer in index- vs non-index tumours and in different grade groups.

Table 11. Identification of tumours with or without cribriform architecture and intraductal prostate cancer with MRI.

Presence of CA/IDC	MRI visible tumours, n = 122	MRI invisible tumours, n = 70	p-value
No CA[1]/IDC[2]	36 (37.1)	61 (62.3)	< 0.001[3]
Any CA/IDC	86 (90.5)	9 (9.5)	

[1] cribriform architecture, [2] intraductal prostate cancer, [3] p-value for no CA/IDC vs any CA/IDC

One MRI index lesion was a false positive finding while in the same case the MRI secondary lesion appeared to be prostatectomy index lesion. Altogether, two MRI index lesions (1.9%) and two MRI secondary lesions (13.3%) were false positive. One MRI index lesion was drawn in the same sector as < 5 mm GG1 solitary cancer and was defined as false positive.

Seventeen of the prostatectomy index lesions were MRI negative (13.7%). Eight of these were GG1 and GG2 tumours with no CA/IDC and ≤ 10% Gleason pattern 4. Clinical significance of these tumours is probably limited. 9 clinically

significant prostatectomy index tumours were missed, but in seven of these cases, a clinically significant secondary prostatectomy lesion was correctly identified with MRI. Four of these missed tumours were GG3–5 and measured 1, 5, 8, and 12 mm, respectively. MRI did not identify any of the prostatectomy index lesions < 12 mm, of which eight were ≥ GG2. Table 12 provides data of pathological and radiological findings and comparisons between them.

Table 12. Study III pathological and radiological findings in 124 prostates.

Characteristic	Result
Pathology index lesion[1] diameter (= MRI[2] index lesion), mm (n = 106)	23 (16-28)
Pathology index lesion diameter (≠ MRI index lesion), mm (n = 18)	10.5 (5-13)
MRI index lesion[3] diameter (= Pathology index lesion), mm (n = 106)	17.0 (14-24)
Pathology non-index lesion diameter, mm (n = 67)	11.0 (7–13)
MRI non-index lesion diameter, mm (n = 15)	9.0 (7-12)
Histopathology grade group	
Index pathological lesions (n = 124)	
GG1	6 (5)
GG2	51 (41)
GG3	28 (23)
GG4	8 (7)
GG5	31 (25)
Non-index pathological lesions (n = 68)	
GG1	28 (41)
GG2	32 (47)
GG3–5	8 (12)
Index MRI lesion PI-RADS[4] score, n (%)	
MRI-negative	17 (14)
3	1 (1)
4	38 (31)
5	68 (55)
Number of tumours, n (%)	
Solitary tumour	70 (56)
2–4 foci	54 (44)

[1] The pathology index lesion was the one with the highest grade group classification and secondarily the lesion with the largest maximal diameter, [2] magnetic resonance imaging, [3] The MRI index lesion was the target with the highest PI-RADS score. If there were two targets with the same PI-RADS score, the one judged clinically to be more suspicious by the radiologist, [4] Prostate Imaging-Reporting and Data System. Data are presented as median (interquartile range), unless otherwise indicated.

ADC mean and ADC min were not significantly different among GG2–3 lesions with or without CA/IDC. Higher Gleason pattern 4 percentage was statistically significantly correlated to lower ADC values.

To analyse the prognostic role of CA/IDC, we analysed BCR among men with a prostatectomy GG2. Follow-up time was 29 (24–34) months. BCR was diagnosed in 11/31 (35.5%) of men with any CA/IDC and in 2/21 (9.5%) of men without CA/IDC. The difference is statistically significant ($p = 0.034$). In Kaplan-Mayer analysis, there was a tendency for poorer BCR-free survival connected to CA/IDC, but the difference was not statistically significant ($p = 0.057$). During the data collection period, all the GG2 patients with metastases ($n = 2$) and with androgen deprivation therapy without diagnosed metastases ($n = 2$) were found to have CA/IDC in their cancer.

6 Discussion

6.1 Main findings and discussion of substudies

6.1.1 Study I

Our main finding is that MRI and TB in a pre-biopsy setting did not improve diagnostic accuracy compared to SB. Further, no statistically significant improvement was achieved in the detection rate of clinically significant cancers. 3/13 MRI-negative patients were found to have GG2 PCa in SB. A distinct difference was discovered in the detection of anterior cancers and the detection rate per biopsy core with TB compared to SB. Furthermore, among patients with MRI lesion, TB performed at least equally compared to SB.

During the planning of our study protocol in 2010–2011, few studies were published of modern prostate MRI with DWI imaging and no randomised studies in pre-biopsy setting were published (Schoots et al., 2015).

Our results seem to be partly conflicting with the results of large multi-centre studies published later suggesting advantages of routine pre-biopsy MRI. The difference in conclusions has to be clarified. During the last few years, prostate MRI has further evolved significantly. The most important advancement has been the PI-RADS system with clear criteria for detection and scoring of cancer suspicious lesions in MRI. Further, implementing high b-value (after our study period) in DWI imaging has improved the detection rate of cancer (Woo, Suh, Kim, Cho, & Kim, 2018). Several studies now indicate that taking several (min. 4–5) targeted biopsies from MRI target improves cancer detection rate and detection of csPCa. The criteria for csPCa has been changing, even if no generally agreed standard exists.

Many recent articles emphasise the advantage of MRI and only TB to diminish the amount of clinically insignificant cancers diagnosed. Our study was not planned to examine if less clinically insignificant cancers will be found with the MRI pathway. Our goal was to evaluate the value of MRI in a routine clinical setting with average volume and ongoing learning curve for both urologists and radiologists.

Finally, when it comes to the detection of significant cancer, numerically our results are similar to the recent Cochrane analysis with only slightly improved detection rates with MRI and TB in prebiopsy setting of 1.05 (Drost et al., 2019).

6.1.2 Study II

The main finding of this study is the remarkable risk of adverse prostatectomy pathology if the maximal diameter of index lesion in MRI is ≥ 15 mm. We were surprised that the diameter ≥ 20 mm was also a significant risk for lymph node metastases in our limited sample size. We found only two studies, published during the same time frame as ours (2017–2018) to report this connection between index lesion size and LNM (Brembilla et al., 2018; Park et al., 2017). Brembilla et al. (2018) retrospectively studied MRI and prostatectomy data of 101 men with lymphadenectomy done as a consequence of > 5% LNM risk based on Briganti nomogram. 23 (22.8%) had LNM, 2/69 and 19/22 with tumour volume of < 1 cm^3 and ≥ 1 cm^3. In multivariate analysis, MRI T-stage and tumour volume had the highest predictive value. Park et al. (2017) retrospectively studied data of 221 men with preoperative MRI and lymphadenectomy done before prostatectomy. 21/221 had LNM all < 8 mm of maximum diameter. The positive predictive value for LNM by PI-RADS 5 was moderate, 20%, but the NPV with PI-RADS < 5 was high, 99.2% and 98.6% among two readers. A recent study by Huang et al. (2019) reported that PI-RADS v.2 score 5 provided high sensitivity (18/20, 90%) and negative predictive value (203/205, 99%) for lymph node metastases among 308 patients with lymphadenectomy performed and 20 LNM found (Huang et al., 2019). As mentioned earlier, combining MRI and TB data improved the value of nomograms to predict LNM among patients with both a positive MRI-targeted biopsy and SB taken (Gandaglia et al., 2019).

Morlacco et al. (2017) retrospectively analysed the incremental value of MRI with qualitative assessment of EPE, SVI, and LNM (positive or negative) for 501 men when combined to Partin tables and the Cancer of the Prostate Risk Assessment (CAPRA) score. They noticed that including MRI data in clinical information improved the ability to predict the risk of EPE, SVI, and LNM (Morlacco et al., 2017).

Krishna et al. (2018) studied quantitative parameters such as tumour size and CCL including ADC entropy for prediction of EPE. Combined tumour maximal diameter ≥ 15 mm and CCL ≥ 11 mm resulted in optimal sensitivity and specificity. With quantitative analyses, higher sensitivity but decreased specificity seems to be obtained (Krishna et al., 2018).

The idea for this study arose while evaluating the results of prostate MRI in our hospital with several radiologists reading prostate MRIs such that individual volume of readings tended to be low even if consultation of more experienced

radiologists is usually done. This is probably not the optimal situation, but something that is everyday praxis in many radiological units in Finland now that MRI has become a general tool for PCa imaging.

Reproducibility of measuring the index lesion is good (Krishna et al., 2018; Lim et al., 2016). Traditionally, when MRI data was not available, radiotherapy has been the preferred treatment for cancers estimated to be locally advanced. Nowadays, multimodality treatments are proposed as well. Informing the patient of the risk for local spread of cancer and the consequences of this for future treatments during planning of the therapy would be valuable. Including information of the lesion size and localisation might further be used for planning of prostatectomy or radiotherapy. Furthermore, according to recent results, the risk of lymph node metastases in case of PI-RADS v.2 score 5 finding should be realized.

6.1.3 Study III

The most important and new finding was the good visibility of tumour foci containing CA/IDC in MRI. Only one previous study with smaller sample size comparing MRI and final prostatectomy histology has been published, and the conclusion was opposite to our results (Truong et al., 2018). Other studies seem to confirm our results. Prendeville at al. published analogous results to ours, but they were not able to compare their results to final prostatectomy pathology (Prendeville et al., 2018).

Correlation with genomic factors linked to aggressive cancer and prostate MRI findings has been suggested. Houlahan et al. (2019) studied the molecular hallmarks of 20 PI-RADS 5 and 20 MRI-invisible GG2 tumours. Gleason pattern 4 percentage was higher in visible tumours, but the most interesting differences were the genetic alterations different in MRI-visible tumours: Overexpression of key noncoding transcripts (the long noncoding RNA second chromosome locus associated with prostate-1 [SChLAP1], small nucleolar RNAs [snoRNAs]), and genomic instability were observed in MRI-visible tumours. Small sample size and known prostate cancer genetic heterogeneity are clear weaknesses of this study. In this study, co-occurrence of genetic alterations with pathological contours such as CA and ICD recently connected to worse prognosis among Gleason pattern 4 subtypes was also noted (Houlahan et al., 2019).

CA/IDC has been connected to worse prognosis in several studies (Iczkowski, Paner, & Van der Kwast, 2018). Genomic alterations involved in aggressive PCa have been recognised in CA/IDC tumours (Bottcher et al., 2018). IDC has also been

connected to germline DNA-repair gene mutations such as breast cancer 2 gene (BRCA2) known to be associated with increased risk of aggressive PCa (Taylor et al., 2017). However, there is still some controversy about the definition of the characters of cribriform glands linked to worse prognosis (Epstein, 2019).

GG2 cancers without CA/IDC subtype might well be candidates to AS, but even TB seems to be at most modest to find/exclude CA/IDC (Ericson et al., 2019; Prendeville et al., 2018; Truong et al., 2018).

As discussed previously, Norris et al. (2019) suggest MRI-negative cancers to be insignificant (Norris, Simpson et al., 2019). In light of our results and studies of adverse genetic changes linked to MRI visibility, there might be a clear sense. However, in our sample, 3/51 GG2 index tumour cancers were MRI negative, but still contained minor amounts ≤ 5%) of CA/IDC.

6.2 Limitations of the thesis

During planning of study I, prostate MRI was not largely used internationally and PI-RADS instructions were not published. Both the radiologists and urologists attending the study were still in their learning curve while the study started. This was a single centre study and during the long enrolment time, some referrals were missed. As stated before, by not using high b-values ≥ 1 400 s/mm^2 and performing only median of 2 TB, we might have missed some tumour foci. The sample size was limited, taking into account the higher cancer detection rate we expected. Furthermore, large trials published since then have pointed out that in pre-biopsy population, the difference between MRI and TB compared to SB is smaller than we expected during sample size calculation.

In study II, MRI protocols vary considerably and material was collected during a quite long period. Measurements of the lesion diameter were not standardised and were not performed along contemporary PI-RADS v.2 suggestions. On the other hand, all the data we used was registered prospectively in medical records and results reflect daily clinical workflow.

Study III was a retrospective, single centre study. There may be inaccuracy while comparing localisations of MRI lesions and histopathology samples as a consequence of tissue sample preparation and possible different axial orientation. There was over-representation of high-risk cancers, although our aim was not to study an unselected cohort. The definition we used for BCR was PSA ≥ 0.1 instead of the more common definition of 0.2. However, there is evidence that our

definition is valid for a high-risk population such as the one we were studying (Mir et al., 2014; Preisser et al., 2019).

6.3 Future perspectives

The accuracy of MRI in studies diagnosing csPCa depends on several variables. What is the pre-test probability (age, race, family history, DRE finding, PSA, PSAd, possible other biomarkers used, previous biopsy/MRI status)? How high-quality is the available MRI study (equipment, protocol) and how experienced is the radiologist? What is the reference standard (SB, TB, TPMB, prostatectomy pathology)? If TB is the reference standard, what is the quality (cognitive, MRI-TRUS fusion, in bore biopsy, the experience of the person taking biopsies)? Furthermore, what is the definition of csPCa used?

EAU guidelines and the up-to-date American Urological Association (AUA) policy statement both suggest prebiopsy MRI (Bjurlin et al., 2019; Mottet et al., 2019). MRI should not be used as screening tool or in low-risk populations as the risk of false-positive MRI results will increase substantially. The definition of low risk is not characterised.

In staging of prostate cancer, no recommendations are made by EAU, but a suggestion that MRI might aid in staging combined with other clinical data available. AUA states that evidence to recommend MRI as a staging tool is still insufficient. No comments on grading with the aid of MRI are given.

The incremental value of MRI for diagnostic purposes in a pre-biopsy setting has been quite small and might turn to negative in low volume and low experience units without strict education and quality-control protocols. Furthermore, use of resources and the costs are an issue. With MRI, there will be more and more control imaging with uncertain benefit. My personal view is that standard TRUS biopsies are still a valid option in the prebiopsy population if good-quality MRI is not easily available/quality can't be ascertained or if there is shortage of resources.

Several cost-effectiveness analyses have been performed. The results depend on the prerequisites to perform MRI or SB, the consequences of negative/positive results of each study protocol in the long run, the cost of quality-adjusted life year set for analysis, and the specific health care system. Furthermore, the expertise of MRI reading and TB procedure and the definition of csPCa are crucial. Barnett et al. (2018) concluded, based on USA system, that MRI is cost-effective compared to SB in screening setting with a PSA limit of > 4 ng/ml when MRI and combined TB and SB are performed (PI-RADS ≥ 3, without biopsies if MRI is negative) (Barnett

et al., 2018). Another analysis by Faria et al. (2018) used PROMIS trial population referred to further investigation for suspicion of prostate cancer. MRI-first strategy was most cost-effective. It included MRI and only TB if MRI is suspicious and further second TB if the first TB was negative (Faria et al., 2018). It did not include any analysis of MRI/TB/SB negative cases or follow-up expenses further on. In community setting, further MRI scans and various biomarker tests will probably be performed for these men in years to come. Further, the assumptions of MRI accuracy were not based on TB in PROMISE as discussed earlier.

What should be done to avoid the surge of "easy and safe" MRI scans to be performed just for safety reasons? New biomarkers are still expensive and not always available. PSAd is cheap and several studies have indicated its value. It just needs prostate volume to be measured reliably. The most accurate volume is achieved by MRI, but TRUS volume is adequate (Christie & Sharpley, 2019). In a retrospective study of 865 men using PSAd > 0.078 as a triage test to perform MRI, 25% of MRI scans would have been avoided with only two GG ≥ 2 cancers missed (Deniffel et al., 2019). Nordstrom, Akre, Aly, Gronberg, and Eklund (2018) retrospectively analysed biopsy outcomes of 5 291 men in a pre-biopsy screening population with PSA ≥ 3. PSAd of ≤ 0.07, 0.1, and 0.15 missed 6.9%, 23% and 51% of ≥ GG2 cancers, respectively. The risk of ≥ GG2 cancer was low in re-biopsy population among PI-RADS score ≤ 3 patients with PSAd ≤ 0.2, such that surveillance instead of biopsy might be the optimal treatment choice (Nordstrom et al., 2018).

In a comparison of different risk estimates with 266 men, the highest negative predictive value of finding csPCa among men with negative MRI (PI-RADS score 1–2) was achieved with low (< 7%) or intermediate (7–18%) 4Kscore risk (96.9% and 97.1% respectively), PSAd < 0.10 ng/ml/cm^3 (98.7%), and ERSPC-RC < 2% (98.7%) (Falagario et al., 2019).

Prostate cancer screening studies combining PSA and new biomarkers (multi-kallikrein panel, STHLM3 test) to estimate the need for MRI and possible biopsies are on the way in Finland and Sweden. To see the preliminary results will take years and for mortality outcome > 10 years (Auvinen et al., 2017; Nordstrom et al., 2019).

MRI is already routine in prostate cancer diagnostics, but will most likely be an established component in staging and grading of PCa in near future. When more prospective data from different populations and from units with different volume and experience accumulates, MRI will probably be an essential part of multivariate risk prediction tools, where clinical data, imaging, and genetic data are used to

construct individual risk-based calculators to be used when treatment is planned with the patient.

AI and machine learning will further change the game in many ways. While ever-increasing data, part of it unstructured, is gathered, machine learning employing artificial intelligence algorithms is capable of data classification. AI is already routine in genetics and is being developed for image analysis of histological and MRI images (Ma et al., 2019). AI has been developed for segmentation of prostate MRI and TRUS images so that, for example, MRI-TRUS fusion biopsies will be faster and more precise when the margins are already marked. Inter-reader agreeability will probably increase for MRI images and histologic samples. But before clinical use, algorithms have to be set to different clinical surroundings, clinicians have to be able to interpret results, and ethical issues have to be solved (Biller-Andorno & Biller, 2019; Goldenberg, Nir, & Salcudean, 2019).

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I Tonttila, P., Lantto, J., Pääkkö, E., Piippo, U., Kauppila, S., Lammentausta, E., Ohtonen, P., & Vaarala, M. H. (2016). Prebiopsy multiparametric magnetic resonance imaging for prostate cancer diagnosis in biopsy-naive men with suspected prostate cancer based on elevated prostate-spesific antigen values: Results from a randomized prospective blinded controlled trial. *European Urology, 69*(3), 419–425. https://doi.org/10.1016/j.eururo.2015.05.024

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Original publications are not included in the electronic version of the dissertation.

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