CHALLENGES IN DIAGNOSIS, GRADING AND STAGING OF LOCALIZED PROSTATE CANCER

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CHALLENGES IN DIAGNOSIS,
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PROSTATE CANCER

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te Nijmegen
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<th>Description</th>
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<tr>
<td>1.5-T</td>
<td>1.5 Tesla</td>
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<tr>
<td>3-T</td>
<td>3 Tesla</td>
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<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
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<tr>
<td>AS</td>
<td>Active Surveillance</td>
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<tr>
<td>AUC</td>
<td>Area under the ROC-curve</td>
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<tr>
<td>BCR</td>
<td>Biochemical Recurrence</td>
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<tr>
<td>BPH</td>
<td>Benign Prostatic Hyperplasia</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CSR</td>
<td>Cancer-Suspicious Region</td>
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<tr>
<td>DCE-MRI</td>
<td>Dynamic Contrast-Enhanced MRI</td>
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<tr>
<td>DRE</td>
<td>Digital Rectal Examination</td>
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<tr>
<td>DWI</td>
<td>Diffusion-Weighted MR Imaging</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EPE</td>
<td>Extraprostatic Extension</td>
</tr>
<tr>
<td>ERSPC</td>
<td>European Randomized Study of Screening for Prostate Cancer</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>mADC</td>
<td>Median ADC</td>
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<tr>
<td>MCCL</td>
<td>Maximum Cancer Core Length</td>
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<tr>
<td>MP-MRI</td>
<td>Multiparametric Magnetic Resonance Imaging</td>
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<tr>
<td>MRGB</td>
<td>MR-guided Biopsy</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
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<tr>
<td>OR</td>
<td>Odds-Ratio</td>
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<tr>
<td>PCa</td>
<td>Prostate Cancer</td>
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<tr>
<td>PI-RADS</td>
<td>Prostate Imaging - Reporting and Data System</td>
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<tr>
<td>PNI</td>
<td>Perineural Invasion</td>
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<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
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<tr>
<td>PRIAS</td>
<td>Prostate Cancer Research International Active Surveillance</td>
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<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
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<tr>
<td>PSA-D</td>
<td>PSA-density</td>
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<tr>
<td>PSM</td>
<td>Positive Surgical Margin</td>
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<td>PVol</td>
<td>Prostate Volume</td>
</tr>
<tr>
<td>PZ</td>
<td>Peripheral Zone</td>
</tr>
<tr>
<td>PZB</td>
<td>Peripheral Zone Biopsy</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>RP</td>
<td>Radical Prostatectomy</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>TRUS</td>
<td>Transrectal Ultrasound</td>
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<tr>
<td>TZ</td>
<td>Transition Zone</td>
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<tr>
<td>TZB</td>
<td>Transition Zone Biopsy</td>
</tr>
<tr>
<td>USPSTF</td>
<td>U.S. Preventive Services Task Force</td>
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<tr>
<td>Vol%</td>
<td>Volume Percentage</td>
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Chapter 1

PREFACE
1. Preface

This thesis is proudly presented to you, as it is the product of years of collaborative work of urologists and radiologists. I think it provides a fine example of integrating knowledge and research interests of both disciplines into one body and is a perfect example of a 1+1=3 doctrine. Also, the pathologists involved in this research have played a crucial role in providing the gold standard for the diagnosis, grading and staging of prostate cancer (PCa). I am convinced that this collaboration will continue in the future in the clinical as well as the research setting, advancing our diagnostic strategies for PCa to a higher level.

The main scope of this thesis is in improving diagnostic algorithms including advanced multiparametric MRI (MP-MRI) techniques to facilitate personalized care for PCa, as it enables more accurate diagnosis, grading and staging of an individual’s PCa. This thesis is comprised of a chapter on increasing the efficacy of PCa diagnosis using prostate biopsy (chapter 3), a chapter on the ability of diffusion-weighted MR imaging (DWI) in grading PCa (chapter 4) and a chapter on risk-stratified staging of PCa by MP-MRI, while also exploring pathological characteristics of the radical prostatectomy (RP) specimen to identify subjects at greatest risk of therapy failure, possibly benefitting from immediate adjuvant therapy (chapter 5). Integrating the results of the research presented in this thesis in clinical practice will help the urologist to define the most accurate strategy for prostate biopsies in case of an elevated PSA, while it enables the radiologist to perform a meaningful MP-MRI evaluation and report in case of a (suspected) PCa diagnosis. Using this knowledge in multidisciplinary consensus meetings has every mean to reduce the individual patient’s risk of overtreatment while improving the outcome of any curative intervention undertaken.

Most importantly, the future perspectives in chapter 8 outline the challenges we will have to meet in ongoing research on this subject.

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Chapter 2

INTRODUCTION
AND OUTLINE OF THESIS
2. Introduction and outline of thesis

Prostate cancer (PCa) has many faces, ranging from low-grade, low-volume cancers, often referred to as clinically insignificant or indolent PCa, to more aggressive cancers, which are likely to progress to or present with metastatic disease. While low-risk PCa is not likely to influence an individual patient’s morbidity and mortality importantly, intermediate and high-risk PCa have the potential of severely limiting the patient’s (future) quality of life and overall survival depending on age and comorbidity\(^1\). Considering this wide range of disease characteristics, it is important to bear in mind that PCa is the most commonly diagnosed non-skin cancer in men and overall PCa-specific mortality is significant\(^1,2\). Incidence of PCa has dramatically risen with the advent of prostate specific antigen (PSA) testing, leading only to a modest decrease in PCa-specific mortality\(^3\). This suggests predominantly an increase in diagnosis of low-risk PCa by PSA testing and it has turned PCa diagnosis into a challenging field of research.

Evidence for reduction of PCa-specific mortality by PSA screening is accumulating, however, at the cost of significant overtreatment of patients diagnosed with low-risk PCa. The European Randomized Study of Screening for Prostate Cancer (ERSPC), the most referenced study on this subject, showed a 20% mortality reduction at the cost of 1410 men needed to screen and 48 additional cases of PCa treated\(^4\). In this landmark series Schröder et al. defined the substantial rate of overdiagnosis as the main limitation for PSA as a screening tool. Prolonged follow-up within the ERSPC shows a reduction of the number needed to screen and number needed to treat\(^5\), but PSA screening will remain controversial as long as the medical community is not able to differentiate those PCa patients that will benefit from early treatment from those that can be safely surveilled, as defined in a mission statement by the European Association of Urology (EAU)\(^6\). More recently the U.S. Preventive Services Task Force (USPSTF) also recommended against population-based PSA screening, defining overtreatment for low-risk PCa as a possible harm induced by a PCa diagnosis following PSA-based screening.

As far as curative treatment for PCa is concerned, the only modality that has shown a significant reduction of PCa-specific mortality compared to expectant management is radical prostatectomy (RP)\(^7\). Whether this stands true in the current PSA-era remains unknown and a recently published series showed
only a significant mortality reduction following RP for a selected population of high-risk PCa patients\(^6\), which was confirmed in another series showing little survival benefit for patients over 70 years old and/or Gleason 6, non-palpable disease\(^6\). In conclusion, one might wonder if limiting overdiagnosis is the real challenge or rather preserving treatment to those patients diagnosed with PCa who will benefit. In this context there is a burning need for tools to differentiate those patients eligible for active surveillance (AS) for their PCa from those who are likely to progress and therefor have an indication for upfront curative treatment.

Currently the indications for AS in a curative setting remain very limited and are based upon PSA, digital rectal examination (DRE) and transrectal ultrasound (TRUS)-guided biopsy criteria\(^16\). Probably, many more patients would be good candidates for AS as RP only influences PCa-specific mortality in a selected category of high-risk patients as mentioned earlier. At this point, however, we are not able to reliably identify those patients who will benefit from curative treatment while diagnosed with localized PCa. AS is most likely the key to reduce overtreatment in low-risk PCa patients, however, at the risk of withholding active treatment in some patients that would benefit. The main limitation for more liberal inclusion in AS protocols is the substantial rate of undergrading and/or understaging in AS candidates, causing the need to adhere to very strict criteria to limit the inclusion of intermediate to high-risk PCa patients in AS protocols as much as possible. Several RP correlated series have shown that up to one-third of patients considered eligible for AS do harbor intermediate to high-risk PCa characteristics in their RP specimen\(^11,15\). This is also underlined in series where immediate restaging TRUS-guided biopsy showed adverse characteristics in about one out of four patients\(^13,14\). While AS studies, such as the Prostate Cancer Research International Active Surveillance (PRIAS) initiative\(^1\), mature, it becomes evident that approximately 30% of patients will be reclassified at the first repeat biopsy at one year, based upon biopsy Gleason score and/or biopsy PCa volume criteria, and will therefor be advised to undergo active treatment. It is, however, very likely that this reclassification group represents a heterogeneous population of patients with either true progression of a low-risk PCa as well as patients undergraded and/or understaged at initial evaluation by TRUS-guided biopsies. We suggest that the focus of AS inclusion should shift to detecting patients subject to incorrect risk stratification as early as possible as this might further increase the safety of such programs and reduce the now substantial secondary intervention rates. Even when risk stratification at inclusion in AS protocols would be very accurate, we are confronted with the limitations of aforementioned criteria to detect progression and thus the indication for curative treatment during follow-up. These two factors limit the value of AS, and withhold AS to evolve to an effective strategy to reduce overtreatment in a majority of eligible PCa patients from a PSA-screened population.

Multiparametric MR-imaging (MP-MRI) of the prostate has evolved to the most adequate diagnostic, grading and staging tool for PCa currently available and combines anatomical imaging of the prostate by T2-weighted sequences with advanced functional parameters, such as dynamic contrast-enhanced (DCE) MRI and diffusion-weighted MR imaging (DWI). DCE-MRI has proven merits in PCa detection and localization both in the pre-therapeutic arena as well as in the area of recurrent disease following treatment with curative intent\(^16,17\). This thesis, however, predominantly focuses on DWI and its quantitative functional derivative, the apparent diffusion coefficient (ADC), as this modality has the most potential in aiding adequate pre-treatment grading of PCa, which might turn out to be the holy grail in correctly identifying PCa patients eligible for AS.

### 2.1 Prostate biopsy for the diagnosis of prostate cancer

On one hand we face overdiagnosis and overtreatment of low-risk PCa. On the other hand we are not able to identify all patients with intermediate to high-risk PCa straightforward with the current standard of care: PSA, digital rectal examination (DRE) and TRUS-guided biopsy.

TRUS-guided biopsy, for example, is known to be false negative in a substantial number of patients with an elevated PSA\(^16\) and (multiple) repeated biopsy sessions are not uncommon in current clinical practice to establish a diagnosis of PCa. Furthermore, the Gleason score is frequently underestimated by TRUS-guided biopsies\(^18,20\), limiting its value as a grading tool. The optimal biopsy strategy in case of an elevated PSA remains unclear and is at least partially based upon data from older series at a time when PSA-testing was not as common as it is nowadays. Current guidelines recommend a 10-12 core peripheral zone (PZ) baseline set of TRUS-guided biopsies, while recommending against incorporating standard transition zone (TZ) biopsies\(^21,22\). Chapter 3.1 of this thesis elaborates on the value of TZ
biopsies (TZB) at baseline TRUS-guided biopsy. For obvious reasons leaving out TZB at baseline biopsy leads to a selection of TZ PCa to be detected by repeat biopsy sets. However, the TZ is technically not easily sampled by TRUS-guided biopsies\textsuperscript{21}. To detect these TZ cancers with better accuracy MR-guided biopsies (MRGB) have been advocated\textsuperscript{22,23}. While MRGB is a promising tool for repeat biopsy following negative TRUS-guided biopsies, the current limitation is that it has only been evaluated in expert centers in highly selected patients\textsuperscript{20-28}. Chapter 3.2 presents an early series of MRGB in patients with at least 2 prior negative TRUS-guided biopsy sets.

Even following a diagnosis of PCa, MRGB can be used as an important adjunct diagnostic tool to better establish the Gleason score, which is especially important in patients considered for AS or delayed treatment with curative intent. It has now been established that biopsy Gleason scores obtained by MRGB correlate significantly better with the true Gleason score at RP than those obtained by TRUS-guided biopsies\textsuperscript{27}. This reduces the level of uncertainty about the Gleason score when using TRUS-guided biopsies, as these are subject to substantial degrees of Gleason undergrading. Chapter 3.3 illustrates the value of a combination of MP-MRI and MRGB in a population considered eligible for AS based upon PSA, DRE and TRUS-guided biopsy characteristics. While AS is the most important mean to reduce overtreatment of low-risk PCa diagnosed in a PSA-screened population, adequate identification of true low-risk PCa is of paramount importance and MP-MRI is a promising tool for this.

2.2 Diffusion-weighted MR imaging (DWI) as a grading tool for prostate cancer

DWI determines the random motion of water molecules, also known as Brownian motion. Brownian motion takes place in an unrestricted environment in which water molecules are able to diffuse freely and in equal extent in every direction (see figure 1A). However, within tissue extra- and intracellular compartments, such as vascular and ductal structures, cellular membranes and intracellular organelles, restrict the free motion of water molecules. Freedom of water movement in tissue is determined by the extracellular structures, such as glandular ducts, and the ratio of extracellular versus intracellular components, as water can move more freely in the extracellular compartment where there is less restriction by intracellular structures (see figure 1B). By means of the ADC DWI is able to quantify this freedom of water movement (or diffusion) which is strongly correlated with the cellular density of tissue\textsuperscript{44}. In PCa, with increasing Gleason grade, cellular density increases and there is significant loss of glandular differentiation (see figure 2), which will both lead to a limitation of diffusion and decrease in the ADC. Correct identification of the most aggressive parts of PCa for obvious reasons can be very helpful to guide targeted biopsies and possibly focal therapy. Beyond the scope of this thesis is the possibility that DWI might also function as a follow-up tool for therapy response in PCa as cellular damage from successful therapies will lead to apoptosis and disruption of cellular membranes\textsuperscript{45}, which can be monitored by DWI (see figure 1C).
MP-MRI combines DWI and DCE-MRI (or perfusion MR imaging) with conventional anatomical T1- and T2-weighted imaging, as described in a review of literature in **chapter 4.1**. In this thesis we explore the ability of MP-MRI to grade PCa and identify candidates suitable for AS. We have also just begun to appreciate the possibilities of MP-MRI to detect progression of low-risk PCa while on AS. It seems likely that, as experience with MP-MRI and MRGB in AS accumulates, in the near future the inclusion criteria for AS can be extended with the use of MP-MRI, while also being able to pick up PCa progression within the curative window. DWI is of special interest in this context and has been shown to be able to predict Gleason grade at RP with good accuracy. **Chapter 4.2** presents a series exploring this ability. Leading investigators from the PRIAS study already supported the potential of MRI to monitor patients with low-risk PCa and to help identify those who might be better off with radical treatment\(^{30}\) and a sub-study of PRIAS incorporating MP-MRI and MRGB at inclusion in PRIAS (MR-PRIAS, Dutch Trial Register, NTR2006) was initiated in 2009 in the Dutch region of Nijmegen (see appendix 1). Within a MP-MRI setting DWI seems the most promising modality to identify patients subject to Gleason upgrading upon TRUS-guided biopsy in an AS population\(^ {31} \). **Chapter 4.3** aims to compare the ADC-characteristics of patients subject to undergrading by TRUS-guided biopsy compared with those correctly graded in a RP correlated series. The first reported results of MR-PRIAS presented in **chapter 4.4** aim to identify patients subject to undergrading in a subset of patients in the PRIAS protocol using MP-MRI and MRGB. MP-MRI, including DWI, with consequent MRGB is used to obtain histological verification of cancer-suspicious regions (CSR), and the ADC-values of CSRs containing no PCa, low-grade PCa or high-grade PCa (any Gleason 4 and/or 5 component) are compared. The rate of understaging detected by MP-MRI/MRGB at inclusion can easily be compared with the ≈10% of patients excluded from the conventional PRIAS for Gleason upgrading upon repeat biopsy at one year\(^ {15,32} \).

### 2.3 Staging of prostate cancer in radical prostatectomy subjects

The overall survival rates of RP are excellent and in absence of extraprostatic extension (EPE) and positive surgical margins (PSM), the rates of biochemical recurrence (BCR) are low. This does not stand true for patients with a PSM, a common pathological feature, with a prevalence reported in up to 43% of cases following RP\(^ {33} \). PSM has been identified as one of the most important predictors for BCR following RP\(^ {34} \). Reduction of the number as well as the extent of PSMs is of major importance to optimize the outcome of RP. As it is the only prognostic factor to be influenced by surgical method and nerve-sparing strategies during RP, correct pre-operative clinical staging of PCa is of paramount importance. Knowledge of the presence and localization of EPE is likely to reduce the rate of PSMs since it enables the surgeon to more accurately select patients eligible for nerve-sparing procedures and counsel the patient accordingly\(^ {35-37} \). The staging performance of 3-T MRI has been thoroughly documented with sensitivity and specificity rates of 67-88% and 67-100%, respectively, depending on technique and reader experience\(^ {16} \). Predictive values of a test are very dependent on the prevalence of a condition in the population evaluated\(^ {38} \), and it is very likely that the predictive values

![Figure 2](image-url)
of MP-MRI for EPE differ for PCa risk categories. Chapter 5.1 outlines the performance of MP-MRI for prediction of EPE at RP, stratified for the different risk groups according to pre-treatment d’Amico criteriaa (see table 1). Knowledge of the predictive values of MP-MRI for EPE for different risk groups enables the urologist to interpret a staging MP-MRI study more accurately and counsel the patient accordingly.

Table 1  d’Amico risk classification for localized prostate cancer

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>PSA</th>
<th>Combined Gleason Score</th>
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<tr>
<td>Low-risk</td>
<td>PSA less than or equal to 10, combined Gleason score less than or equal to 6, and clinical stage T1a-2a</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>PSA between 10 and 20 and/or Gleason score 7 and/or clinical stage T2b</td>
<td></td>
</tr>
<tr>
<td>High-risk</td>
<td>PSA more than 20 and/or combined Gleason score equal or larger than 8 and/or clinical stage T2c-3a</td>
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PSA: prostate specific antigen
Adapted from d’Amico et al. JAMA 1998.

Even in case of correct pre-operative staging by MP-MRI, PSM’s will continue to occur. In these cases adjuvant therapy, such as radiotherapy, could be considered. The EORTC 22911 trial established that adjuvant radiotherapy following RP improves BCR-free survival in patients with locally advanced PCa40. However, if all expectantly managed patients in this trial had received immediate radiotherapy, over fifty percent would have received adjuvant treatment without ever progressing to BCR at the cost of potentially considerable radiotherapeutic toxicity. Re-evaluation of the EORTC 22911 data stressed that amongst patients with adverse pathological features upon RP, those with a PSM benefit most from adjuvant radiotherapy, preventing 291 BCR events for every 1,000 treated41. Characterization of patients at high risk for BCR following RP would be of great help to identify those patients most likely to benefit from immediate adjuvant radiotherapy. While several predictors of BCR in a population with a PSM have been identified, including length and localization of PSM42-44, bilateral and/or multiple PSM could be an important and easy-to-use predictor of BCR. As such we hypothesized in chapter 5.2 that the number and/or bilaterality of PSMs are an additional risk factor for BCR following RP, and may indicate who might be ideal candidates for adjuvant post-operative radiotherapy.

References


Chapter 3

PROSTATE BIOPSY FOR PROSTATE CANCER DIAGNOSIS AND RISK STRATIFICATION
Chapter 3.1

Incremental value of transition zone and midline apical biopsy at baseline TRUS-guided biopsy for prostate cancer detection

Diederik M. Somford, Willem Vreuls, Tim S. Jansen, Jean-Paul van Basten, Henk Vergunst

Accepted for publication World J Urol
Chapter 3 Prostate biopsy for prostate cancer diagnosis and risk stratification

Introduction

The most recent published (inter)national guidelines on prostate cancer (PCa) advocate an eight to twelve core random biopsy scheme for baseline transrectal ultrasound (TRUS)-guided prostate biopsy. At the same time most guidelines recommend that a baseline biopsy set should be focusing on the posterior and lateral regions of the prostate, thus predominantly sampling the peripheral zone (PZ), and should not include transition zone (TZ) sampling. However, the number of published series on the value of TZ sampling upon baseline TRUS-guided biopsy remains limited and exhibit conflicting results. Interestingly, TZ cancers are been reported to have better prognosis as estimated by biochemical recurrence (BCR) free survival. This finding is underlined by a series reporting PCa detected by initial 21-core biopsy, including TZ biopsy, to display significantly less unfavourable PCa characteristics upon radical prostatectomy (RP) than PCa detected by sextant PZ biopsy alone.

Most RP series predominantly report PZ cancers with involvement of the TZ in 6.4-24.7% of cases. One might argue that, while most clinically used schematic TRUS-guided biopsy scheme are predominantly focusing upon extensive PZ sampling, the higher incidence of PZ cancers in most RP series could be due to a sampling error, which is underlined by a series by Davis et al. showing that the volume of TZ cancers, if detected at all, is more frequently underestimated by TRUS-guided biopsy than PZ cancers. It has been established in autopsy series that the majority of incidental prostate cancers originate from the PZ as well, and about 25% of all synchronous diagnosed PCa in a cystoprostatectomy series for bladder cancer were TZ cancers.

In our series we performed a classical sextant biopsy scheme of the PZ with addition of one TZ biopsy (TZB) on either side of the prostate as well as one midline apical biopsy (MAB), thus accounting for a 9-core baseline prostate biopsy protocol. Our first objective was to establish whether TZB and MAB at baseline TRUS-guided biopsy would improve detection rates for PCa. Secondly, we investigated whether TZB and MAB positive for PCa in the context of positive PZ biopsies (PZB) would add clinically relevant information, such as additional high-grade (Gleason 4 and/or 5 components) PCa, not sampled by PZB.

Abstract

Purpose To determine the diagnostic yield of transition zone (TZB) and midline apical biopsies (MAB) in baseline transrectal ultrasound (TRUS)-guided biopsies and to establish whether TZB and MAB for the diagnosis of prostate cancer (PCa) add clinical relevant information.

Methods We performed baseline 9-core TRUS-guided biopsy in 412 consecutive subjects using sextant biopsies of the PZ (PZB), with an additional TZB on either side and a MAB at the prostatic apex. We determined the incremental diagnostic value of additional TZB an MAB to sextant PZB.

Results Within a cohort of 412 patients with a median PSA of 7.5 ng/ml, 178 (43.2%) patients were diagnosed with PCa upon baseline TRUS-guided biopsies. In 102 cases at least one TZB was positive for PCa, with 6/412 (1.4%) cases displaying PCa in the TZB only. MAB alone was positive for PCa in 4/412 (1.0%) cases. One case (1/412; 0.2%) had only a TZB and a MAB positive for PCa without positive PZB. Thus 11/412 (2.7%) of cases would not have been diagnosed with PCa at baseline TRUS-guided biopsy had only sextant PZ biopsy been performed. TZB detected a high-grade Gleason component (Gleason 4 and/or 5) not present in the PZB in 2.4% of PCa cases.

Conclusions There is limited value for TZB and MAB in the context of sextant PZB at baseline TRUS-guided biopsies for PCa.

Purpose

To determine the diagnostic yield of transition zone (TZB) and midline apical biopsies (MAB) in baseline transrectal ultrasound (TRUS)-guided biopsies and to establish whether TZB and MAB for the diagnosis of prostate cancer (PCa) add clinical relevant information.

Methods

We performed baseline 9-core TRUS-guided biopsy in 412 consecutive subjects using sextant biopsies of the PZ (PZB), with an additional TZB on either side and a MAB at the prostatic apex. We determined the incremental diagnostic value of additional TZB and MAB to sextant PZB.

Results

Within a cohort of 412 patients with a median PSA of 7.5 ng/ml, 178 (43.2%) patients were diagnosed with PCa upon baseline TRUS-guided biopsies. In 102 cases at least one TZB was positive for PCa, with 6/412 (1.4%) cases displaying PCa in the TZB only. MAB alone was positive for PCa in 4/412 (1.0%) cases. One case (1/412; 0.2%) had only a TZB and a MAB positive for PCa without positive PZB. Thus 11/412 (2.7%) of cases would not have been diagnosed with PCa at baseline TRUS-guided biopsy had only sextant PZ biopsy been performed. TZB detected a high-grade Gleason component (Gleason 4 and/or 5) not present in the PZB in 2.4% of PCa cases.

Conclusions

There is limited value for TZB and MAB in the context of sextant PZB at baseline TRUS-guided biopsies for PCa.
Materials and Methods

We retrospectively searched our institutional database for patients who underwent TRUS-guided prostate biopsy between January, 2010 and November, 2011. Patients that underwent repeat TRUS-guided biopsy with an interval less than two years from their previous set were excluded from analysis as we aimed to evaluate a true baseline TRUS-guided biopsy series. Repeat biopsies within an active surveillance setting were also excluded. Patients who underwent an alternative biopsy scheme, including targeted biopsies of abnormal regions upon digital rectal examination (DRE), TRUS or MRI, or a different number of biopsy cores were excluded as well. From the remaining cohort the patients’ charts were searched for patient characteristics (age, pre-biopsy PSA, DRE) and the pathology reports were revised for biopsy results.

TRUS-guided biopsy protocol

We used a BK ProFocus ultrasound machine (BK Medical, Herlev, Denmark) with a bi-plane side-firing TRUS probe (Type 8808, 5-10 MHz; BK Medical, Herlev, Denmark) for TRUS-guided biopsy. DRE and systematic TRUS of the prostate were performed before biopsy, reporting any abnormal or suspect regions. Prostate volume (PVol) was calculated in every patient using the tool provided by the ultrasound manufacturer, incorporating width (at maximal transversal diameter), length (bladder neck to apex in the sagittal plane) and height (at maximal transversal diameter) for calculation of PVol. Schematic TRUS-guided biopsy was performed consequently according to the scheme depicted in figure 1, using a disposable 18-gauge core biopsy instrument (Bard Monopty, core length 1.7cm; Bard, Tempy, AZ, USA). In case of a TZB the needle-point was introduced up to the boundary of the PZ and TZ before firing the biopsy instrument and the biopsy core was thus taken predominantly from the TZ. The MAB was taken from the apical PZ just lateral from the urethra, avoiding unnecessary injury to the urethra.

Pathology Processing of TRUS-guided biopsy cores

All TRUS-guided prostate biopsy cores sent for pathological analysis were coded for location of biopsy as follows: sextant biopsy of basal PZ, mid-prostate PZ and apical PZ on both sides, TZB on both sides and MAB. At reception in our pathology department all biopsy cores were embedded and assessed by the pathologist separately. For every biopsy core the presence of PCa, combined Gleason score and volume-percentage (Vol%) of PCa was documented using the International Society of Urogenital Pathology (ISUP)-modified Gleason score classification.

Statistical analysis

T-testing was performed to detect differences in patient characteristics between patients with or without a diagnosis of PCa upon baseline TRUS-guided biopsy. Detection rates and diagnostic yield for the different subsets of biopsy cores according to location (PZB versus TZB versus MAB) were established. Univariate analysis was performed using the Mann-Whitney U test, followed by multivariable analysis using logistic regression analysis for the whole group to identify predictors of any PCa positive biopsy or a TZB positive for PCa, incorporating the significant predictors of any PCa positive biopsy upon univariable analysis. Statistics were performed using the SPSS software package version 19.0 (Statistical Package for Social Sciences™, Chicago, IL, USA), with the 2-tailed level of significance set at p<0.05.
**Results**

We identified 600 consecutive subjects that underwent TRUS-guided prostate biopsy in the specified period. Of these, 116 patients underwent repeat biopsy following earlier negative TRUS-guided prostate biopsy or within the context of an active surveillance protocol and were therefore excluded. In 72 subjects a biopsy protocol violation was established with a different number of cores taken or an alternative biopsy scheme performed at the physician’s discretion or due to patients discomfort. This leaves a cohort of 412 patients for further analysis that underwent baseline TRUS-guided prostate biopsy according to our institutional protocol. Mean age for this cohort was 66.1 years (range 41-86), with a median PSA of 7.5 ng/ml (range 0.5-1582). DRE was classified as suspicious for PCa in 164 (39.8%) cases. Detailed patient characteristics stratified for PCa negative and PCa positive baseline TRUS-guided biopsies are shown in table 1. Mean follow-up after baseline TRUS-guided biopsy was 25.1 months (SD: 6.4 months). A histological diagnosis of PCa at baseline TRUS-guided biopsy was established in 178/412 patients (43.2%). Univariable analysis identified age, PSA, abnormal DRE and lower PVol as significant predictors of PCa upon baseline TRUS-guided biopsy. These variables were consequently included in the multivariable analysis, establishing abnormal DRE as the strongest predictor of PCa upon biopsy with an OR of 4.025, see table 2. Lower PVol was a statistically significant predictor of PCa, however, with a very high standard deviation its clinical significance is limited. Multivariable analysis of these characteristics to identify predictors of positive TZB within the subset diagnosed with PCa identified PSA as the only significant predictor of a positive TZB (p=0.03), see table 2. However with an OR of 1.04 the clinical significance of this finding for identifying patients at increased risk of positive TZB before baseline TRUS-guided biopsy remains very limited.

**Biopsy characteristics**

In 178 patients diagnosed with PCa upon 9-core TRUS-guided prostate biopsy, 11 cases (6.2%) were diagnosed with PCa in the context of negative sextant PZB, representing a minority of 2.7% (11/412) of the whole cohort that underwent TRUS-guided biopsy for a suspicion of PCa. For the men diagnosed with PCa upon baseline TRUS-guided biopsy, in 6/178 (3.4%) of cases a single TZB core was positive for PCa. In 6/178 (2.2%) cases only a MAB was positive for PCa. In a single case (0.6%) a TZB and the MAB core were positive for PCa. For individual patient characteristics of these subsets we refer to table 3. The diagnostic yield for TZB over sextant PZB thus was 4.0% with 7 extra PCa cases diagnosed. In all other patients (167/178, 93.8%) at least one PZB was positive for PCa. In this group of 167 patients the TZB was positive for PCa in 95/167 (56.9%) in the context of one or more positive PZB, whereas 65/167 (38.9%) of patients had PCa established in a MAB in the context of one or more positive PZB. A higher combined Gleason score in the TZB than in the PZB was detected in 10/167 (6.0%) of patients, however TZB only detected a high-grade Gleason component (Gleason 4 and/or 5) not present in the PZB in 4/167 (2.4%) cases. For MAB a higher combined Gleason score than in the PZB was detected in 4/167 (2.4%) patients, with a high-grade Gleason component not present in PZB in 2/167 (1.2%) cases.
Follow-up

Of 178 patients diagnosed with PCa upon baseline TRUS-guided biopsy 17 were included in an active surveillance protocol, 74 underwent RP, 28 were referred for external beam radiotherapy with or without neo-adjuvant hormonal treatment, 3 patients underwent brachytherapy, 2 patients were treated with primary cryosurgery of the prostate, 14 were followed with watchful waiting and 34 patients were treated with palliative androgen suppression therapy. For six patients the definitive treatment could not be established. Of the 234 patients not diagnosed with PCa upon baseline TRUS-guided biopsy, 51 patients underwent one or more repeated prostate biopsy sessions (median 1, range 1-2) culminating in a total of 71 procedures of which 13 were MR-guided biopsy (MRGB) procedures leading to a diagnosis of PCa in 19/234 (8.1%) of patients and 19/71 (26.8%) of biopsy procedures during follow-up (mean 25.1 months ± 6.4). MRGB was positive for PCa during follow-up in 7/13 (53.8%) cases.

Table 2

<table>
<thead>
<tr>
<th>Uni- and multivariate analysis of predictors of a PCa positive baseline TRUS-guided biopsy with the total population (n=412) and uni- and multivariate analysis in the subset diagnosed with PCa (n=178)</th>
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<tr>
<td>Uniivariate analysis</td>
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<tr>
<td>PSA (continuous)</td>
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<tr>
<td>Abnormal DRE (yes/no)</td>
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<td>PVol (continuous)</td>
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</table>

PCa: prostate cancer; TRUS: transrectal ultrasound; TZB: transition zone biopsy; PZB: peripheral zone biopsy. *significant at p<0.05

Table 3

<table>
<thead>
<tr>
<th>Individual characteristics of patients with positive TZB and/or MAB in absence of positive PZB</th>
</tr>
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<tbody>
<tr>
<td>Patient 1.</td>
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<td>Patient 2.</td>
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<td>Patient 3.</td>
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<td>Patient 4.</td>
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<td>Patient 6.</td>
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<td>Patient 7.</td>
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<td>Patient 8.</td>
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<td>Patient 9.</td>
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<td>Patient 10.</td>
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<tr>
<td>Patient 11.</td>
</tr>
</tbody>
</table>

TZB: transition zone biopsy; PZB: peripheral zone biopsy; DRE: digital rectal examination; PSA: prostate-specific antigen; PVol: prostate volume; PSA-D: PSA-density; Vol%: volume percentage; MAB: midline apical biopsy; RP: radical prostatectomy.
Discussion

In our presented series 93.8% of diagnosed PCa at baseline TRUS-guided biopsy would have been detected by sextant PZB alone, leaving little incremental value for TZB and/or MAB in a baseline biopsy setting. Furthermore, TZB positive for PCa in addition to PCa positive PZB did not add significant clinically relevant information as only in 2.4% of cases a high-grade Gleason component (Gleason 4 and/or 5) not present in the sextant biopsies was detected. Reissigl et al. found 28% of screen-detected PCa in TZB only in the context of sextant PZB and therefore conclude that TZB should not be omitted for baseline TRUS-guided biopsy. Although their TRUS-guided biopsy scheme is comparable to ours, we could not reproduce their high diagnostic yield of TZB. This might be attributed to their evaluation of an early screening population without an abnormal DRE in all cases, whereas we performed our series in a referral population with a higher proportion of abnormal DRE, more likely to represent higher volume and/or predominant PZ PCa. Guichard et al. concluded from their series that TZB had to be considered at baseline biopsy as the addition of TZB to a 12-core PZB scheme increased the diagnostic yield by 7.2%, however increasing the cancer detection rate only slightly from 38.7% to 41.5%. This is comparable to the present series in which TZB increased the detection rate of sextant biopsy from 40.5% to 42.2%, with a diagnostic yield for TZB of 4.0%. Pelzer et al. documented a diagnostic yield of 0.6% for TZB in the context of a 10-core schematic TRUS-guided biopsy scheme. However, their series is not directly comparable to ours as they included imaging-guided (contrast enhanced color Doppler TRUS) targeted biopsies in their baseline biopsy set. This might have led to an underestimation of the diagnostic yield of TZB in a schematic TRUS-guided biopsy setting, improving the diagnosis rates of PZ PCa in comparison to TZ PCa by using augmented TRUS. The overall low incremental value of TZB for baseline TRUS-guided biopsy was underlined by a review of the literature by Chun et al. and has led to the removal of baseline TZB in most recent guidelines on PCa diagnosis.

Following baseline sextant biopsies the additional value of TZB at repeat TRUS-guided biopsy remains limited, and its value following a more extended baseline PZB protocol (10-12 cores), as advised by all current guidelines, remains unknown. Other series found the location of PCa in repeat TRUS-guided biopsy in the regions typically less sampled by an initial biopsy set, including the apical and ventral regions of the prostate. Using a transperineal approach it is easier to target the TZ and using transperineal biopsy procedures, following one or more negative previous TRUS-guided biopsy sets, 45.3-85% of the detected PCa cases involve the TZ and/or ventral areas of the prostate. MRGB following one or more negative TRUS-guided biopsy sessions is reported to have a high rate of PCa detection ranging from 41% to 59% in different small series from a limited number of centers. Interestingly, in patients diagnosed with PCa upon MRGB, PCa lesions are located in the anterior and apical regions of the prostate in the majority of patients, again suggesting a bias of TRUS-guided biopsy towards diagnosing PCa in the PZ, regardless of the incorporation of TZB in the TRUS-guided biopsy scheme.

Limitations of our series are its retrospective nature, thus allowing for alternative biopsy schemes at the physicians discretion, possibly excluding a relative high proportion of patients with an abnormal DRE, suspect lesion upon TRUS, or a high PSA-level suggestive for advanced local or metastatic disease. Furthermore, PZ sampling in our series might have been inadequate with 6-core sextant biopsy. Probably, in the context of more extensive PZ sampling, even less PCa diagnoses would have been attributed to TZB and/or MAB only. Therefor we think that the already limited value of TZB and/or MAB as found in our series might even be considered an overestimation of its diagnostic value in the context of state-of-the-art extended PZB protocols. In general, it remains questionable whether adequate TZ sampling is obtained with TRUS-guided TZB. Earlier series showed that positive TZB did not correlate well with TZ cancer upon RP, with 39.5% of patients with a positive TZB having no PCa in the TZ upon RP. This underperformance of TRUS-guided TZB for prediction of involvement of the TZ upon RP underlines the suggested value of other techniques (eg. imaging-based) and/or approaches (eg. transperineal) for prostate biopsy in a population with an expected high prevalence of TZ PCa, such as patients with a persistent suspicion of PCa following a negative baseline set of schematic TRUS-guided biopsies of the PZ. Another limitation of our series might be the fact that the indications for repeat TRUS-guided biopsy or MRGB during follow-up were not well defined and decisions regarding any repeat biopsy procedure were made upon the physician’s discretion.

We conclude that the incremental value of TZB at baseline schematic TRUS-guided biopsy is limited and could therefore be omitted. The ideal...
Prostate biopsy for prostate cancer diagnosis and risk stratification

A scheme for repeated TRUS-guided biopsy remains to be determined. It is important to acknowledge that based upon their RP specimen 54.5% (6/11) patients with a PCa diagnosis upon TZB and/or MAB only had a Gleason \(3+3=6\) and/or stage pT3a PCa, see table 3., and there remains a need for repeated biopsies following initial negative PZ biopsies. As the prevalence of T2 PCa is likely to increase in a population following negative baseline TRUS-guided biopsy aimed at the PZ, we assume that there might be a role for TZB in the repeat biopsy setting. More importantly, PCA detection in a repeat biopsy population might be improved by a transperineal schematic and/or imaging-guided approach, as TRUS-guided biopsy might be unable to adequately sample the TZ. As far as the presented diagnostic yield of MAB is concerned, we think in our series it should be regarded as an additional PZB. As it is known that increasing the number of PZB from sextant to 8-12 core biopsy increases diagnostic yield, MAB of the PZ should be seen in this context. Thus we agree that the focus of baseline TRUS-guided biopsy should be on adequate, more extensive PZ sampling rather than on the addition of TZB. Prospective series on added value of TZB in repeat TRUS-guided biopsies will be on adequate, more extensive PZ sampling rather than on the addition of MAB. The most appropriate scheme and/or approach for repeat prostate biopsy in case of a persistent suspicion of PCa following a negative baseline set of TRUS-guided biopsies are warranted.

References


Chapter 3.2

Magnetic resonance imaging guided prostate biopsy in men with repeat negative biopsies and increased prostate specific antigen

Thomas Hambrock, Diederik M. Somford, Caroline Hoeks, Stefan A. Bouwense, Henk-Jan Huisman, Derya Yakar, Inge M. van Oort, J. Alfred Witjes, Jurgen J. Fütterer, Jelle O. Barentsz

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Abstract

**Purpose** Undetected cancer in repeated transrectal ultrasound (TRUS)-guided prostate biopsies in patients with increased prostate specific antigen (PSA) greater than 4 ng/ml is a considerable concern. We investigated the tumor detection rate of cancer-suspicious regions (CSR) on 3-Tesla (3-T) multi-parametric magnetic resonance imaging (MP-MRI) and subsequent magnetic resonance guided biopsy (MRGB) in 68 men with repeat negative TRUS-guided prostate biopsies. We compared results to those in a matched TRUS-guided prostate biopsy population. Also, we determined the clinical significance of detected tumors.

**Materials and Methods** A total of 71 consecutive patients with PSA greater than 4 ng/ml and 2 or greater negative TRUS-guided prostate biopsy sessions underwent 3-T MP-MRI. In 68 patients this was followed by MRGB directed towards CSRs. A matched multisession TRUS-guided prostate biopsy population from our institutional database was used for comparison. The clinical significance of detected tumors was established using accepted criteria, including PSA, Gleason grade, stage and tumor volume.

**Results** The tumor detection rate of multimodal 3 Tesla magnetic resonance imaging guided biopsy was 59% (40 of 68 cases) using a median of 4 cores. The tumor detection rate was significantly higher than that of TRUS-guided prostate biopsy in all patient subgroups (p<0.01) except in those with PSA greater than 20 ng/ml, prostate volume (PVol) greater than 65 cc and PSA-density (PSA-D) greater than 0.5 ng/ml/cc, in which similar rates were achieved. Of the 40 patients with identified tumors 37 (93%) were considered highly likely to harbor clinically significant disease.

**Conclusions** MP-MRI is an effective technique to localize prostate cancer. MRGB of CSRs is an accurate method to detect clinically significant prostate cancer in men with repeat negative TRUS-guided prostate biopsies and increased PSA.

Introduction

In 2008 prostate cancer (PCa) was the most commonly diagnosed cancer in men, accounting for 25% of all cancers. The most widely used tests to screen for PCa are digital rectal examination (DRE) and the prostate-specific antigen (PSA) blood serum test. Increased PSA is not cancer-specific since numerous benign prostate conditions can increase PSA. Urologists are increasingly faced with the dilemma of how best to treat a patient with increased PSA in whom repeat transrectal ultrasound (TRUS)-guided biopsies reveals no cancer.

Systematic prostate TRUS-guided biopsy is the standard procedure for prostate histological sampling. Prostate cancer is often multifocal and the volume sampled by systematic TRUS-guided biopsies is relatively small. The value of magnetic resonance imaging (MRI) to accurately localize prostate cancer is well established. The accuracy of cancer localization on anatomical T2-weighted imaging remains low. Thus, dynamic contrast-enhanced MR imaging (DCE-MRI) and diffusion weighted MR imaging (DWI) have been implemented to improve the accuracy of prostate cancer localization. A multiparametric MRI (MP-MRI) approach using a combination of these techniques appears to be optimal.

Imaging-guided biopsies are advocated to improve tumor detection. However, grayscale TRUS, the most commonly used technique for biopsy guidance, has low sensitivity to localize prostate cancer. A combined approach that appears more useful is systematic and additional lesion directed biopsies of suspicious areas at contrast-enhanced TRUS.

Our principal aim was to determine the tumor detection yield of MP-MRI followed by directed MR-guided biopsy (MRGB) in a large patient group clinically suspicious for cancer but with repeat negative systematic TRUS-guided biopsies. We also determined whether detected tumors were clinically significant.
Methods

Patients
Between August 2006 and March 2008, 71 consecutive patients with PSA greater than 4 ng/ml and 2 or greater negative TRUS-guided biopsy sessions (of which the last session included at least an extended scheme of 8, 9 or 10 cores, including TZ sampling) were referred from the departments of Urology at the Radboud University Nijmegen Medical Centre and the Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands, for clinically routine prostate MP-MRI. The institutional review board approved this study.

The histopathology database at our institution was searched for consecutive patients from January 2000 to December 2006 with 2 or more TRUS-guided biopsy sessions. Only patients who underwent at least 1 systematic biopsy protocol of 8 to 10 cores, including TZ biopsy, were included in analysis. At each TRUS-guided biopsy session the principal diagnosis, patient age, PSA and prostate volume were noted. To remove the bias effect of differences in PSA and prostate volume tumor detection rates were compared by subgroup analysis of PSA, prostate volume (PVol) and PSA-density (PSA-D).

Localization
To identify possible tumor site(s) MRI was done with a 3-T MR scanner (Trio Tim, Siemens, Erlangen, Germany) with an endorectal coil (Medrad) in 28 patients and with pelvic phased array coils only in 40. Axial, sagittal and coronal T2-weighted images, axial DWI and DCE-MR images were obtained using 15 ml gadopentetate dimeglumine. Prostate images were viewed on an in-house developed analytical software work station that projected calculated DCE-MRI parameters and apparent diffusion coefficient (ADC) maps as color overlays over T2-weighted images. All patient images were read in consensus by 2 readers (TH, JF) with 2 and 5 years of experience, respectively, with prostate MRI. MP-MRI images were used to determine up to 3 cancer-suspicious regions (CSR) per patient using features described in the literature.

MR Guided Biopsy
An average of 2 weeks (range 1 to 6) after initial MP-MRI to localize possible tumors and identify CSR for MRGB planning patients underwent 3-T prostate MRGB. Antibiotic prophylaxis was given with 500 mg ciprofloxacin orally. A previously described translation technique using a MR compatible biopsy device was used to obtain 18 gauge biopsy cores of re-identified CSRs with a MR compatible biopsy gun. Briefly, a needle guider attached to the arm of the biopsy device was inserted rectally and adjusted to aim toward the CSR in the prostate. Biopsies were obtained through the needle guider. Only CSR-directed biopsies were obtained with no random biopsies. All biopsies were done by one radiologist (TH). Samples were processed by routine histopathological fixation and staining, and evaluated by a histopathologist.

Statistical Analysis
The chi-square test was used to calculate significant differences between the MRGB and TRUS-guided biopsy subgroups. The Mann-Whitney U test was done to compare mean age, PSA, PVol and PSA-D between groups with significant differences considered at p<0.05. Statistical analysis was performed with SPSS®, version 16.0.01.

Tumor Clinical Significance
The clinical significance of detected tumors was determined by currently accepted criteria. In patients in whom radical prostatectomy (RP) was done after positive biopsy a Gleason grade 4 or 5 component, stage pT3 or tumor volume greater than 0.5cc was considered to represent clinically significant disease. In patients diagnosed with cancer in whom no RP was done cancer was considered significant when PSA at biopsy was greater than 10 ng/ml and PSA-D greater than 0.15 ng/ml/cc or Gleason grade 4 or 5 was found at biopsy.

Results
In 70 of 71 patients CSRs were identified on MP-MRI. One patient refused biopsy and in another none was performed due to a high bleeding risk and no certain evidence of tumor on MP-MRI. Thus, 68 patients underwent MRGB.

In the 68 patients mean age was 63 years (range 48 to 74) and median PSA was 13 ng/ml (range 4 to 243). They underwent a median of 3 previous negative TRUS-guided biopsy sessions (range 2 to 7). The median duration of prostate MRGB was 30 minutes (range 14 to 75). The tumor detection rate of MRGB was 59% (40 of 68 cases). A total of 260 prostate cores (directed cores only with no random cores) were obtained from 114 CSRs with a CSR tumor.
detection rate of 40% (46 of 114). The median number of biopsies per patient was 4 (range 2 to 7). Table 1 lists patient and pathological findings. A total of 28 patients had no tumor.

RP was done in 20 of the 40 patients with tumor. A Gleason score 7 or greater was found in 10 of these 20 patients (50%) with extracapsular disease evident in 6 of 20 (30%). In 10 of 20 cases tumor volume was greater than 0.5 cc with Gleason score 6. Thus, all patients with RP harbored clinically significant disease. The remaining 20 patients underwent external beam radiotherapy (11), brachytherapy (3), hormonal ablation (3) or active surveillance (3). In these patients biopsy Gleason score, PVol and PSA were used to assess clinically significant disease with biopsy Gleason score 7 or greater in 9 and PSA greater than 10 ng/ml plus PSA-D greater than 0.15 ng/ml/cc in 10. One patient had skeletal metastasis. Thus, clinically significant disease was considered present in 17 of the 20 patients (85%) and in 37 of all 40 (93%) with tumor. Aggressive cancer was evident in at least 19 of the 40 patients (48%) with tumor (Gleason score 7 or greater and/or pT3/N1/M1). Table 2 lists tumor characteristics. The principal tumor site was the most ventral aspect of the TZ in 26 of 46 cases (57%), followed by the PZ paramedian region in 9 (20%) and the PZ anterior horns in 5 (11%) (fig. 1). Figure 2 shows MRI in a patient in whom tumor was detected by MRGB.

In our reference database we identified 248 patients with at least 2 TRUS-guided biopsy sessions and 65 with 3 sessions. No MRI was done before biopsy in these men and biopsies were performed on a systematic basis only. Overall tumor detection rate at biopsy sessions 2 and 3 was 22% (55 of 248 cases) and 15% (10 of 65), respectively. Table 2 shows tumor detection rate in the TRUS-guided biopsy and MRGB subgroups according to PSA, PVol and PSA-D. MRGB achieved a significantly higher tumor detection rate in all PSA subgroups (p<0.01), and for prostate volume (p<0.01) and PSAD (p<0.05). However, in patients with PSA greater than 20 ng/ml, PVol greater than 65cc, and PSA-D less than 0.15 and greater than 0.5 ng/ml/cc superior results were evident but not significant (p>0.05, figs. 3 to 5). Self-limiting transurethral hemorrhage and uncomplicated urinary tract infection in one case each were the only procedure-related complications.

Table 1  Patient, radiological and pathological features

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<td>No. suspicious DRE (%)</td>
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Figure 1  Prevalence of 46 tumor positive CSRs (for 9 biopsies 2 adjacent regions were positive for total of 55 tumor maps) in prostate on MRGB

Prostate was divided into 5 craniocaudal segments equal to apex (a), mid apex (b), mid (c), mid base (d) and basal (e) levels. Red areas indicate 5 or greater positive CSRs. Orange areas indicate 4 positive CSRs. Yellow areas indicate 3 positive CSRs. Green areas indicate 2 positive CSRs. Blue areas indicate 1 positive CSR. R, right, L, left, VT, ventral TZ. MT, middle TZ. DT, dorsal TZ. AH, PZ anterior horn. DL, dorsolateral PZ. D, dorsal PZ.

Figure 2  ERC 3-T MP-MRI in 64-year-old male with 4 previous negative TRUS-guided biopsies, including 2×8, 10 and 12 cores, and PSA 18 ng/ml

T2-weighted axial (a) and coronal (b) images show low signal intensity lesions (arrow) in ventral portion of apex. This area showed restriction on ADC-map (c) and high K"trans on DCE-MRI (d). Axial T2-weighted true fast imaging with steady state precession during MRGB demonstrates needle guider (dashed red line) directed toward CSR (dashed yellow oval) (e). Histopathological analysis of biopsy cores revealed GS 4+3=7 PCa, consequent pelvic lymph node dissection showed metastatic disease.
### Table 2: TRUS-guided biopsy versus MRGB population

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<th>TRUS-GB2</th>
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### Table 2

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Discussion

Using state-of-the-art 3-TMP-MRI to localize tumors we noted that a definite diagnosis of prostate cancer could be made in 40 of 68 patients (59%) in whom repeated TRUS-guided prostate biopsies remained negative but continuous concern regarding cancer was evident. Of the 40 patients diagnosed with prostate cancer 37 (93%) were considered to harbor clinically significant disease. Therefore, it is justifiable to deduce that prostate MRI accurately portrays tumor sites and, thus, offers urologists a method to improve biopsy outcomes. Since MRGB is limited by restricted general availability, other methods of MRI targeted biopsy techniques could be considered, such as MR-TRUS fusion during TRUS-guided biopsy. Nevertheless, MRGB is probably the most accurate technique because translating CSRs to another imaging modality is not required.

For comparison we selected a TRUS-guided biopsy population from our institution that was clinically matched for age, atypia prevalence on previous biopsy, PSA, PVol and PSA-D. We also determined tumor detection rate in each subgroup. In most studies of 8 to 12-core extended schemes cancer was detected in around 10% to 17% of patients on the second biopsy. Thus, the overall 22% and 15% tumor detection rates at TRUS-guided biopsy sessions 2 and 3, respectively, at our institution are in agreement with reported data.

Since different PSA values can predict the likelihood of finding tumor and represent a bias for comparison, cases were substratified according to different PSA levels. MRGB detection rate was superior to repeat TRUS-GB sessions in all PSA subgroups (p<0.01) except in the group with a PSA greater than 20 ng/ml, in which a similar detection rate was achieved (50% vs 43%). PVol is another important factor that has a role in the tumor detection rate achieved by different biopsy protocols. In a previous series 8 cores were appropriate in patients with less than 30 cc prostates, 10 to 12 were needed in 30 to 50 cc prostates and greater than 12 were needed in prostates greater than 50 cc. In all prostate volume groups MRGB significantly outperformed TRUS-GB for tumor detection (p<0.05) except in excessively large prostates greater than 65 cc, in which similar rates were achieved.

In patients with tumor, PSA-D less than 0.15 ng/ml/cc is considered a good prognostic feature with a low progression rate. MRGB did not achieve significant detection improvements over TRUS-guided biopsies in this patient subset with probably insignificant disease. In contrast, in the greater than 0.50 ng/ml/cc PSA-D group tumors were likely to have larger volume and, therefore, they were more easily diagnosed by TRUS-guided biopsy.

In cases of negative TRUS-guided biopsies radical measures involving 24 to 64-core saturation biopsy were advocated with a reported detection rate of 18% to 34% at session 2. No widespread application and acceptance of this technique by urologists exist with conflicting published results. Saturation biopsy appears to increase tumor detection in high risk cases but the additional use of analgesia/anesthesia, the higher incidence of side effects and the high cost of processing the large amount of pathological material are its greatest drawbacks. Since our study shows that MRGB has a high tumor detection yield and requires a low number of cores (median 4), this method could be an appealing alternative to patient, urologist and pathologist alike.
Whether prostate MRGB detects a substantial proportion of potentially insignificant tumors is a legitimate question. Higher sensitivity to detect tumor implies a higher chance of finding tumors that do not need treatment, so-called clinically insignificant cancer. For PCA overtreatment of these tumors remains controversial\textsuperscript{24}. In the 1990s the concept of insignificant PCa based on tumor size and favorable pathological characteristics was proposed\textsuperscript{25}. Clinical criteria to predict such tumors were later defined as PSA of 10 ng/ml or less, Gleason score 6 or less, clinical stage pT2 or less and tumor volume 0.5 cc or less\textsuperscript{11,12,26}. In RP series the predominant tumor site is the PZ in almost 70\% of cases\textsuperscript{27}. Therefore, current systematic biopsy schemes extensively sample the PZ and, thus, the prostate dorsal region. In contrast, 31 of the 46 tumors (68\%) in our series were anterior, 26 (57\%) were in the ventral TZ and 5 (11\%) were in the PZ anterior horns. This may explain the previous negative TRUS-guided biopsies in our patient group.

The current literature on prostate MRGB is sparse. The few currently available reports included a small number of patients, had excessively long imaging and biopsy times, and described only conventional T2-weighted MRI to determine CSRs for MRGB after 1 previous negative TRUS biopsy\textsuperscript{28-30}. Limitations of the current study relate principally to the fact that a direct comparison of our results to other literature could not be made. This was because of differences in PSA, PVol, the number of previous negative biopsies sessions and the biopsy schemes used at the initial sessions. A prospective, randomized trial would be superior. To determine the potential benefit we compared our study cohort with our institutional database, selecting similar patients but with TRUS-guided multiple biopsies and sub grouped by PSA, PVol and PSA-D. Since our institution is a referral hospital, patients with MRGB underwent heterogeneous previous biopsy protocols. The highest number of cores per biopsy session was 8 to 10, 12 and 18, and even saturation biopsy was done. Patients selected for study inclusion based on PSA greater than 10 ng/ml may represent a selection bias in relation to determining the clinical significance of detected tumors.

**Conclusions**

Results indicate that MP-MRI is highly effective to detect and localize clinically significant prostate cancer. Since guided biopsies toward CSRs on MP-MRI detect clinically significant tumor in a substantial proportion of patients, MRI should be considered essential in any evaluation protocol in patients suspected of harboring malignancy but who have had successive negative biopsies. Also, MRGB directed toward CSRs on MP-MRI is useful to accurately validate the correct sampling of suspicious prostate tissue. Because of the low number of cores needed, MRGB appears to be an appealing alternative to procedures such as saturation biopsy. Finally, detected tumors were mostly located in areas not explicitly sampled by routine schemes. Future studies of tumor detection rate using MR-TRUS fusion during TRUS-guided biopsies, including saturation targeting of suspicious areas, transperineal sampling of the anterior prostate or changing sampling sites on TRUS-guided biopsies in patients with repeat sessions, are needed and ideally should be compared to a MRI directed MRGB technique.
Chapter 3 Prostate biopsy for prostate cancer diagnosis and risk stratification

References


28. Anastasiadis AG, Lichy MP, Nagele U et al. MRI-guided biopsy of the prostate increases diagnostic performance in men with increased or increasing PSA levels after previous negative TRUS biopsies. Eur Urol 2006;50:738-748.

Chapter 3.3

Value of 3-T multiparametric MR imaging and MR-guided biopsy for early risk restratification in active surveillance of low-risk prostate cancer: a prospective multicentre cohort study

Caroline M. Hoeks, Diederik M. Somford, Inge M. van Oort, Henk Vergunst, Jorg Oddens, Geert Smits, Monique Roobol, Meelan Bul, Thomas Hambrock, J. Alfred Witjes, Jurgen J. Fütterer, Jelle O. Barentsz

Submitted Invest Radiol
Chapter 3 Prostate biopsy for prostate cancer diagnosis and risk stratification

Introduction

Prevalence of low-risk prostate cancer (PCa) has increased due to the application of prostate specific antigen (PSA) testing. Low-risk PCa patients are prone to overtreatment and its complications, which can undermine a patient’s quality of life. To avoid overtreatment, active surveillance (AS) is an accepted treatment alternative for low-risk PCa patients.

AS is mostly performed within trials, such as the Prostate Cancer Research International Active Surveillance (PRIAS) initiative. Selected patients with presumed low-risk PCa are followed by regular PSA measurements, digital rectal examinations (DRE) and annual repeat systematic transrectal ultrasound (TRUS)-guided biopsy. PSA kinetics, Gleason grade upgrading (Gleason 4 and/or 5 component) and volume progression are generally used as criteria for disease progression. However, rather due to TRUS-guided biopsy undersampling upon inclusion than due to true cancer progression, 20-30% of AS patients actually harbor intermediate- to high-risk PCa at inclusion.

Early identification of these patients, who were incorrectly deemed suitable for AS, may be essential to maintain the opportunity for appropriate curative treatment within their window of curability. The detection of a Gleason 4 and/or 5 component or of a larger cancer volume or of multifocality of a Gleason $\leq 3$ PCa, results in re-stratification of these PCa patients into a higher risk category. Risk re-stratification implies that a patient cannot continue AS and needs radical treatment.

MR-guided biopsy (MRGB) has shown to improve identification of patients with Gleason 4-5 cancers due to a better highest Gleason grade concordance (88%) with prostatectomy specimens compared to TRUS-guided biopsies (55%, p=0.001). This higher Gleason concordance of MRGB specimens with radical prostatectomy (RP) specimens is possible due to better detection and targeting of the most aggressive area of a cancer suspicious region (CSR) on MP-MRI. Only a few studies have related MR imaging results to AS outcome.

To our knowledge, MRGB has not previously been evaluated at AS inclusion. Our hypothesis is that combined MP-MRI and MRGB will improve current TRUS-guided biopsy based selection of patients for AS by early detection of patients harboring intermediate- to high-risk PCa. Therefore, our purpose is...
Materials and Methods

Within 4 reference centers participating in PRIAS, a prospective side-study was initiated (MR-PRIAS) consecutively including patients from August 2009 to March 2012. Patient selection is presented in Figure 1. Patient informed consent was obtained for the study as well as for the side-study and institutional review boards of the participating hospitals approved our study. Inclusion and exclusion criteria are depicted in Appendix 1. In our side-study, patients on AS underwent MP-MRI in the second and MRGB in the third month of follow-up after initial PCa diagnosis upon systematic TRUS-guided biopsy (time-point zero). Initial systematic TRUS-guided biopsy existed of 9-10 cores, sampling both the peripheral zone (PZ) and the transition zone (T2). Part of our patient population has been reported earlier. The earlier paper described the value of apparent diffusion coefficient (ADC) values of diffusion-weighted MR imaging (DWI) scans for PCa differentiation in PCa on AS. The current study reports on overall outcome of incorporating MP-MRI and MRGB in AS and the consequences for patient management.

MR Imaging
Pelvic MR imaging for lymph node and bone staging (30 min) was followed by MP-MRI of the prostate, consisting of T2-weighted MR imaging, DWI and dynamic contrast-enhanced MR imaging (DCE-MRI) (40 min protocol). Imaging was performed on a 3-T MR system (Trio Tim, Siemens, Erlangen, Germany) using a pelvic phased-array and an endorectal coil (ERC) (Medrad, Pittsburgh, USA) filled with 40 mL of perfluorocarbon (Fomblin, Solvay-Solexis, Milan, Italy). DCE-MRI was performed by initial acquisition of proton-density weighted images, followed by spoiled T1-weighted gradient echoes during fast (2.5 mL/s) intravenous injection of 0.1 mmol of gadopentetate dimeglumine (Dotarem, Guerbet, Paris, France) per kilogram of bodyweight. MR imaging parameters are presented in appendix 2.

MR Imaging Interpretation
An experienced radiologist (JOB) with 18 years of experience in prostate MR imaging evaluated the MP-MRI examinations on in-house developed

Figure 1  Study-flow-diagram showing patient selection
software, while disposing of clinical patient data\textsuperscript{35}. On the software, T2-weighted MR imaging, DWI and DCE-MRI were interpreted simultaneously\textsuperscript{15}. The PI-RADS system was used to define CSRs\textsuperscript{16}. Every CSR was scored on a 1-5 point scale for T2-weighted MR imaging, DWI and DCE-MRI separately. Subsequently an overall 5 point score, based on the whole MP-MRI exam, was given for every CSR\textsuperscript{21}. The five-point scale was defined as 1) highly unlikely 2) unlikely 3) equivocal 4) likely 5) highly likely presence of clinically significant PCa. PCa staging was performed in compliance with established criteria\textsuperscript{41}. When MP-MRI lacked CSRs, AS was continued without performing MRGB.

MR guided prostate biopsy
Only when MP-MRI showed one or more CSRs, another experienced radiologist (CMH) with 3 years of experience in MRGB performed MRGB of every predefined CSR on a 3-T scanner in a separate examination session (MAGNETOM Skyra, Siemens, Erlangen, Germany)\textsuperscript{16}. MRGB was performed for every CSR, regardless of CSR PI-RADS scores.

Risk re-stratification
Risk re-stratification was 1) based on MR imaging by histopathologically proven MR imaging suspicion of node/bone PCa metastases\textsuperscript{4} and/or 2) based on MRGB specimens (of local prostate MR imaging CSRs) using criteria of presence of a Gleason grade 4 and/or 5 component\textsuperscript{4} and/or a stage $\geq$ pT3 cancer (cancer invading (peri-prostatic) fat or seminal vesicles)\textsuperscript{40} and/or multifocality of $\geq$ 3 foci (including foci on initial TRUS-guided biopsies) Gleason score $\geq$3+3 cancer. The latter criterion of cancer multifocality was applied to evaluate the number of additionally detected cancer foci after including MRGB specimens and to compare it to the PRIAS risk re-stratification criterion of $> 2$ cores with PCa in TRUS-guided biopsy\textsuperscript{4}. An MRGB focus located contralateral to the initial TRUS-guided biopsy cancer location or a focus in the apex versus the base and vice versa was considered a separate cancer focus. Risk re-stratified patients were no longer eligible for active surveillance and underwent radical treatment. In order to evaluate cancer volume using MRGB, we retrospectively measured maximal cancer core length (MCCL): the longest MRGB cancer core length taken from one CSR. A MCCL $\geq$ 6 mm is related to a cancer volume $\geq$ 0.5cc in RP specimens using schematic mapping biopsy\textsuperscript{20}.

Follow-up
After 11-12 months of follow-up repeated MP-MRI of the prostate, with identical imaging parameters to the initial MR imaging exam, was performed. Pelvic nodal and skeletal MR imaging was only repeated when the initial exam was suspicious for lymph node or bone metastases. Based on repeat MP-MRI, an additional repeated MRGB, similar in procedure to the initial MRGB, was performed in a second separate imaging session. After repeated MRGB, a repeated TRUS-guided biopsy was also performed later on the same day. TRUS-guided biopsy risk re-stratification criteria consisted of PCa presence in $> 2$ cores or a GS $\geq 7$ (7). Risk re-stratification criteria for repeat MP-MRI and repeat MRGB were conform initial criteria.

Histopathology
All biopsy samples were processed by routine fixation and staining and were evaluated by one genitourinary pathologist (CHK) with 19 years of experience, who was blinded to prior histopathology results. Gleason grading was performed according the consensus of the International Society of Urological Pathology in 2005\textsuperscript{21}.

Statistical analysis
Patient risk re-stratification rates were determined for initial and repeated MRGB and for repeated TRUS-guided biopsy. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test variables for normality. Parametric continuous variables were reported as mean +/- 95% confidence interval, whereas and non-parametric continuous variables were reported as median and the inter-quartile range. Parametric variables were analyzed using independent t-tests and non-parametric variables were evaluated using Mann-Whitney U tests. Two-sided Pearson Chi-square tests were used to compare proportions. ROC analyses were applied to compare different MP-MRI techniques. Analyses were performed using PASW Statistics version 18 (SPSS Inc. Hong Kong). The threshold for significance was set at $P<0.05$.

Results
Initial risk re-stratification
Sixty-six patients were included in our side-study and underwent MP-MRI. Two patients requested to be excluded from the protocol before MRGB.
Patient characteristics of the remaining 64 AS patients are shown in table 1. One patient was excluded due to MR imaging suspicion of a bone metastasis in his third lumbar vertebra, which upon biopsy appeared to be a metastasis from malignancy of unknown origin. MRGB was performed in 62 out of the 63 remaining patients. In one patient MRGB was not performed, as MP-MRI did not show a CSR and this patient remained on active surveillance. In the other 62 patients, a median of 2 (IQR 1-2) CSRs were present and a median of 4 MRGB cores (IQR 3-5) were taken. A patient example is illustrated in figure 1. Twenty four percent (15/63) of the 63 patients were risk re-stratified and thus underwent radical treatment. MRGB and MCCL results are presented in table 2.

Sixty percent (9/15) of risk re-stratified patients had an MCCL ≥ 6.0 mm. The remaining 48 patients continued AS. Sixty-three percent (30/48) of these patients had a cancer-negative MRGB specimen. In 70% (21/30) of these patients with a cancer-negative MRGB, prostatitis was present in the histopathology specimen.

Risk re-stratification at 12 months follow-up
In 37 out of 48 remaining patients (77%) a follow-up of 12 months was available at July 31st 2012. Of these 37 patients 7 patients did not undergo repeat examinations due to other reasons as summarized in figure 1. Follow-up MRGB and MCCL results for the remaining 30 patients are presented in table 3. Forty-seven percent of these follow-up patients (14/30) were risk re-stratified based on MRGB (10% (3/30) MRGB only) and/or TRUS-guided biopsy. Forty-three percent (6/14) of risk re-stratified patients had an MCCL ≥6.0 mm. These fourteen risk re-stratified patients remained undetected on initial combined MP-MRI and MRGB. In 4 of these patients the CSR was detected on initial MP-MRI. The initial MRGB, however, did not sample prostate tissue (n=2) or did not detect small cancers (MCCL 1.5-2 mm) (n=2). In the other 10 out of 14 patients small lesions (<0.5 cc) were missed on MP-MRI (MCCL 0.3-4.5 mm).

For 14 out of 30 patients with an initial cancer-negative MRGB, repeat examinations were available. The negative predictive value (NPV) of a cancer-negative MRGB for risk re-stratification at repeat examinations was 79% (11/14) with a 95% confidence interval of 52%-93%).

Table 1  Patient characteristics of 64 MP-MRI patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All included patients (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Median (IQR)</td>
<td>65.7 (62.1-70.1)</td>
</tr>
<tr>
<td>PSA (ng/ml), Mean (CI)</td>
<td>6.5 (5.99-6.93)</td>
</tr>
<tr>
<td>PSA density (ng/ml/cc), Mean (CI)</td>
<td>0.1 (0.12-0.14)</td>
</tr>
<tr>
<td>Prostate volume (cc), Median (IQR)</td>
<td>45.8 (38.0-66.1)</td>
</tr>
<tr>
<td>Number previous negative TRUS-GB sessions, Median (Range)</td>
<td>0 (0-7)</td>
</tr>
<tr>
<td>Total number of TRUS-GB cores at diagnosis, Median (IQR)</td>
<td>10 (9-10)</td>
</tr>
<tr>
<td>TRUS-GB to MRI interval in months, Median (IQR)</td>
<td>2.1 (1.6-2.7)</td>
</tr>
<tr>
<td>TRUS-GB to MRGB interval months, median (IQR)</td>
<td>2.7 (2.0-3.3)</td>
</tr>
<tr>
<td>Clinical stage, (Percentage, (fraction), [95% confidence interval])</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>76.6 (49/64), [64.8-85.4]</td>
</tr>
<tr>
<td>T2a</td>
<td>18.8 (12/64), [10.9-30.1]</td>
</tr>
<tr>
<td>T2b</td>
<td>3.1 (2/64), [0.2-11.3]</td>
</tr>
<tr>
<td>T2c</td>
<td>1.6 (1/64), [0.0-9.1]</td>
</tr>
<tr>
<td>Positive TRUS-GB cores at diagnosis, 1</td>
<td>67.2 (43/64), [55.0-77.5]</td>
</tr>
<tr>
<td>2</td>
<td>32.8 (21/64), [22.5-45.0]</td>
</tr>
<tr>
<td>Gleason score at diagnosis, 3+3=6</td>
<td>93.8 (60/64), [84.6-98.0]</td>
</tr>
<tr>
<td>lower</td>
<td>6.3 (4/64), [2.0-15.4]</td>
</tr>
</tbody>
</table>

Prostate volume (I) was the only non-parametric continuous variable. P-values were calculated using an independent t-test for parametric, a Mann-Whitney u test for non-parametric variables and a Chi-square test for proportions. A p-level <0.05* was considered to represent a significant difference. * = all patients did not include patients excluded on patient request. However this column does include the patient, who was excluded due to a bone metastasis of cancer of unknown origin. *= n=47 MRGB patients + 1 patient without MRGB due to lack of CSRs on MP-MRI. |= this column of patients with risk re-stratification does not include the patient who was risk re-stratified based on a bone metastasis of unknown cancer origin. SD= standard deviation, IQR= inter-quartile range, TRUS- Bx= systematic transrectal ultrasound biopsy, AS= active surveillance, PSA= prostate specific antigen, MRI= magnetic resonance imaging, CI= 95% confidence interval, MRGB= MR guided prostate biopsy
In cancer-negative CSRs, DCE-MRI was more frequently false-positive (with a score of 1-3 points higher than the T2-weighted MR imaging score in 43% (46/107) as compared with DWI (in 32% (33/107), p=0.07). An overall CSR PI-RADS ≤ had a NPV of 84% (38/45) for detection of cancer and a NPV of 60% (45/75) for detection of a Gleason grade 4 and/or 5 PCa upon MRGB. A CSR PI-RADS ≥ had a sensitivity of 65% (36/56) and of 70% (11/16) for detection of cancer and of Gleason grade 4 and/or 5 PCa upon subsequent MRGB respectively. Sixty-four percent (69/107) of cancer-negative CSRs had an overall PI-RADS ≥.

### MR imaging

MP-MRI evaluation on both 3 and 12 months resulted in a total of 168 CSRs. As this study started at the beginning of the PI-RADS implementation, PI-RADS scores were available for 155 CSRs. Seventy-eight percent (121/155) of CSRs were located in the PZ, 15% (23/155) were located in the TZ or at the border of the PZ and TZ or seminal vesicles (7% (11/155)). MRGB specimens showed cancer in 48/155 (31%) CSRs. Cancer-negative MRGB specimens mainly contained prostatitis in 41% (44/107) and healthy prostate tissue in 38% (41/107). AUC for PCa and Gleason grade 4 and/or 5 PCa detection using overall PI-RADS scores were 0.73 (0.65-0.82) and 0.81 (0.70-0.92) respectively.

### Table 2

<table>
<thead>
<tr>
<th>MRGB results: active surveillance unsuitable patients with risk re-stratification</th>
<th>Number (%)</th>
<th>Biopsy core specimen maximal cancer core length in mm (mean, (95% confidence interval))</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRGB GG 4 or 5 and stage ≥pT3</td>
<td>2 (13)</td>
<td>8.8 (7.2-10.4) ≥6 mm: n=2</td>
</tr>
<tr>
<td>MRGB GG 4 or 5</td>
<td>5 (31)</td>
<td>9.7 (7.7-11.7) ≥6 mm: n=4</td>
</tr>
<tr>
<td>MRGB Multifocality</td>
<td>2 (13)</td>
<td>4.0 (0.0-7.9) ≥6 mm: n=1</td>
</tr>
<tr>
<td>MRGB 2 foci GS 3+3</td>
<td>4 (25)</td>
<td>4.3 (0.9-7.7) ≥6 mm: n=1</td>
</tr>
<tr>
<td>MP-MRI suspicion ≥T3, local MRGB: GS 3+3 without extra-capsular extension</td>
<td>2 (13)</td>
<td>8.5 (6.5-10.5) ≥6 mm: n=1</td>
</tr>
<tr>
<td>Total (% MRGB)</td>
<td>15 (24)</td>
<td>6.9 (4.3-9.5) ≥6mm: n=9</td>
</tr>
</tbody>
</table>

# not conform predefined risk re-stratification criteria, MRGB: MR guided prostate biopsy, GG: Gleason grade, GS: Gleason score, MP-MRI: multiparametric MR imaging, MCCL: maximal cancer core length. Calculation of MRGB maximal cancer core length is based on the highest MRGB maximal cancer core length for every patient. # The total amount of 63 patients exists of the 62 patients undergoing MR guided biopsy and 1 patient not undergoing MR guided biopsy due to the lack of CSRs.

### Table 3

<table>
<thead>
<tr>
<th>Repeat MRGB results: active surveillance unsuitable patients with risk re-stratification at 12 months of follow-up</th>
<th>Number (% subtotal risk re-stratification patients)</th>
<th>MRGB maximal cancer core length* in mm (mean, (95% confidence interval))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both MRGB and TRUS-GB GG 4 and/or 5</td>
<td>4 (31)</td>
<td>5.3 (3.8-6.8) ≥6 mm: n=2</td>
</tr>
<tr>
<td>MRGB GG 4 and/or 5 and TRUS-GB GS ≤3+3 cancer in &gt;2 cores</td>
<td>1 (8)</td>
<td>4.4 (n.a.)</td>
</tr>
<tr>
<td>Only TRUS-GB GG 4 and/or 5</td>
<td>1 (8)</td>
<td>2.7 (n.a.)</td>
</tr>
<tr>
<td>TRUS-GB GS ≤3+3 cancer in &gt;2 cores and MRGB multifocality</td>
<td>2 (14)</td>
<td>6.5 (5.5-7.5) ≥6 mm: n=2</td>
</tr>
<tr>
<td>Only MRGB multifocality, (2 foci, n=1#)</td>
<td>3 (21)</td>
<td>4.2 (1.3-7.0) ≥6 mm: n=1</td>
</tr>
<tr>
<td>Only TRUS-GB GS ≤3+3 cancer in &gt;2 cores</td>
<td>3 (23)</td>
<td>5.7 (2.8-8.6) ≥6 mm: n=1</td>
</tr>
<tr>
<td>Total (% MRGB)</td>
<td>14 (47)</td>
<td>5.0 (3.0-6.0) ≥6 mm: n=6</td>
</tr>
</tbody>
</table>

# not conform predefined risk re-stratification criteria. Calculation of MRGB maximal cancer core length is based on the highest MRGB maximal cancer core length for every patient, MRGB: MR guided prostate biopsy, TRUS-Bx: TRUS-guided biopsy, GG: Gleason grade, GS: Gleason score, MP-MRI: multiparametric MR imaging.
Chapter 3 Prostate biopsy for prostate cancer diagnosis and risk stratification

Figure 2  Sixty-one year-old male on active surveillance with a PSA level of 7.1 ng/ml, a PSA-D of 0.19 ng/ml/cc and a clinical stage T1c. This patient was diagnosed with Gleason score 3+3=6 PCa in 5 volume-percent in 1 out of 12 cores in the PZ at the right base. MP-MRI and 4-core MRGB were performed within 3 months after diagnosis.

(a) Axial T2-weighted turbo spin echo image (TR 4280 ms, TE 99 ms): a low signal intensity (white arrows) is present in the ventral transition zone at the level of the mid-prostate. The inhomogeneous nodular pattern of the transition zone has been replaced by a drop-shaped homogeneous low-signal intensity. This cancer suspicious region has asymmetry to the right side.

(b) Axial apparent diffusion coefficient (ADC) map of diffusion weighted imaging (single-shot echo planar imaging, TR 2600 ms, TE 90 ms, b-values 0/50/500 and 800 s/mm²) at the level of the mid-prostate. A low ADC value of ADC 0.50×10⁻³ mm²/s, suspicious for prostate cancer, was present in the right side of the ventral transition zone (dotted line).

(c) Axial overlay of Ktrans parameter in dynamic contrast enhanced MR imaging (three-dimensional spoiled gradient echo TR 36 ms, TE 1.4 ms, temporal resolution 3.4 s), as calculated by the Tofts model, on the axial T2-weighted turbo spin echo image (TR 4280 ms, TE 99 ms). Red areas of increased contrast enhancement are present in large areas of the prostate. Increased enhancement may be present in case of benign prostate hyperplasia, prostatitis and prostate cancer. Also in the right ventral prostate (dotted line) increased enhancement is present. Enhancement in this region was suspicious for prostate cancer, due to wash-out: a decline at the end of the relative gadolinium contrast-to-time curve (d).

(d) Axial angulated balanced gradient echo image (TR 4.48 ms, TE 2.24 ms) of the needle position in the lesion presented in a–c directly after biopsy. The lesion (green dotted line) can be appreciated in the prostate (blue dotted line). The needle artifact (white line) is present in the lesion. The needle guide (white arrows) is also depicted. The MR guided biopsy specimen (total only 4 cores) contained a Gleason score 4+3=7 prostate cancer in 80 volume-percent. This patient’s management was subsequently redirected towards definitive therapy, which existed of EBRT.
Discussion

Our initial results show that the application of MP-MRI and MRGB in an AS protocol may contribute in early identification of patients with Gleason grade 4 and/or 5 PCa, while also improving the selection of AS suitable patients. Our initial risk re-stratification rate using MP-MRI and MRGB at 3 months (24%) is comparable to risk re-stratification rates (17-27%) in studies on repeated TRUS-guided biopsy within 3 months after initial diagnosis. At 12 months of follow-up, combined MP-MRI and MRGB added little to repeat systematic TRUS-guided biopsy, as MRGB only additionally risk re-stratified 3 patients (21% (3/14)) due to PCA multifocality. Most patients, which were risk re-stratified by MRGB also were risk re-stratified by TRUS-guided biopsy. Due to TRUS-guided systematic sampling of Gleason grade 2 and/or 3 PCA or of small(ler) volume Gleason grade 4 and/or 5 PCa, which may have been missed on initial and/or repeat MR imaging, repeated TRUS-guided biopsy may have risk re-stratified a similar amount of patients compared with MRGB. Fourteen patients with risk re-stratification at repeat examinations were missed on initial combined MP-MRI and MRGB. Missing cancers on initial MP-MR imaging may be caused by low tumor Gleason grade and/or a small volume Gleason grade 4 and/or 5 components. In general, detected cancers at 12 months of follow-up had a lower cancer volume (5.0mm MCCL) compared with cancers detected at 3 months of follow-up (6.9mm MCCL).

MP-MRI had a sensitivity of 92% for detection of Gleason grade 4 and/or 5 PCa in case of higher PI-RADS scores (≥4) and a NPV of 100% for detection of Gleason grade 4 and/or 5 PCa in case of lower PI-RADS scores (≤2). Furthermore, an initial cancer-negative MRGB specimen had a NPV of 79% for risk re-stratification at 12 months follow-up. These results are comparable to those of Vargas et al., who reported an NPV of 96-100% and a sensitivity of 87-96% for biopsy upgrading in case of an MR imaging score ≤2 and ≥5 for PCA presence. While both scoring systems predicted presence of cancer from highly unlikely to highly likely on a 5-point scale, the system used by Vargas et al. was based on lower signal intensity on T2-weighted MR imaging and/or restricted diffusion on ADC maps, while the PI-RADS system also took shape and invasion of surrounding structures into account.

Our results for PCa detection accuracy using MP-MRI and MRGB in patients on AS are difficult to compare to literature. Other studies on MRI implementation in active surveillance did not use MP-MRI and/or MRGB. Our accuracies of 73% and 81% for detection of PCa and Gleason grade 4 and/or 5 PCa were quite reasonable considering the expected prevalence of predominantly lower Gleason grade PCa in this selected AS patient population. Lower Gleason grade cancers are known to have lower detection rates compared to higher Gleason grade cancers.

Upon simultaneous MP-MRI reading, DCE-MRI had more false-positive results compared to DWI. DCE-MRI may have false-positive results in case of benign conditions like prostatitis and/or benign prostatic hyperplasia. As our study is the first to evaluate MRGB in active surveillance, we applied low threshold criteria for CSR determination on MP-MRI followed by biopsy of all CSRs, also including equivocal (PI-RADS 1-3) regions. This resulted in a high number of patients (48% (30/63)) with cancer-negative CSRs upon MRGB. With increasing MR imaging experience in AS patients, false-positive results may be reduced. However, within the current explorative phase of MP-MRI implementation in AS, an important clinical implication of our study is that in AS patients acquisition of histopathology of a MP-MRI CSR is required due to the large amount of false-positive CSRs. Lack of histopathologic confirmation of a CSR may explain the poor results for MP-MRI as a predictive tool for active surveillance outcome in other studies.

Limitations of this study are firstly its small patient population and secondly its limited follow-up. Thirdly, as mentioned earlier, our risk re-stratification criteria may have been too strict as patients with multifocal Gleason score ≥3+3+6 cancer in both MRGB and TRUS-guided biopsy also were risk re-stratified. Therefore, our risk re-stratification rates may be inaccurate. Fourthly, as MP-MRI studies were read by an experienced radiologist, the general applicability of our results may be limited.

Conclusion

Incorporation of MP-MRI and MRGB in patients on AS may be useful as it results in early additional risk re-stratification and radical treatment of patients with intermediate to high-risk PCa, who were undersampled by initial TRUS-guided biopsy. Standardized MP-MRI interpretation using PI-RADS reveals that MP-MRI is a promising technique for differentiation
between AS suitable patients and patients with Gleason grade 4 and/or 5 PCa, the latter needing radical treatment. However, smaller cancers may be missed by MP-MRI and MRGB. Follow-up of our preliminary results of initial cancer-negative MRGB specimens showed a NPV of 79% of an initial cancer-negative MRGB specimen for risk re-stratification after 12 months. This finding shows that a cancer-negative initial MRGB may be a promising prognostic parameter for active surveillance patient selection. In conclusion, application of MP-MRI and MRGB biopsy in AS may contribute in early identification of patients with Gleason grade 4 and/or 5 PCa, while also selecting AS suitable patients.

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Chapter 4

GRADING OF PROSTATE CANCER USING DIFFUSION-WEIGHTED MR IMAGING (DWI)
Chapter 4.1

Diffusion and perfusion
MR imaging of the prostate

Diederik M. Somford, Jurgen J. Fütterer, Thomas Hambrock, Jelle O. Barentsz

Introduction

MR imaging plays an important role in the initial detection, localization, and staging of prostate cancer (PCa) and the assessment of post-treatment changes in PCa. In the near future, more image-guided techniques will become available, permitting precise biopsies and targeted focal treatment. Accurate and detailed information on tumor localization and size is needed to perform these image-guided interventions and therapies optimally. This article focuses on the role of diffusion-weighted MR imaging (DWI) and dynamic contrast-enhanced (DCE) MR imaging (or perfusion-weighted MR imaging) of the prostate. Background aspects and the clinical usefulness of DWI and DCE-MRI imaging for assessment of prostate cancer are reviewed.

Diffusion-Weighted MR Imaging

Diffusion and Prostate Cancer

Water molecules exhibit random motion in tissue, related to temperature (Brownian effect). DWI can quantify this water motion in an indirect manner. The DWI pulse sequence labels hydrogen nuclei in space, of which most is water molecules at any moment, and determines the length of the path that water molecules travel over a short period of time. DWI estimates the mean distance traveled by all hydrogen nuclei in every voxel of imaged tissue. The greater this mean distance the more self-diffusion of water molecules has occurred in a certain time interval. The degree of restriction to water diffusion in biologic tissue is inversely correlated to tissue cellularity and the integrity of cell membranes. Free motion of water molecules is more restricted in tissues with a high cellular density. The sensitivity of the DWI sequence to water motion can be varied by changing the gradient amplitude, expressed as the b-value. By performing DWI using different b-values, quantitative analysis can be made to determine the apparent diffusion coefficient (ADC).

In a volume of pure water this self-diffusion is equal in all directions, hence isotropic, and not restricted by any barrier. Because diffusion in tissue is limited by cellular structures, to establish a reliable estimate of this mean distance traveled by hydrogen nuclei, DWI is acquired in at least three different orthogonal directions for each b-value. This phenomenon of
extracellular water molecules have a far higher range of self-diffusion because they are not bound within membranes or by other cellular structures. When this is translated to prostate tissue, which is predominantly glandular tissue, the predominant contribution of the extracellular component is from tubular structures and their fluid content, whereas the intracellular component is determined by the epithelial and stromal cells. Fractional anisotropy is determined along the axis of the tubular structures of normal prostate tissue. A prerequisite for the correct interpretation of diffusion and ADC images relies on good knowledge of the diffusion characteristics of the different anatomic zones of the prostate and of benign prostatic conditions compared with prostate cancer.

The normal prostatic gland is rich in tubular structures. This allows for abundant self-diffusion of water molecules within their contents and provides high ADC values. In most cases, the peripheral zone can be easily discriminated from the central gland on DWI, because it displays relative higher ADC values. The exact background of this phenomenon remains unclear, because the exact ratio of extracellular to intracellular components for the different anatomic zones of the prostate has not yet been described. The central gland by observation consists of more compact smooth muscle and sparser glandular elements than the peripheral zone (PZ), however, leading to lower extracellular to intracellular fluid ratio. Furthermore, an age-related increase of T2 signal intensity of the PZ compared with the central gland has been observed, and an age-related increase in ADC values in both central gland and PZ has been observed, which are most likely caused by atrophy in the prostate leading to reduced cell volume and enlarged glandular ducts.

Benign prostatic hyperplasia (BPH) gives rise to nodular adenomas in the transition zone (TZ) and with time these compress the central zone to form a pseudocapsule, occupying the complete central gland. The PZ is usually not affected by BPH and retains its own histologic characteristics. BPH is defined by hyperplasia of all cells that constitute the TZ, with glandular, muscular, and fibrous compartments more or less evenly involved. This nodular hyperplasia gives rise to inhomogeneous diffusion patterns and because tubular structures often remain in place, the increased cellular density of hyperplasia, which is far less predominant than in PCa, might explain the observed reduction in ADC levels of the TZ on DWI, because of varying restriction of self-diffusion along different axes is called “anisotropy” and can also be used for tissue characterization. As in linear aligned tissue this anisotropy is more pronounced because there is one direction that contributes most to the DWI. Diffusion tensor imaging is a specific technique that quantifies the level of anisotropy in tissue, expressed in a fractional anisotropy value. This is low in imaged tissue without substantial anisotropy and is higher in imaged tissue in which the larger part of diffusion takes place in one direction. Diffusion tensor imaging can be used in addition to DWI to determine the structural organization of tissue along which diffusion takes place.

DWI typically has T2- and diffusion-weighted characteristics. The intensity of the signal on the diffusion-weighted image represents a combination of signal from the T2 relaxation and the dephasing caused by water motion in the presence of the diffusion gradients. At low b-values there is greater contribution from the T2 signal, and at higher b-values contrast is determined more by relative diffusion. When a diffusion image is bright because of high T2 signal rather than restricted diffusion, it is known as “T2 shine-through” effect. ADC maps should be obtained with at least two b-values to correct for the T2 shine-through effect, typically a low b-value, between 0 and 50 s/mm², and a high b-value. Tissue microperfusion can contaminate the signal attenuation in DWI acquisition, which could be decreased by using an additional low b-value greater than 0 (eg, b=50 s/mm²) and a high b-value.

To minimize the influence of bulk motion as a distorting factor and minimizing T2 shine-through, typically a TE as short as possible is chosen. Typical sequence parameters for the prostate (as used in the authors’ institution) include TR 2600 milliseconds; TE 91 milliseconds; and b-values of 0, 50, 500, 800 s/mm² in three orthogonal directions with parallel imaging (see appendix 2).

Diffusion-Weighted MR Imaging Characteristics of Prostate Tissue

DWI was initially used for the early detection of cerebral ischemia. The evolution of DWI characteristics in cerebral ischemia over time has classically been attributed to the extracellular to intracellular distribution of hydrogen nuclei caused by different types of edema. It has been postulated that extracellular water molecules have a far higher range of self-diffusion because they are not bound within membranes or by other cellular structures. When this is translated to prostate tissue, which is predominantly glandular tissue, the predominant contribution of the extra-cellular component is from tubular structures and their fluid content, whereas the intracellular component is determined by the epithelial and stromal cells. Fractional anisotropy is determined along the axis of the tubular structures of normal prostate tissue. A prerequisite for the correct interpretation of diffusion and ADC images relies on good knowledge of the diffusion characteristics of the different anatomic zones of the prostate and of benign prostatic conditions compared with prostate cancer.

The normal prostatic gland is rich in tubular structures. This allows for abundant self-diffusion of water molecules within their contents and provides high ADC values. In most cases, the peripheral zone can be easily discriminated from the central gland on DWI, because it displays relative higher ADC values. The exact background of this phenomenon remains unclear, because the exact ratio of extracellular to intracellular components for the different anatomic zones of the prostate has not yet been described. The central gland by observation consists of more compact smooth muscle and sparser glandular elements than the peripheral zone (PZ), however, leading to lower extracellular to intracellular fluid ratio. Furthermore, an age-related increase of T2 signal intensity of the PZ compared with the central gland has been observed, and an age-related increase in ADC values in both central gland and PZ has been observed, which are most likely caused by atrophy in the prostate leading to reduced cell volume and enlarged glandular ducts.

Benign prostatic hyperplasia (BPH) gives rise to nodular adenomas in the transition zone (TZ) and with time these compress the central zone to form a pseudocapsule, occupying the complete central gland. The PZ is usually not affected by BPH and retains its own histologic characteristics. BPH is defined by hyperplasia of all cells that constitute the TZ, with glandular, muscular, and fibrous compartments more or less evenly involved. This nodular hyperplasia gives rise to inhomogeneous diffusion patterns and because tubular structures often remain in place, the increased cellular density of hyperplasia, which is far less predominant than in PCa, might explain the observed reduction in ADC levels of the TZ on DWI, because of varying restriction of self-diffusion along different axes is called “anisotropy” and can also be used for tissue characterization. As in linear aligned tissue this anisotropy is more pronounced because there is one direction that contributes most to the DWI. Diffusion tensor imaging is a specific technique that quantifies the level of anisotropy in tissue, expressed in a fractional anisotropy value. This is low in imaged tissue without substantial anisotropy and is higher in imaged tissue in which the larger part of diffusion takes place in one direction. Diffusion tensor imaging can be used in addition to DWI to determine the structural organization of tissue along which diffusion takes place.
Chapter 4 Grading of prostate cancer using Diffusion-Weighted MR Imaging (DWI)

Details exceptionally well with high resolution. Because BPH has inhomogeneous diffusion characteristics, however, an increase in ADC also has been observed.

Prostatitis almost uniquely originates in the PZ. With respect to MR imaging, chronic prostatitis is of far more importance than the acute prostatitis counterpart because it is asymptomatic in many cases or its symptoms might mimic BPH, often associated with elevated prostate specific antigen (PSA) levels, raising the suspicion of PCa. Histologically, chronic prostatitis is characterized by extracellular edema surrounding the involved prostatic cells with concomitant aggregation of lymphocytes, plasma cells, macrophages, and neutrophils in the prostatic stroma. This abundance in cells as compared with normal prostatic tissue may lead to an ADC decrease because of decreased extracellular to intracellular fluid volume ratio. To the authors’ knowledge, no reports are available on the DWI characteristics of chronic prostatitis.

PCa is histologically characterized by a higher cellular density than normal prostate tissue, with replacement of the normal glandular tissue. This leads to a decrease in ADC values, compared with normal prostate gland (Fig. 1). Concomitantly with destruction of tubular structures in PCa, fractional anisotropy is also reduced. Interestingly, whereas well-differentiated PCa displays some tubular formation, with worsening differentiation the tubular structures become less predominant, and the cellular component of the cancer increases.

**Diffusion-Weighted MR Imaging in Addition to T1- and T2-Weighted MR Imaging**

One of the main drawbacks of DWI of the prostate is its suboptimal spatial resolution, even with currently widely available 3-T MR imaging scanners, combining pelvic phased array surface coil in combination with an endorectal coil for signal reception. T1-weighted imaging has a very limited role for the zonal delineation of the prostate and for tumor detection. The main usefulness of T1-weighted imaging is for the detection of post-biopsy hemorrhage, which can cause restricted diffusion, a possible confounding factor for both T2-weighted images and DWI.

T2-weighted imaging is currently the most widely used sequence for localization and staging of prostate carcinoma because it depicts anatomic

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**Figure 1** A 52-year-old man with prostate cancer of the left peripheral zone imaged at 3-T

(A) Axial T2-weighted MR image showing the presence of a low signal intensity area (white arrows) in the left peripheral zone. (B) ADC map at the same level as in figure A shows decreased ADC compared with the normal peripheral zone (black arrows). Whole-mount section histopathology (C) confirmed the findings and showed a tumor with Gleason Score of 3+3=6 (red area).
improve the staging performance\(^{24-27}\), mostly because of the improved localization, and thereby better evaluation of the prostatic capsule on T2-weighted images.

**Clinical Applications of Diffusion-Weighted MR Imaging for Prostate Carcinoma**

Recently, several reports on the use of DWI in patients with PCa, using endorectal or phased array coils have been published, with recent reports on the use of 3-T systems, proving that the clinical use of DWI is possible. The described diffusion acquisition parameters differ, however, mostly regarding the use of different b-values. This makes comparison between different reports difficult, but a clear identifiable trend in performance is present.

Several small studies have shown that PCa displays significantly lower ADC values compared with benign prostate tissue\(^{19,21,28,29}\), making it a potential useful measure for the localization of PCa. In various reports, mean ADC values range between 1.30 and 1.35x10^-4 mm²/s for normal TZ and 1.60 and 1.96x10^-4 mm²/s for benign tissue, including PZ and central gland\(^{14,21-28}\). DWI seems to perform better in localization of PCa compared with T2-weighted imaging\(^{13,30}\). At 1.5-T, T2-weighted imaging yielded sensitivities of 50% to 73%, whereas DWI yielded sensitivities of 73% to 84%, with only slightly reduced or comparable specificity. These results suggest a potential role of DWI in localization of PCa, especially in combination with T2-weighted imaging\(^{14,15,21,28}\). Because of the higher baseline ADC of the PZ, DWI performs best in differentiation of PCa from normal PZ in which more than 70% of the tumors originate. Compared with normal TZ ADC levels, PCa ADC levels are significantly lower\(^{14,15}\).

Because of lack of spatial resolution, DWI alone is not very useful in staging of PCa and lags behind conventional T2-weighted imaging. Like other advanced MR imaging techniques, however, such as DCE-MRI and MR spectroscopy, DWI draws attention to cancer suspicious regions (CSR) and this may help the radiologist in identifying regions of interest for local staging. Even with increasing spatial resolution caused by improved acquisition techniques the value of DWI alone in staging of PCa remains limited, but improves localization of lesions in combined reading with conventional and other functional MR imaging sequences. To the authors’ knowledge, no reports have yet been published on this subject.

DWI might have potential for grading of PCa. The histopathologic Gleason score remains one of the most important prognostic factors for progression-free and disease-specific survival in prostate cancer\(^{31-37}\). It is known that Gleason score obtained with transrectal ultrasound (TRUS)-guided biopsies can underestimate the final Gleason score obtained at radical prostatectomy (RP) in a substantial number of patients\(^{38-42}\). With evolving therapeutic options to consider in patients with localized PCa, accurate pretreatment grading for clinical decision making is of paramount importance. These therapies range from active surveillance (AS) to minimally invasive therapies, such as cryotherapy and high-intensity focused ultrasound, to radical therapies, such as RP in all its forms, brachytherapy, and external beam radiation therapy. Wang and colleagues\(^{43}\) investigated the ability of MR imaging to grade PCa. They found that higher Gleason grades were associated with lower tumor-muscle signal intensity ratios on T2-weighted imaging. Hypothetically, DWI has far more potential than any other MR imaging sequence in grading of PCa, because increased cellular density and loss of tubular structures implicate a higher Gleason score and also seriously hamper self-diffusion in the involved tissue leading to lower ADC levels on DWI\(^{34}\).

Few reports have been published on the detection of metastasis of PCa using DWI and currently this technique is not used for this purpose. One report by Nakanishi et al.\(^{42}\) did not show convincing superiority of DWI over skeletal scintigraphy for detection of osseous metastasis in a heterogeneous group of malignancies, 9 out of 30 being PCa patients. Skeletal scintigraphy still remains the gold standard for detection of osseous metastasis in prostate cancer. This is supported by a recent report on patients who underwent cerebral MR imaging including DWI, in which DWI proved insensitive to skull metastasis of PCa when compared with skeletal scintigraphy\(^{44}\). No significant reports on the detection of lymph node metastasis in prostate cancer have been reported to the authors’ knowledge.

**Technical Considerations in 3-T Diffusion-Weighted MR Imaging of the Prostate**

3-T systems, which are increasingly available, provide improved signal-to-noise ratios, with improved spatial and temporal resolution compared with 1.5-T systems\(^{45}\). Functional MR imaging methods, such as MR spectroscopy, DCE-MRI and DWI, will likely benefit from 3-T systems, because those have so far been hampered by limited resolution\(^{46}\). T2-weighted imaging, which has
been performed at 1.5-T for years with fair results, also has been proved to benefit; however, the window of improvement, as far as signal-to-noise ratio and spatial resolution is concerned, is much smaller. The authors’ experience is that improved spatial resolution with the use of DWI at 3-T improves zonal and tumor delineation and allows improved ability to compare ADC mapping with whole-mount sectioned RP specimens for research purposes. It has been shown that use of an endorectal coil significantly improves imaging quality in T2-weighted imaging. Rectal gas in the absence of an endorectal coil may lead to susceptibility artifacts. The endorectal coil enables better staging performance and improves sensitivity for the localization of prostate carcinoma with conventional MRT. In the authors’ experience, the use of an endorectal coil in conjunction with surface coils and parallel imaging improves image quality of DWI. This may result in improved overall performance of DWI in the localization, characterization, and delineation of PCa.

Limitations of DWI in PCa remain its low spatial resolution, which can be overcome by using this technique in combination with conventional T2-weighted MR imaging at 3-T by projecting the ADC maps as color overlay images on T2-weighted images. Furthermore, DWI is very susceptible to motion artifact, but when using a combination of surface and endorectal coil, these facilitate shortened imaging time and the use of a lower TE, while concomitantly improving image quality by diminishing susceptibility artifact from gas in the rectum.

**Dynamic Contrast-Enhanced MR Imaging**

**Angiogenesis and Prostate Cancer**

For a tumor, one critical factor that affects development, growth, invasiveness, and progression into the metastatic form is the ability of the tumor to generate new blood vessels. Angiogenesis, the sprouting of new capillaries from existing blood vessels, and vasculogenesis, the de novo generation of new blood vessels, are the two primary methods of vascular expansion by which nutrient supply to tumor tissue is adjusted to match physiologic needs. Tumor growth beyond 1 to 2 mm in solid tissues cannot occur without vascular support. The importance of angiogenesis in PCa is well established. The angiogenic process is a complex multistep sequence involving many growth factors and interactions between varieties of cell types. Circulating endothelial progenitor cells derived from bone marrow are recruited to sites of active angiogenesis by tumor-derived growth factors, such as vascular endothelial growth factor. The angiogenic process in PCa is highly dependent on vascular endothelial growth factor. Concomitantly, Jackson and colleagues detected vascular endothelial growth factor in tumor cells and peritumoral stromal cells of PCa specimens and in nonmalignant glandular epithelial cells and interglandular stromal cells in BPH specimens. With respect to the vasculature, it is clear that vascular endothelial growth factor is required for vascular homeostasis in BPH, and the overproduction of vascular endothelial growth factor maintains a high fraction of immature vessels (those without investigating pericytes or smooth muscle cells) in PCa.

A number of features are characteristic of malignant vasculature, many of which are amenable to study by DCE-MRI imaging and DWI techniques. These include (1) spatial heterogeneity and chaotic structure; (2) poorly formed fragile vessels with high permeability to macromolecules because of the presence of large endothelial cell gaps, incomplete basement membrane, and relative lack of pericytes or smooth muscle association with endothelial cells; (3) arteriovenous shunting; (4) intermittent or unstable blood flow; and (5) extreme heterogeneity of vascular density, with areas of low vascular density mixed with regions of high angiogenic activity.

These tumor-induced vascular and structural abnormalities result in functional impairments that are important to DCE-MRI observations. These include (1) increased interstitial pressure as a result of increased vascular permeability and poor lymphatic drainage, resulting in an enlarged interstitial space; (2) the transcapillary permeability is increased, allowing a more rapid exchange of low-molecular-weight contrast agents; and (3) the total vascular cross-sectional area may increase and can be combined with arteriovenous shunts. This gives rise to increased blood flow overall. The global increase in flow in cancers causes the bolus of contrast agent to arrive just a little earlier than it does in surrounding normal tissue. In the prostate, differences in arrival time between normal and abnormal tissues are short.

**Dynamic Contrast-Enhanced MR Imaging of the Prostate**

DCE-MRI is a noninvasive method to probe tumor angiogenesis. DCE-MRI following the administration of low-molecular-weight contrast media (≤1
MR imaging sequences can be designed to be sensitive to the vascular phase of contrast medium delivery, so-called “susceptibility-weighted (T2*-weighted) DCE-MRI”, which reflects tissue perfusion and blood volume; or to the presence of contrast agent, so-called T1-weighted DCE-MRI, which reflects the perfused microvessel area, permeability, and extravascular extracellular leakage space. Only the latter technique is discussed because this is by far the most common method used. Low-molecular-weight extravascular and extracellular contrast agents (gadolinium chelates) shorten the T1 relaxation of water and results in an increase in signal intensity on T1-weighted MR images. One essential aspect of DCE-MRI includes the dynamic MR imaging, referring to the temporal component, with complete coverage of the prostate with a fast T1-weighted sequence, which is required before, during, and after the bolus injection of a low-molecular-weight contrast agent (see Appendix 2, DCE-MRI protocol). DCE-MRI findings are related to differences in microvascular characteristics observed between normal and malignant prostatic tissues. The obtained T1-weighted DCE-MRI imaging data can be assessed in two ways.

The first is a semi-quantitative approach describing signal intensity changes by using a number of parameters, such as (1) the onset time of the signal intensity curve (t0-time from appearance in an artery to the arrival of contrast agent in the tissue of interest); (2) the slope and height of the enhancement curve (time-to-peak); (3) maximum signal intensity (peak enhancement); and (4) wash-in-washout gradient or plateau phase. These parameters are limited by the fact that they may not accurately reflect contrast agent concentration in tissues and can be influenced by the MR imaging scanner settings (including gain and scaling factors).

The second is a quantitative approach using pharmokinetic modeling, which is usually applied to changes in the contrast agent concentrations in tissue. Concentration-time curves are mathematically fitted by using one of many described pharmokinetic models, and quantitative kinetic parameters are derived. These include (1) transfer constant of the contrast agent (Ktrans); (2) rate constant (k1); and (3) interstitial extravascular extracellular space (Vr). Uncertainties exist with regard to the reliability of kinetic parameters estimates derived from the application of kinetic models to T1-weighted DCE-MRI datasets. The vascular input function used in the calculations also affects the reliability of the data obtained. Robust methods for measuring the arterial input function are essential. Currently, these methods are emerging but are still not widely available.

Currently, there are no FDA-approved DCE-MRI post-processing software packages available. Every institution is using its own developed software for analyzing these large datasets. Some companies are developing these packages for data evaluation; however, too little data are available for discussion. Furthermore, quantitative evaluation of the kinetic parameters has not been performed. There are no thresholds available, like in MR spectroscopy, for differentiation between benign and malignant tissue. This is probably caused by the inter-patient variability (variable vascular anatomy, atherosclerosis, cardiac output). Almost all imaging data in literature are evaluated based on qualitative assessment rather than quantitative thresholds.

Functional dynamic imaging parameters are estimated as follows: each MR imaging signal enhancement-time curve is first fitted to a general exponential signal intensity model. Consequently, the curve is reduced to a model with five parameters (t0, time-to-peak, peak enhancement, and wash-in-washout gradient or plateau). The reduced signal enhancement-time curve is converted to a reduced tracer concentration–time curve (with the tracer concentration in millimoles per milliliter) such that peak enhancement is effectively converted to gadolinium concentration. In the authors’ institution, the reduced plasma concentration–time curve is estimated by using a reference tissue method. Deconvolution of the plasma profile and estimation of the pharmacokinetic parameters conformed to the theorectic derivaitions but are implemented in the reduced signal space as Ktrans=Vr x k1, where Vr is an estimate of the extracellular volume (expressed as a percentage); Ktrans is the volume transfer constant (1 per minute); and k1 is the rate constant (1 per minute) between the extracellular extravascular space and the plasma space.
Clinical Application of Dynamic Contrast-Enhanced MR Imaging for Prostate Carcinoma

A fair number of studies have been performed to assess the value of DCE-MRI in PCa. Hara et al.\textsuperscript{62} showed that DCE-MRI was able to detect clinically important PCa in 93% of the cases, with TRUS-guided biopsy as the gold standard. In patients with at least two negative TRUS-guided biopsy sessions and rising PSA level, MR imaging plays an important role\textsuperscript{63}.

DCE-MRI is of importance in localization and staging of PCa (Fig. 2); several studies have found that DCE-MRI is superior to T2-weighted MR imaging for PCa localization. The authors’ group showed in a recent study that the area under the ROC-curve (AUC) for localizing PCa increased significantly from 0.68 with T2-weighted imaging to 0.91 when adding DCE-MRI\textsuperscript{24}. DCE-MRI is less accurate in the localization of tumor within the TZ, whereas PZ localization is markedly improved. Although the literature is sparse on the additional value of DCE-MRI in local staging, such imaging does seem to improve local staging performance. With the use of DCE-MRI the staging performance of the less experienced showed a significant improvement of the AUC compared with T2-weighted imaging alone (0.66 and 0.82, respectively; p<0.01)\textsuperscript{48}.

The application of DCE-MRI for detection of local recurrence after RP or external beam radiation therapy is increasingly being used. Haider and colleagues\textsuperscript{64} found that DCE-MRI performs better than T2-weighted imaging for the detection and localization of PCa in the PZ after external beam radiotherapy. DCE-MRI had significantly better sensitivity (72% versus 38%), positive predictive value (PPV) (46% versus 24%), and negative predictive value (NPV) (95% versus 88%) compared with T2-weighted imaging. Sciarra et al.\textsuperscript{65} reported the use of DCE-MRI and MR spectroscopic imaging for the detection of local recurrence in patients post-RP, and they concluded that the combination of these techniques is accurate for identification of local prostate cancer recurrence with biochemical failure (87% sensitivity and 94% specificity). This information could be helpful in the planning of salvage therapy.

Current research and focuses for the future in diffusion-weighted MR imaging and dynamic contrast-enhanced MR imaging of the prostate

The technical feasibility of DWI and DCE-MRI techniques for prostate imaging is now well established. Current and future research should focus on the additive values of DWI and DCE-MRI to conventional and other MR imaging techniques of the prostate.

The performance of prostate DWI and DCE-MRI is likely to gain from computer-assisted diagnosis\textsuperscript{66}. The combination of the quantitative functional data makes these techniques very suitable for computer analysis and prospective malignancy likelihood calculations. It was recently shown in 18 patients imaged at 3-T, that computer-assisted diagnosis software had a good diagnostic accuracy of discriminating normal from malignant prostate tissue with an AUC of 0.77 for DWI alone. For differentiation between PCa and normal PZ the AUC reached 0.89, whereas for differentiation from normal TZ the AUC was limited to 0.64. This is in concordance with other reports\textsuperscript{13,14,30,32}.

Figure 2 68-year-old man with prostate cancer of the right peripheral zone

(A) Axial T2-weighted MR image shows a low signal intensity area in the right peripheral zone. Color parametric maps were calculated (B) and demonstrated increased washout in the right peripheral zone. (C and D) Increased K\textsuperscript{trans} and k\textsubscript{ep}. (E) ADC map at the same level as in image A shows reduced ADC compared with the normal peripheral zone. (F) Histo-pathology confirmed these findings and showed a tumor with Gleason Score of 4+3=7 (red area).
Computer-assisted diagnosis seems to perform at least at a comparable level as conventional ADC mapping.

The strength of DWI and DCE-MRI might be in its potential to characterize tumors and possibly predict tumor behavior, making it a valuable tool in selecting patients for different therapies or active surveillance.

Summary

DWI is an advanced MR imaging technique that still needs to be clinically validated in addition to the more commonly used anatomic MR imaging sequences, such as high-resolution T2-weighted imaging. With the increasing availability of 3-T systems, and with the concomitant use of an endorectal coil, the quality of prostate DWI will further improve and this will likely increase its clinical usefulness.

DCE-MRI of the prostate is increasingly recognized as a potential tool for imaging of PCa, helping PCa localization, and improving local staging performance for less experienced readers. This technique should always be used in conjunction with T2-weighted imaging. Differentiation of prostatitis and BPH from PCa is inadequate with current anatomic MR imaging techniques. The combination of T2-weighted imaging, DWI and DCE-MRI (multiparametric MR imaging) may overcome these limitations and may be able accurately to detect, localize, stage, and grade PCa.

References

Grading of prostate cancer using Diffusion-Weighted MR Imaging (DWI)


Chapter 4.2

Relationship between apparent diffusion coefficients at 3-T MR imaging and Gleason grade in peripheral zone prostate cancer

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Abstract

Purpose To retrospectively determine the relationship between apparent diffusion coefficients (ADC) obtained with 3-T diffusion-weighted MR imaging (DWI) and Gleason grades in peripheral zone (PZ) prostate cancer (PCa).

Materials and Methods The requirement to obtain institutional review board approval was waived. Fifty-one patients with prostate cancer underwent MR imaging before radical prostatectomy (RP), including DWI with b values of 0, 50, 500, and 800 sec/mm². In RP specimens, separate slice-by-slice determinations of Gleason grade groups were performed according to primary, secondary, and tertiary Gleason grades. In addition, tumors were classified into qualitative grade groups (low-, intermediate-, or high-grade tumors). ADC maps were aligned to step-sections and regions of interest annotated for each tumor slice. The median ADC of tumors was related to qualitative grade groups with linear mixed-model regression analysis. The accuracy of the median ADC in the most aggressive tumor component in the differentiation of low- from combined intermediate- and high-grade tumors was summarized by using the area under the ROC curve (AUC).

Results In 51 RP specimens, 62 different tumors and 251 step-section tumor lesions were identified. The median ADC in the tumors showed a negative relationship with Gleason grade group, and differences among the three qualitative grade groups were statistically significant (p<.001). Overall, with an increase of one qualitative grade group, the median ADC (±standard deviation) decreased 0.18 × 10⁻³ mm²/s ± 0.02. Low-, intermediate-, and high-grade tumors had a median ADC of 1.30 × 10⁻³ mm²/s ± 0.30, 1.07 × 10⁻³ mm²/s ± 0.30, and 0.94 × 10⁻³ mm²/s ± 0.30, respectively. ROC analysis showed a discriminatory performance of AUC=0.90 in discerning low-grade from combined intermediate- and high-grade lesions.

Conclusion ADCs at 3-T showed an inverse relationship to Gleason grades in PZ PCa. A high discriminatory performance was achieved in the differentiation of low-, intermediate-, and high-grade PCa.

Introduction

Gleason grade of prostate cancer (PCa) is an important determinant of biologic activity and aggressiveness. A vast body of literature has established the Gleason grade as one of the paramount pathologic factors in the prediction of disease outcome in PCa. In fact, the grading scheme has now become so vital that it is often used as an integral piece of information for both disease management and treatment stratification in patients with prostate cancer before and after definitive therapy. Pretreatment knowledge of the final Gleason grade would be an important advance; however, such information remains elusive. Biopsy determination of Gleason grade often does not provide an accurate reflection of final Gleason grade (ie, whole-organ pathologic characteristics). Partin tables and risk stratification schemes that incorporate information from biopsy-determined Gleason grades into decision making are therefore rendered less accurate and less reliable. There is a definite need for a noninvasive method with which to improve the accuracy in determining the true Gleason grade before treatment.

Diffusion-weighted MR imaging (DWI) is a functional imaging technique that quantifies random Brownian motion properties of water molecules (diffusion) in tissue. The degree of restriction to water diffusion in biologic tissue is inversely correlated to tissue cellularity and the integrity of cell membranes. Diffusion of molecules also occurs across tissues, especially from areas of restricted diffusion to areas with free diffusion. The net displacement of molecules is called the apparent diffusion coefficient (ADC). With MR imaging, the ADC can be calculated by acquiring two or more images with a different magnetic field gradient duration and amplitude (b value). The contrast in the ADC map is dependent on the spatially distributed diffusion coefficient of the acquired tissues and does not contain T1 and T2* values. The role of DWI in tumor localization within the prostate has been extensively reported. However, its use in stratifying low- and high-grade PCa has not received much attention and is limited to biopsy-determined Gleason grades.

The purpose of our study was to determine the relationship between ADCs obtained with 3-T DWI and Gleason grades for peripheral zone (PZ) PCa.
Materials and Methods

Patients
Between August 2006 and January 2009, 70 consecutive patients with biopsy-proven prostate cancer, who were scheduled to undergo radical prostatectomy (RP), were referred from the departments of Urology at the Radboud University Nijmegen Medical Centre and the Canisius Wilhelmina Hospital in Nijmegen, The Netherlands, for clinically routine preoperative MRI of the prostate. The requirement to obtain institutional review board approval was waived.

MR Imaging Protocol
MRI was performed by using a 3-T MR system (Trio Tim; Siemens, Erlangen, Germany) and both an endorectal coil (Medrad, Pittsburgh, Pa) and a pelvic phased-array coil. The endorectal coil was filled with a 40-mL perfluorocarbon preparation (Fomblin; Solvay-Solexis, Milan, Italy). Peristalsis was suppressed with intramuscular administration of 20 mg of butylscopolamine bromide (Buscopan; Boehringer-Ingelheim, Ingelheim, Germany) and 1 mg of glucagon (Glucagen; Nordisk, Gentofte, Denmark).

After the correct endorectal coil position was confirmed with fast gradient-echo imaging, T2-weighted turbo spin-echo MRI was performed with the following parameters: in-plane resolution of 0.4×0.4 mm, repetition time of 3250 msec and echo time of 116 msec (3250/116), 120° flip angle, 15–19 sections, 3.0-mm-thick sections, echo train length of 15, 180×180-mm field of view, and 448×448 matrix; imaging was performed in transverse, coronal, and sagittal planes, covering the prostate and seminal vesicles. Then, single-shot echo-planar imaging was performed with diffusion-module and fat-suppression pulses. Water diffusion in three directions was measured by using \( b \) values of 0, 50, 500, and 800 s/mm\(^2\), 2500/81, a parallel imaging factor of three, 15–19 sections, 3-mm-thick sections, and an in-plane resolution of 1.5×1.5 mm. ADC maps were automatically calculated by the imager software with use of all four \( b \) values.

Reconstructed Whole-Mount Step-Section Preparation
After RP, prostate specimens were uniformly processed and entirely submitted for histologic investigation. Immediately after surgical resection, specimens were fixed in 10% neutral buffered formalin by using fine-needle formalin injections and stored overnight. Subsequently, the entire surface was marked with ink by using three different colors, after which the entire prostate specimen was cut into serial transverse 4.0-mm-thick slices perpendicular to the dorsal-rectal surface. All slices were macroscopically photographed with a charge-coupled device camera. The apex and base were sliced sagittally to assess the caudal and cranial surgical margins. Seminal vesicles were amputated at their junction with the prostate, sliced parallel to their junction, and embedded in total. The remaining slices were subdivided into halves or quadrants to fit routine cassettes. After histologic staining, all specimens were evaluated by one expert urological pathologist (CHK), with 17 years of experience. Tumors were outlined on the microscopic slides and subsequently mapped on the macroscopic photographs to allow reconstruction of tumor extent and multifocality. Each individual tumor was graded according to the 2005 International Society of Urological Pathology Modified Gleason Grading System. Tumors were staged according to the 2002 TNM classification, see appendix 3.

Annotations of MR Images
Retrospectively, after RP, annotations of MR images were performed in consensus by one radiologist (TH) and one urologist (DMS). To achieve good objective spatial coalignment accuracy, a number of strategies were applied. First, both ADC maps and RP step-sections were obtained perpendicular to the dorsal surface of the prostate. Second, the section and slice thicknesses used were similar. Third, objective mapping of MR sections to RP step-sections was performed by aligning the apex and base on MR images and step-sections in the cranial-caudal direction (Fig 1a). Starting from the apex, each consecutive ADC map was matched to the consecutive pathologic step-section. Finally, a per-slice subdivision was made. The PZ and transition zone (TZ) were identified on each slice and, with use of the urethra as reference, the PZ in both left and right halves was subdivided into the anterior horns, dorsolateral region, and dorsal segment (Fig 1b). The PZ, TZ, and urethra are well visible on ADC maps, allowing the schematic subdivision to be performed on ADC maps as well. The urethra again served to help identify the anterior horns, dorsolateral region, and dorsal segment. This schematic mapping allowed objective translation of tumor-containing regions from RP to ADC maps with a high degree of certainty.

A region of interest (ROI) was annotated and drawn to match the size and extent of the tumor determined from histologic examination as closely as
possible (Fig 1). ROIs were also placed in the contralateral segment of the PZ in mirror position to the tumor and were similar in size to the tumor ROIs. Normal regions were annotated purely to provide a visual reference of heterogeneity within the PZ compared with tumor values. Each separate step-section–ADC section match was annotated as a different tumor ROI and normal ROI. Only tumors originating in the PZ were annotated. Annotation of the following was omitted if applicable: (a) tumor ROI for a particular section if the corresponding pathologic step-section revealed a tumor smaller than 5 3 5 mm. This was due to the limit in spatial resolution of the DWI images. (b) Normal contralateral ROI of a particular section if the tumor extended beyond the midline (no mirror ROI possible) or if a second tumor was present in the mirror position of the first tumor.

Figure 1  (a) Images illustrate the systematic method used to obtain RP step-sections and corresponding ADC maps. The prostate was cut into step-sections perpendicular to the dorsal surface of the prostate (left), and the MR images were divided into the same number of sections (center). For each step-section, the corresponding ADC map was identified. GI = Gleason grade, Mid = midline, T = tumor.
Assessment of histologic tumor grade
Following annotations of ROIs on ADC maps, one radiologist (TH), together with one genitourinary pathologist (CHK) re-evaluated all step-sections that contained tumor. For each tumor present in the PZ of the prostate, separate Gleason grades were identified and quantified in percentages of the tumor slice volume. For each step-section, the primary, secondary, and tertiary tumor grade components were noted; these are referred hereafter as the Gleason grade group. A qualitative grade per step-section was also made, as follows: (a) low-grade lesions consisting of grade 2 or 3 components only; (b) intermediate-grade lesions consisting of grade 4 secondary or tertiary components (without any grade 5 components); and (c) high-grade lesions consisting of grade 4 primary components and/or grade 5 primary, secondary, or tertiary components. Each tumor ROI on ADC maps was subsequently correlated to the matching Gleason grade group, and the qualitative grade was determined for each step-section slice. An MR analytical software workstation developed in-house was used to draw ROIs and summarize the median and standard deviations of ADCs (in $10^{-3}\text{mm}^2/\text{s}$) calculated for each ROI.

Statistical Analysis
To determine the relationship between median tumor ADC and ordinal Gleason grade groups, a linear mixed-effect regression model with random tumor effect was used. This mixed-model regression analysis incorporates the dependency of repeated measurements within the same tumor. In an additional mixed-model analysis, the differences in median ADC between the three qualitative grade groups were estimated.

Apart from establishing a relationship between ADC and Gleason score, the diagnostic accuracy of using ADC to differentiate low-grade from combined intermediate- and high-grade tumors is of clinical importance. To this end, for every tumor, the histopathologic slice with the highest Gleason grade was matched to the corresponding ADC section, thereby identifying the median ADC that matched the most aggressive part of the tumor. If identical highest Gleason grade compositions were evident for different slices within the same tumor, the slice showing the lowest median ADC was used. The diagnostic accuracy of the median ADC in the differentiation of low-grade from combined intermediate- and high-grade groups was quantified with the area under the ROC curve (AUC). A significant difference was considered when $p<0.05$. Statistical analyses were performed with software (SPSS, version 16.0.01; SPSS, Chicago, Ill.).

Results
Of the 70 consecutive patients, 56 had clinically significant PZ tumors (>0.5 mL). In the remaining 14 patients, 11 had TZ tumors only and three had PZ tumors that were less than 0.5cc in volume (with Gleason grade 2 and/or 3 components only). In addition, five of the 56 patients were excluded owing to severe motion artifacts ($n=3$), widespread intraprostatic hemorrhage ($n=1$), or

Table 1  Summary of clinical and pathological characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>51</td>
</tr>
<tr>
<td>Clinical characteristics*</td>
<td></td>
</tr>
<tr>
<td>Median PSA level (ng/ml)</td>
<td>6.8 (1.7–42)</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>64 (49–69)</td>
</tr>
<tr>
<td>Pathological characteristics**</td>
<td></td>
</tr>
<tr>
<td>Stage T2a</td>
<td>5</td>
</tr>
<tr>
<td>Stage T2c</td>
<td>23</td>
</tr>
<tr>
<td>Stage T3a</td>
<td>18</td>
</tr>
<tr>
<td>Stage T3b</td>
<td>4</td>
</tr>
<tr>
<td>Stage T4</td>
<td>1</td>
</tr>
<tr>
<td>Gleason score ***</td>
<td></td>
</tr>
<tr>
<td>3+2</td>
<td>3</td>
</tr>
<tr>
<td>3+3</td>
<td>18</td>
</tr>
<tr>
<td>2+4</td>
<td>1</td>
</tr>
<tr>
<td>3+4</td>
<td>13</td>
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</tr>
<tr>
<td>4+4</td>
<td>2</td>
</tr>
<tr>
<td>4+5</td>
<td>3</td>
</tr>
</tbody>
</table>

* PSA: prostate-specific antigen. Numbers in parentheses are ranges. **Data are given as numbers of specimens. *** Data are given as number of tumors. PSA: prostate-specific antigen
severe ghosting artifacts on the MR images (n = 1). In the 51 RP specimens from these 51 patients, histologic analysis revealed a total of 62 different PZ tumors and 251 tumor lesions on different step-sections of the specimens. In none of the patients were tumors identified with a volume of less than 0.5cc and containing a Gleason grade 4 and/or 5 component. In total, 14 different Gleason grade groups were identified according to the primary, secondary, and tertiary features present. The patient and tumor characteristics are summarized in Table 1, and the ADCs are summarized in Table 2.

Table 2 Summary of ADCs and pathological characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of step-sections</th>
<th>Median ADC (×10^-3 mm^2/s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All peripheral zone lesions</td>
<td>251</td>
<td>1.02 ± 0.29</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+3</td>
<td>4</td>
<td>1.40 ± 0.18</td>
</tr>
<tr>
<td>3+2</td>
<td>11</td>
<td>1.16 ± 0.14</td>
</tr>
<tr>
<td>2+3(+4)</td>
<td>3</td>
<td>0.95 ± 0.04</td>
</tr>
<tr>
<td>3+2(+4)</td>
<td>3</td>
<td>1.20 ± 0.05</td>
</tr>
<tr>
<td>3+3</td>
<td>73</td>
<td>1.36 ± 0.26</td>
</tr>
<tr>
<td>3+3(+4)</td>
<td>3</td>
<td>1.29 ± 0.02</td>
</tr>
<tr>
<td>2+4</td>
<td>1</td>
<td>1.25 ± 0.00</td>
</tr>
<tr>
<td>3+4</td>
<td>46</td>
<td>0.97 ± 0.22</td>
</tr>
<tr>
<td>3+4(+5)</td>
<td>8</td>
<td>0.99 ± 0.11</td>
</tr>
<tr>
<td>4+3</td>
<td>54</td>
<td>0.92 ± 0.17</td>
</tr>
<tr>
<td>4+3(+5)</td>
<td>7</td>
<td>0.79 ± 0.15</td>
</tr>
<tr>
<td>4+4</td>
<td>17</td>
<td>0.68 ± 0.13</td>
</tr>
<tr>
<td>4+4(+5)</td>
<td>2</td>
<td>0.74 ± 0.02</td>
</tr>
<tr>
<td>4+5</td>
<td>19</td>
<td>0.79 ± 0.10</td>
</tr>
<tr>
<td>Qualitative grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-grade tumor</td>
<td>94</td>
<td>1.30 ± 0.30</td>
</tr>
<tr>
<td>Intermediate grade tumor</td>
<td>50</td>
<td>1.07 ± 0.30</td>
</tr>
<tr>
<td>High-grade tumor</td>
<td>107</td>
<td>0.94 ± 0.30</td>
</tr>
<tr>
<td>Normal mirror ROI</td>
<td>186**</td>
<td>1.60 ± 0.25</td>
</tr>
</tbody>
</table>

* data are give as medians ± standard deviations. ** in 65 matches, the normal mirror ROI could not be annotated due to the presence of contralateral tumor or tumor extending beyond the midline. ADC: apparent diffusion coefficient, ROI: region of interest.

The median tumor ADCs showed an association with the 14 Gleason grade groups (Fig 2). Results of the linear mixed-model analysis showed an inverse relationship (slope, -0.18×10^-3 mm^2/s; standard error, ±0.04; p<.001) between the median ADC and the three qualitative grade groups (Fig 3). Additional mixed-model analysis revealed that the difference (±standard deviation) between median ADCs of low- and intermediate grade tumors was 0.22×10^-3 mm^2/s ±0.03 (p<.001). The difference between intermediate- and high-grade tumors was 0.14×10^-3 mm^2/s ±0.03 (p<.001), and the difference between low- and high-grade tumors was 0.36×10^-3 mm^2/s ±0.04 (p<.001). Low-, intermediate-, and high-grade tumors had a median ADC of 1.30×10^-3 mm^2/s ±0.30, 1.07×10^-3 mm^2/s ±0.30, and 0.94×10^-3 mm^2/s ±0.30, respectively. Overall, the median ADC for normal mirror ROIs in the peripheral zone was 1.60×10^-3 mm^2/s ±0.25.

With use of ROC analysis of only the most aggressive part of the tumor, the median ADC enabled the differentiation of low-grade tumors from combined intermediate- and high-grade tumors with an AUC of 0.90 (95% confidence interval: 0.81-0.98) (Fig 4). Furthermore, it was noted that in 94% of tumors

Figure 2 Graph shows the relationship between median tumor ADC and Gleason grade groups

Chapter 4 Grading of prostate cancer using Diffusion-Weighted MR Imaging (DWI)
Chapter 4 Grading of prostate cancer using Diffusion-Weighted MR Imaging (DWI)

(58 of 62 tumors), the ADC section with the lowest median tumor ADC was in exact concordance with the pathologic slice with the most aggressive tumor composition. Figure 5 shows the visibility of different grade tumors on ADC maps.

**Figure 3** Graph shows the relationship between median ADC, qualitative grade groups, and the normal mirror ROI in the peripheral zone (PZ) by using the tumor section with the lowest median ADC. Slope estimate with the linear mixed-effect regression model was $-0.18 \times 10^{-3} \text{mm}^2/\text{s}$.

**Figure 4** ROC curve demonstrates the discriminating performance of median ADC in the differentiation between low-grade versus intermediate- and high-grade lesions. The tumor slice with the highest Gleason grade composition was used.

**Figure 5** Histologic step-sections and corresponding ADC maps for three patients with tumors (T) of different aggressivity. Window levels were kept the same for all patients. Gl. = Gleason grade, mADC = median ADC. (1) Images in a patient with a low-grade tumor (Gleason grade 3 + 3) and median tumor ADC of $1.24 \times 10^{-3} \text{mm}^2/\text{s}$. (2) Images in a patient with an intermediate-grade tumor (Gleason grade 3 + 4) and a median tumor ADC of $0.99 \times 10^{-3} \text{mm}^2/\text{s}$. (3) Images in a patient with a high-grade tumor (Gleason 4 + 5) and a median tumor ADC of $0.66 \times 10^{-3} \text{mm}^2/\text{s}$. Dashed lines on ADC maps indicate the tumor region.
Discussion

The results of this study showed that Gleason grade, and by inference aggressiveness, is related to the ADC determined at DWI. With use of a linear mixed-model approach, we determined that the median ADC significantly decreased an average of $0.18 \times 10^{-3}$ $\text{mm}^2/\text{s}$ per qualitative grade group interval. Further analysis showed that the difference between the median ADCs of low- and intermediate-grade tumors was larger than that between intermediate- and high-grade tumors. With use of the most aggressive component within the tumor as an end point, median ADC revealed an AUC of 0.90 in the differentiation of low-grade tumors from combined intermediate- and high-grade tumors.

The Gleason grade subgrouping enables better comparison and assessment of the effect of microscopic glandular differentiation, growth features, and structure of different PCa subgrades on the free diffusivity of water. Correlation of ADC to qualitative grade groups potentially allows a more practical utilization of the information in routine clinical decision making, risk stratification, and patient-tailored treatment options. Furthermore, the subdivision into low-, intermediate-, and high-grade tumors can allow meaningful cutoff points to be defined and can be used to help differentiate patient groups with different prognoses and, therefore, different management needs.

DWI is increasingly being incorporated into oncologic imaging, and information obtained with this technique is appealing as an imaging biomarker. Although the low ADCs found in most tumors have been attributed to increased cellular density, diffusion can also be influenced by fibrosis, glandular and stromal organization, and shape. Within the prostate, the predominant contribution of DWI signal is from the extracellular component (from tubular structures and their fluid content), with a lesser contribution from the extracellular stromal space and the intracellular components (epithelial and stromal cells). Because of the abundant self-diffusion of water molecules within the predominant tubular components within the PZ, their contents provide a high signal on ADC maps.

A rationale for the relationship between PCa aggressiveness and ADC can be suggested from the current understanding of the structural and organizational features of the epithelial, glandular, and extraductal components that exist in different grades of cancer. With increasing Gleason grade, the change in tissue organization to a more solid and compact architecture (with higher cellular density) should be reflected in restrictions in the distances of free water motion within the tissue. Well-differentiated prostate carcinomas display tubular formation with a concomitant higher contribution of unrestricted water motion to ADCs. Lower grade tumors are also known to have a remarkable heterogeneity in glandular size and the ability to grow between pre-existing ducts. Conversely, poorly differentiated adenocarcinomas show more expansive masses of small, tightly packed cell groups with small-to-absent lumina. Gleason grade 2 tumors are defined histologically by tightly packed, well-differentiated glandular components, whereas grade 3 tumors show wider-spaced tubuli with heterogeneity in ductal size and density, imposing fewer restrictions on extraglandular free water diffusivity motion. This basis also seems to be reflected in the finding that the ADCs for tumors with a grade 2 component were slightly lower than those in tumors with purely grade 3 components. Of the different Gleason grade groups, pure grade 3 (3 + 3) tumors showed the largest variation in median ADC, possibly reflecting the heterogeneity of lesions with sparse versus dense growth, akin to these. A large space for diffusion both between ducts and within ductal lumina in well-differentiated compared with poorly differentiated tumors is the most likely explanation for the observed differences in ADCs in low-grade compared with high-grade tumors.

Despite the fact that true Gleason score is not represented in transrectal ultrasound (TRUS)–guided biopsy cores in 30%–50% of patients, biopsy-determined Gleason score remains one of the most important factors in decision making. An accurate noninvasive method that improves the prediction of Gleason score may enable a substantial improvement in patient treatment by (a) enabling better treatment selection; (b) improving the targeting of lesions for biopsy, which would, therefore, provide a more representative Gleason score; (c) enabling better risk stratification and follow-up for patients who are being treated with active surveillance protocols; and (d) helping plan intensity-modulated radiation therapy for treatment of the dominant aggressive component.

For correlation analysis, each step-section that contained tumor was matched to an ADC map as a separate tumor lesion. The reasoning behind this...
approach was that tumors display remarkable intratumoral heterogeneity in their Gleason grade patterns and the ability to grow in between existing normal ducts and stromal tissue. This was evident, for example, in one tumor in which one slice revealed pure grade 4 components, one revealed mixed grade 4 and 3 components, and one revealed pure grade 3 components. Because the ADC maps and pathologic step-sections were matched to a high degree of certainty and an individual Gleason grade and ADC quantification provided for each match, a good impression on the assessment of the effect of Gleason grade on water diffusivity was obtained. At DWI, the section showing the tumor with the lowest median ADC will in clinical practice most often be used prospectively to predict aggressiveness, guide therapy, or direct targeted biopsies. Because this study was set up as a validation study, data selection for ROC analysis was done by choosing the tumor slice with the highest Gleason grade composition (ie, tumor slice with the highest proportion of Gleason grade 4 or 5 components). In 94% of tumors, this was the exact same slice that showed the lowest median ADC for the tumor, therefore indicating that, in a prospective setting, it may be useful to use the tumor section with the lowest median ADC as a starting point.

The clinical relevance of this imaging biomarker has noticeable potential. On a solitary basis, median ADC may contribute to patient risk stratification. With a good discriminatory performance between low-, intermediate-, and high-grade tumors, incorporating this information into decision-making will depend on the clinical question and of course the particular sensitivity and specificity desired. Differentiating men who can be treated expectantly (active surveillance) from those requiring active treatment is therefore a potential application of DWI.9 Patients with high-grade cancer (including those with Gleason grade 4 as a primary pattern or Gleason grade 5 as a primary, secondary, or tertiary pattern) represent a group with a particularly detrimental prognosis.8–9 The noninvasive identification of these patients before surgery could be of importance to avoid unnecessary surgery, consider early adjuvant therapy, or order additional diagnostic tests for the assessment of metastasis. A prospective advantage of identifying the most abnormal part of the tumor on the basis of the median ADC is that this can facilitate targeted biopsies to obtain cores from the regions with the worst Gleason scores, providing a better basis for further patient treatment. Furthermore, when focal therapy (ie, intensity-modulated radiation therapy) is used, the most aggressive component could receive the highest dose, therefore improving outcome. With currently available prognostic factors such as preoperative prostate specific antigen (PSA) levels, tumor stage, and biopsy-determined Gleason grade, such a selection cannot be made with sufficient accuracy on an individual level.35,36 Our findings suggest that DWI has the potential to play a role as a non-invasive adjuvant in the characterization of PCas. To which degree our findings will in practice affect individual patient treatment should be assessed with future prospective studies.

Although the role of multiparametric MRI (MP-MRI) in accurately staging and localizing prostate cancer has been firmly defined,11–13, data regarding its value in improving the prediction of PCa aggressiveness are limited. A correlation between hydrogen 1 MR spectroscopy–determined choline + creatine/citrate ratios at 1.5-T and RP Gleason score has been reported,15,36; however, the overlapping groups appear to be too large to determine meaningful cutoff points. Further observations have confirmed that T2-weighted signal intensity correlates to Gleason grade, as poorly differentiated tumors are more readily detected on T2-weighted images than are well-differentiated ones.16 A correlation between ADC and PCa cellularity, proliferation activity, and density of growth has recently been demonstrated in two studies.10,36 In addition, a correlation between ADC and biopsy-determined Gleason grade has been reported by Tamada et al.37 These authors have shown a significant correlation (r = 0.497, p < .0001) between the biopsy Gleason grade and ADC. Furthermore, the same visual trend in the relationship between Gleason grade and ADC was also shown.

Our study had a number of limitations. We did not include TZ tumors in this study. TZ tumors are known to have different genetic mutations, biologic behavioral features, and prognoses.22–24. In addition, ADCs for TZ tumors are known to differ from those for PZ tumors.45 Therefore, the conclusions drawn from this study cannot be applied to TZ tumors. Another potential limitation is the reliability of the method we used to match transverse MR images to histologic step-sections.11,36,45. We believe that using a number of strategies to improve the spatial mapping of MR images and step-sections allowed us to obtain good matching with a high degree of certainty. After section-by-section matching of step-sections to ADC maps, we annotated ROIs on the basis of a schematic translation of the ground truth according to zonal subdivision and use of the urethra as a landmark.
We have demonstrated the relationship between ADC and tumor aggressiveness; in the future, prospective multireader studies should be performed to validate the ability of DWI to improve risk stratification on an individual patient basis, in addition to clinical parameters. The effect of such stratification on patient treatment should also be evaluated. Evaluation of the reproducibility of absolute ADCs between vendors and field strengths as well as correlation of ADCs with TZ cancers should also be priorities for future studies.

In conclusion, quantitative DWI may be a noninvasive biomarker that is well suited for determining PCa aggressiveness. Median tumor ADCs inversely relate to Gleason grade groups and qualitative grade groups. A high discriminatory accuracy of AUC=0.90 suggests that ADC will prove to be a useful biomarker that can help improve the identification of patients with a particular tumor aggressiveness risk.

References
Chapter 4
Grading of prostate cancer using Diffusion-Weighted MR Imaging (DWI)


Chapter 4.3

Initial experience with identifying high-grade prostate cancer using diffusion-weighted MR imaging (DWI) in patients with a Gleason score $\leq 3+3=6$ upon schematic TRUS-guided biopsy - a radical prostatectomy correlated series

Diederik M. Somford, Thomas Hambrock, Christina A. Hulsbergen - van de Kaa, Jurgen J. Fütterer, Inge M. van Oort, Jean-Paul van Basten, Herbert F. Karthaus, J. Alfred Witjes, Jelle O. Barentsz

Introduction Diffusion-weighted MR Imaging (DWI) might be able to fulfill the need to accurately identify high-grade prostate carcinoma, in patients initially selected for active surveillance in the PSA screening era based upon transrectal ultrasound (TRUS)-guided biopsy Gleason score. We aimed to determine whether DWI is able to correctly identify those patients with a biopsy Gleason score of ≤3+3=6, but harboring Gleason 4 and/or 5 components in their radical prostatectomy (RP) specimen.

Materials and methods Whole-mount RP specimens were used to identify regions of interest (ROI) corresponding with tumor on the DWI-derived Apparent Diffusion Coefficient (ADC) maps in 23 patients with a Gleason ≤3+3=6 upon biopsy. ADC values were correlated with RP Gleason grades. Statistical analysis was performed by calculating area under the ROC-curve (AUC) for identification of prostate cancer with Gleason 4 and/or 5 components using DWI, and Mann-Whitney U-testing was performed to detect differences in median ADC values for tumors with presence of Gleason grade 4 and/or 5 versus a highest Gleason grade of ≤3 upon RP.

Results A diagnostic accuracy of median ADC values for identifying patients subject to TRUS-guided biopsy undergrading with an AUC of 0.88 was established using RP Gleason score as a reference. In patients harboring a Gleason 4 and/or 5 component the median ADC was 0.86×10⁻³ mm²/s (SD±0.21), whereas patients harboring no Gleason 4 and/or 5 component displayed a median ADC of 1.16×10⁻³ mm²/s (SD±0.19) for the single tumor slice with the lowest median ADC (p<0.002).

Conclusions DWI is able to predict the presence of high-grade tumor in patients with a Gleason ≤3+3=6 upon biopsy, providing important information for treatment decisions.

Abstract

Introduction Prostate specific antigen (PSA) testing for prostate carcinoma (PCa) has led to earlier detection of PCa, with a tendency to downstaging for the entire population. Recent publications from the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial showed a significant prostate cancer mortality reduction from PSA screening, however at the cost of 1410 men screened and, more importantly, 48 additional cases of PCa treated to prevent one PCa death.

The dilemma of the clinical insignificant tumor has been addressed with increasing frequency and would even become more important with the implementation of PSA screening. In a recent European Association of Urology (EAU) position statement on PSA screening for PCa, the authors underline the paramount importance of the development of reliable monitoring and prognostic markers and/or imaging modalities to prevent overtreatment before widespread implementation of population-based PSA screening.

Clinical staging and accurate grade assessment of PCa has become of utmost importance in decision making regarding the need for active treatment at any time point following the diagnosis of PCa in individual cases.

Accurate identification of insignificant and/or low-risk PCa remains the cornerstone of selection of patients for active surveillance (AS), but is currently severely hampered by absence of reliable pre-treatment predictors. PSA levels in patients with histological proven PCa do grossly correlate with the risk of extraprostatic extension (EPE), seminal vesicle invasion (SVI) and positive surgical margins (PSM), but correlate poorly with differentiation. Other PCa markers, such as PCA3 or hK2, have not been able to identify low-risk PCa with sufficient accuracy for clinical decision making. In current practice, transrectal ultrasound (TRUS)-guided schematic prostate biopsies are the predominant method to obtain a histological diagnosis of PCa and to determine pathological characteristics of the tumor. Subsequently, biopsy-determined combined Gleason score remains a cornerstone of pre-treatment risk stratification for localized PCa. However, when correlated with radical prostatectomy (RP) specimens, Gleason grading obtained by TRUS-guided biopsy has been shown to underestimate tumor Gleason score in up to 40% of cases, a phenomenon further referred to as Gleason undergrading in this paper.
RP series including patients considered eligible for AS according to contemporary inclusion criteria showed that up to 27% of patients had a Gleason score of at least 7 upon RP\textsuperscript{14,15}. An AS series by Duffield et al. outlined that most patients progressing on such a protocol did so 1 to 2 years after diagnosis, suggesting significant undergrading upon initial TRUS-guided biopsy\textsuperscript{16}. Only 52% of patients consequently undergoing RP had a combined Gleason score of \(\leq 3+3=6\). These series clearly underline the need for more accurate grading and staging of PCa precluding inclusion in AS protocols.

Diffusion-weighted MR Imaging (DWI) is a functional MR technique that quantifies the freedom of movement of hydrogen protons, predominantly a part of water molecules, in tissue. In PCa the diffusion of water will be limited due to increased cellular density of tumor compared with normal glandular prostate tissue, leading to lower apparent diffusion coefficient (ADC) levels in PCa when compared with benign prostate tissue\textsuperscript{17}. Previous reports on the value of DWI in the detection and localization of PCa have been published\textsuperscript{18-20}. Furthermore the correlation of ADC to tumor Gleason score and tumor volume has recently been shown\textsuperscript{21-23}. Therefore, another merit of DWI might be in correctly identifying those patients that would have been selected for AS protocols based on their TRUS- guided biopsy Gleason score of \(\leq 3+3=6\), but do harbor Gleason 4 and/or 5 components not sampled by random biopsies. In this series we aimed to establish the potential value of DWI to identify patients subject to pre-operative Gleason undergrading by TRUS-guided biopsy, using RP Gleason score as a gold standard, thus enabling more accurate pre-treatment risk stratification and treatment decision-making.

Materials and Methods

Study population

Inclusion criteria were histologically proven PCa with a Gleason score of \(\leq 3+3=6\) upon TRUS-guided biopsy in patients consequently scheduled for RP. Patients were referred for multiparametric MRI (MP-MRI) from two hospitals, following the histological diagnosis of PCa by 8-10 core schematic TRUS-guided biopsies. In these patients endorectal coil (ERC) MP-MRI at 3 Tesla (3-T) preceding RP was performed. Patients in whom the diagnosis of PCa was established using MR-guided biopsy (MRGB) were excluded. Patient characteristics for the complete cohort were registered.

Imaging parameters

MP-MRI of the prostate was performed using a 3-T MR scanner (Siemens Trio Tim, Erlangen, Germany) combined with an ERC (Medrad, Pittsburgh, USA) in combination with a pelvic phased array coil. The routine MR imaging protocol consisted of anatomical T2-weighted turbo spin echo sequences in the axial, sagittal and coronal direction, covering the prostate and seminal vesicles. Axial images were obtained perpendicular to the dorsal surface of the prostate to facilitate comparison with whole-mount sectioned RP specimens. DWI was performed using a fat-saturated single-shot-echo-planar imaging sequence with 3-scan trace imaging with b-values of 0, 50, 500, and 800 \(s/mm^2\). The scanner software automatically calculated ADC maps using all b-values. Further imaging parameters are shown in appendix 2.

Specimen handling

Following RP, prostate specimens were fixed overnight in 10% neutral buffered formaldehyde and routinely processed according to protocol\textsuperscript{24}. In brief, after inking of the surface, the prostate specimen was cut into serial transverse 3-4 mm thick slices, perpendicular to the dorsal-rectal surface and all slices were macroscopically photographed. The apex and base were sagittally sectioned to assess the caudal and cranial surgical margins. Seminal vesicles were amputated at their junction with the prostate and sectioned parallel to their junction and embedded in total. The remaining slices were subdivided into halves or quadrants to fit routine cassettes. After histological staining all specimens were evaluated by one expert urological pathologist (CHK). Tumors were outlined on the microscopic slides and subsequently mapped on the macroscopic photographs to allow reconstruction of tumor extent and multifocality. For every RP specimen and each separate tumor in case of multifocality the presence of primary, secondary and tertiary Gleason grade pattern as well as a combined Gleason score was recorded. For every tumor slice a separate Gleason grade assessment was made. The presence of EPE was reported for all cases.

Data retrieval

Retrospectively, after RP, annotations of MR images were performed in consensus by one urologist (DMS) and one radiologist (TH). To achieve good objective spatial co-alignment accuracy, a number of strategies were applied. First, both ADC maps and RP step-sections were obtained perpendicular to the dorsal surface of the prostate. Secondly, a similar slice thickness was
predicting correct Gleason grading versus Gleason undergrading was calculated. Furthermore, the Mann-Whitney U-test was performed to determine whether there was a difference in mean PSA, mean ADC (of the single slice with the lowest median tumor ADC) and mean index tumor volume for these groups. Level of significance was set at $P<0.05$. Statistical analysis was performed using SPSS software (SPSS, version 16.0.01, Chicago, Illinois, USA.).

Results

Twenty-three patients were identified with a Gleason score $\leq 3+3=6$ upon TRUS-guided biopsy that underwent 3-T MP-MRI before RP. The mean age was 61 years (range 42-69) with a mean PSA of 8.0 ng/ml (range 1.7-37.5). In 23 prostatectomies, 56 different tumors were found. The prevalence of PZ tumors was 68% (38/56) and for TZ tumors this was 32% (18/56). In all patients one index prostate cancer exceeding a volume of 0.2cc in the RP specimen was identified. The median index tumor volume was 4.09cc (range

statistical analysis

Patients with a Gleason score of $\leq 3+3=6$ upon TRUS-guided biopsy were stratified according to their final RP Gleason score for the presence or absence of a Gleason 4 and/or 5 component. This resulted in two groups. The first, where the TRUS-guided biopsy Gleason score $\leq 3+3=6$ had an exact concordance with RP Gleason score and the second, where TRUS-guided biopsy resulted in Gleason undergrading (combined Gleason score $\geq 7$ in RP).

The median ADC for the tumor slice with lowest ADC values was identified and matched to these two groups. Area under the ROC curves (AUC) were determined for the median ADC’s for predicting correct Gleason grading versus Gleason undergrading. In addition, the AUC for median PSA values...
Eleven of the 23 (48%) included patients had a primary or secondary Gleason 4 and/or 5 component in their final RP specimen, leaving 12 cases that were correctly identified as low-grade prostate cancer by pre-operative TRUS-guided biopsy. Patients subject to Gleason undergrading had a median PSA of 6.10 (range 1.7 - 37.5), while patients with a Gleason score of \(\leq 3+3=6\) upon RP had a median PSA of 6.08 (range 2.2-9.8; \(p=0.11\)). Furthermore, the median index tumor volume in patients with Gleason undergrading was 6.62cc (range 0.31 – 28cc) compared to patients with a final Gleason score of \(\leq 3+3=6\) where this was 2.59cc (range 0.36-10.01; \(p=0.006\)). None of the patients correctly identified by TRUS-guided biopsy as Gleason \(\leq 3+3=6\) PCa had EPE. In contrast, 82% (9/11) of patients that had been undergraded by TRUS-guided biopsy displayed EPE upon RP.

A diagnostic accuracy of median ADC for discriminating patients subject to pre-operative Gleason undergrading by TRUS-guided biopsy with an AUC of 0.88 (95% CI: 0.64 – 1.00) was established (figure 2). In patients harboring a primary or secondary Gleason 4 and/or 5 component the median ADC was \(0.86 \times 10^{-3}\) mm\(^2\)/s (SD±0.21), whereas patients harboring no significant

Table 1  Patient, pathology and ADC characteristics

<table>
<thead>
<tr>
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<th>No Undergrading</th>
<th>Undergrading</th>
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<td>11</td>
<td>N/A</td>
</tr>
<tr>
<td>Median PSA value ng/ml (range)</td>
<td>6.08 (2.2 - 9.8)</td>
<td>6.10 (1.7 - 37.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Median Index Tumor Volume cc (range)</td>
<td>2.59 (0.36 – 10.01)</td>
<td>6.62 (0.31 – 28)</td>
<td>0.006 *</td>
</tr>
<tr>
<td>Extraprostatic Extension (EPE)</td>
<td>0% (0/12)</td>
<td>82% (9/11)</td>
<td>N/A</td>
</tr>
<tr>
<td>Median ADC values (x10^{-3}) mm(^2)/s (±SD)</td>
<td>1.16 (±0.19)</td>
<td>0.86 (±0.21)</td>
<td>0.002 *</td>
</tr>
</tbody>
</table>

Figure 2  ROC curve for differentiation of low-grade (no Gleason 4 and/or 5 component) and high-grade prostate carcinoma upon RP using median ADC in a TRUS-guided biopsy Gleason \(\leq 3+3=6\) population (AUC 0.88)

Figure 3  Box-plot of median ADC of low-grade (no primary or secondary Gleason 4 and/or 5 component) and high-grade prostate carcinoma upon RP in a TRUS-guided biopsy Gleason \(\leq 3+3=6\) population (\(p<0.002\))
The diagnostic accuracy of mean PSA values in discriminating patients into these two groups revealed an AUC of 0.58 (95% CI: 0.32-0.83).

**Discussion**

In this study we have primarily shown that median quantitative ADC values obtained from 3-T DWI are able to accurately separate patients where a histological diagnosis of Gleason $\leq 3+3=6$ PCa upon TRUS-guided biopsy represents undergrading of true Gleason score from those subjects where it is a correct assessment of true Gleason score at RP. Because it is known that biopsy Gleason score is a poor predictor of true Gleason score identified in RP, a definite need exists to improve identification of undergraded patients as this has important implications in treatment selection and prognostication. From our results, it seems that DWI has a strong potential to fill this current gap in pretreatment aggressiveness determination for PCa.

DWI has been established to reliably localize areas of PCa within a 3-T MP-MRI approach. Reported ADC values for PCa (1.13-1.38×10$^{-3}$ mm$^2$/s) and normal prostate tissue (1.58-1.96×10$^{-3}$ mm$^2$/s) differ widely$^{17,10,25,26}$, which to some degree can be explained by different sequences using varied b-values, and thus obtaining different levels of diffusion-weighting. Also, population-based differences in Gleason score prevalences can also account for differences in ADC values for PCa in different series.

Reliable pre-treatment grading of PCa remains a major issue, especially with the emergence of AS programs for low-risk prostate cancer and the growing interest for focal ablative therapies. A RP correlated series by Haider et al. showed a very promising role of DWI in combination with T2-weighted imaging in the detection of significant prostate cancer, defined by a Gleason score $\geq 6$ and tumor diameter $>4$mm. They reported a sensitivity of 81% and a specificity of 84% for T2-weighted MRI and DWI combined$^{18}$. Low-grade tumors reveal low tumor cellularity, intermixed with various amounts of normal prostatic stroma and glands as well as showing larger extracellular and glandular luminal spaces compared with higher-grade tumors. The latter are characterized by higher cellularity density and loss of glandular duct formation$^{27,28}$. As a consequence, the space for free water movement both intraluminally and extracellularly, reduces as the Gleason grade of the tumor increases. Based on the results from Wang et al.$^{29}$ it is evident that the ADC of

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**Figure 4** Patient with TRUS-guided biopsy Gleason score of 3+3=6 and a PSA of 5.2 ng/ml

Histopathological step sections 1a - 3a reveal the extent of prostate carcinoma in the peripheral zone (light-blue area). For every separate slice, a Gleason grade composition expressed in grade and volume percentage of tumor region is given. Every histopathology slice is matched to the corresponding ADC map (1b - 3b) and the tumor-containing region translated for placement of a ROI placed over the tumor. For each ADC slice, a median ADC (mADC) value was calculated. The mADC values are expressed in $10^{-3}$ mm$^2$/s. The region of tumor with the largest proportion of higher Gleason grades (3a) corresponds also to the slice with the lowest mADC tumor values (3b). The window level for ADC maps are defined to range from 0.5-1.5×$10^{-3}$ mm$^2$/s. A small additional insignificant transition zone tumor (green region) is also shown in 1a. The red line indicates the area of extraprostatic extension. The final diagnosis on RP was Gleason 3+4=7 PCa, stage pT3a.
PCa decreases with an increase in tumor cellularity and proliferation rate. This association has also been shown by Zelhof et al.\textsuperscript{30} Apart from inherent tumor cellularity, the degree of tumor intermixing with normal prostatic tissue, also infers variation in ADC values between tumors. Langer et al.\textsuperscript{31} identified sparse vs. dense growing prostate tumors and determined a correlation with ADC. They identified that all sparse growing tumors (with normal tissue intermixing) had a combined Gleason score $\leq 6$. Therefore, it appears that inherent tumor cellularity (which is directly related to the Gleason grade) as well as intermixing pattern, are important factors that influence the diffusion characteristics of PCa on ADC.

The ability of ADC to predict biopsy Gleason score has been established in several series\textsuperscript{32-34}, but this approach is methodologically hampered by the well-known phenomenon of Gleason undergrading of true combined Gleason score by pre-operative biopsies. Two earlier reports on the correlation of ADC and RP Gleason score have recently been published showing a high diagnostic accuracy of ADC in predicting high-grade PCa\textsuperscript{21,23}. To our knowledge we are the first to report on the use of DWI in identifying patients subject to Gleason undergrading upon TRUS-guided biopsy.

For selection of patients for AS protocols or focal therapy a reliable technique with a high sensitivity for any Gleason 4 and/or 5 component could be a parameter of paramount importance to increase reliability and safety of such protocols. It is known that higher PSA values are associated with increased odds of undergrading by TRUS-guided biopsies. Isariyawongse et al.\textsuperscript{35} have shown that patients with PSA values between 10-20 ng/ml had odds ratios of 2.11 compared to patients with PSA < 10 ng/ml for harbouring undergrading of true Gleason score upon RP. Despite this, PSA values alone are insufficient for accurate stratification in this regard. This was reaffirmed in our series by the relative poor AUC of 0.58 achieved using PSA values as classifier. In this retrospective series we were able to identify cases subject to pre-operative biopsy Gleason undergrading with good accuracy using median ADC of the most aggressive part of the tumor. Notably, none of the patients in this series that were correctly graded as $\leq 3+3=6$ PCa by TRUS-guided biopsy displayed EPE in their final RP pathology.

A major limitation of our series might be the establishment of pre-operative Gleason score based upon 8-10 core TRUS-guided biopsies. However, while more extensive TRUS-guided biopsy schemes have been shown to improve detection rates and decrease the rate of Gleason undergrading, this issue still remains substantial\textsuperscript{34}. We therefore are of the opinion that the effect of more TRUS-guided biopsies taken might not have altered the outcome of our series significantly; further investigation in a series with extended biopsy schemes is however warranted. A further limitation is the fact that we only included patients with a Gleason score $\leq 3+3=6$ upon TRUS-guided biopsy for our analysis. However, as the clinical approach is based upon a biopsy Gleason score $\leq 3+3=6$ upon TRUS-guided biopsy as representative of the true tumor features, we opted to only include these patients for this series. This however resulted in a fairly low number of patients in each subgroup. A further drawback is that, although TZ tumors represented 32% of all tumors found in our patients, the index tumor in 96% of patients was a PZ tumor. Because the normal TZ and PZ are known to have different ADC values, our results may therefore be biased towards revealing the discriminatory performance of ADC exclusively for PZ tumor undergrading. A larger cohort with more patients harboring TZ index tumors is needed to establish the value of ADC in a larger perspective.

DWI has been established as a diagnostic modality in oncology now for over a decade. Its main merits lie in the detection of solid tumor within surrounding normal tissue and more recently research has focused upon the ability of DWI to characterize the aggressiveness of tumors. We confirmed this potential of DWI to characterize prostate cancer aggressiveness. DWI should be an integral part of any MP-MRI approach to PCa, whether localizing or characterizing the tumor is the aim. Its main contribution to the diagnostic arena for PCa might lie in its ability to identify high-grade components in PCa precluding adequate pre-treatment risk stratification and aiding in therapeutic decision-making. Prospective research will need to focus upon the performance of DWI in candidates for AS to predict and evaluate progression to curative therapy.
Chapter 4 Grading of prostate cancer using Diffusion-Weighted MR Imaging (DWI)

References


Chapter 4.4

Evaluation of diffusion-weighted MR imaging at inclusion in an active surveillance protocol for low-risk prostate cancer

Diederik M. Somford, Caroline M. Hoeks, Christina A. Hulsbergen-van de Kaa, Thomas Hambrock, MD, Jurgen J. Fütterer, J. Alfred Witjes, Chris H. Bangma, Henk Vergunst, Geert A. Smits, Jorg R. Oddens, Inge M. van Oort, Jelle O. Barentsz

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Chapter 4
Grading of prostate cancer using Diffusion-Weighted MR Imaging (DWI)

Introduction
With the increasing incidence of low-risk prostate cancer (PCa) due to prostate specific antigen (PSA) testing, active surveillance (AS) for PCa has become an appealing strategy in an increasing number of patients. Although there is an ongoing debate on the use and implications of PSA screening on a population-based scale, AS as a strategy for low-risk PCa may turn out to be an important measure to prevent overtreatment of patients with PSA-detected low-risk PCa. Because more experience is accumulating with AS, a consistent intervention rate of 14% to 37% has been reported within the first years after diagnosis following unfavorable PSA kinetics and/or Gleason score/cancer volume progression at repeated transrectal ultrasound (TRUS)-guided biopsy, even when the wide diversity in inclusion criteria and definition of progression renders comparison between series difficult. This substantial intervention rate could be explained by true PCa progression or incorrect risk stratification at the time of initiation of AS. At this moment, the initiation of AS has been based predominantly upon PSA and TRUS-guided biopsy histopathological characteristics. Our hypothesis is that multiparametric MR imaging (MP-MRI) and MR-guided biopsy (MRGB) at the initiation of AS might provide better risk stratification of PCa resulting in lower intervention rates during follow-up. Limited reports on the use of diffusion-weighted MR imaging (DWI) as a monitoring tool within AS protocols for PCa have been published, showing that the DWI-derived apparent diffusion coefficient (ADC) is a highly significant predictor of adverse random repeat biopsy findings in an AS cohort. We describe a series of AS participants in which DWI/ADC was performed at inclusion with immediate histopathological verification by targeted biopsies by MRGB of the abnormal regions suspicious for PCa. To the best of our knowledge, this is the first report on the use of DWI at inclusion in an AS protocol, with histopathological verification obtained by targeted biopsies of cancer-suspicious regions (CSR).

Materials and Methods
We prospectively identified patients eligible for AS according to the PSA and biopsy criteria as used within the Prostate Cancer Research International Active Surveillance (PRIAS) study (Dutch Trial Register NTR1718): asymptomatic cT1c/cT2 PCa, PSA level of 10.0 ng/mL or lesser, PSA density of

Abstract

Purpose We aimed to determine whether diffusion-weighted MR imaging (DWI), by means of the apparent diffusion coefficient (ADC), is able to guide MR-guided biopsy (MRGB) in patients fit for active surveillance (AS) and identify patients harboring high-grade Gleason components not suitable for AS.

Materials and Methods Our study was approved by the institutional review board of all participating hospitals, and all patients signed informed consent at inclusion. Fifty-four consecutive patients with low-risk prostate cancer (PCa) underwent multiparametric MRI (MP-MRI) at inclusion for AS. Cancer suspicious regions (CSRs) upon 3-T MP-MRI were identified in all patients, and MRGB was performed in all CSRs to obtain histopathological verification. For all CSRs, a median ADC (mADC) was calculated. Wilcoxon signed ranks and Mann-Whitney tests were performed to detect differences between the groups. We used the area under the ROC curve (AUC) to evaluate the accuracy of mADC to predict the presence of PCa in a CSR. Level of statistical significance was set at P<0.05.

Results Mean mADC in the CSRs with PCa was 1.04 ×10⁻³ mm²/s (SD: 0.29), whereas the CSRs with no PCa displayed a mean mADC of 1.26 ×10⁻³ mm²/s (SD: 0.25; p<0.001). CSRs with a high-grade Gleason component displayed a mean mADC of 0.84 ×10⁻³ mm²/s (SD: 0.35) vs. a mean mADC for the low-grade CSRs of 1.09 ×10⁻³ mm²/s (SD: 0.25; p<0.05). A diagnostic accuracy of mADC for predicting the presence of PCa in a CSR with an AUC of 0.73 was established (95% confidence interval: 0.61-0.84).

Conclusions Median ADC is able to predict the presence and grade of PCa in CSRs identified by MP-MRI.

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Conclusions Median ADC is able to predict the presence and grade of PCa in CSRs identified by MP-MRI.
Determination of ADC Characteristics
In a consensus reading by 2 observers (DMS, CMH) who were blinded to patient and biopsy characteristics, regions of interest (ROI), measuring 5×5×1 mm, were annotated on the MRGB procedure ADC maps according to needle position (Fig. 1). In case of multiple MRGB cores of a single CSR, the 1 biopsy with the presence of PCa and/or the highest combined Gleason score upon histologic examination was used for the ROI analysis. In case of a cancer-negative MRGB, the 1 biopsy with the most adequate position in the CSR was used for further ROI analysis. A contralateral normal ROI was also annotated when appropriate; in case of a bilateral CSR, no contralateral normal ROI was annotated. For every ROI, the median ADC (mADC) was calculated and used for further analysis.

Pathology Review
All TRUS-guided biopsy results were centrally reviewed by a single pathologist with 18 years of experience in uropathology (CAH) using the International Society of Urological Pathology- modified Gleason score classification\textsuperscript{11}. Identically, all biopsy cores obtained by MRGB were evaluated by the same pathologist in a separate session.

Statistics
Mann-Whitney U testing was performed to detect differences in PSA, PSA-density (PSA-D), or number of positive TRUS-guided biopsy cores for patients with Gleason upgrading vs those without Gleason upgrading upon MRGB. The acquired ADC characteristics were used for analysis of all ROIs. For detecting the differences between CSRs and contralateral normal ROIs, the Wilcoxon signed ranks test was used. For detecting the differences between CSRs harboring low-grade PCa vs. those harboring high-grade (Gleason 4 and/or 5 component) PCa, Mann-Whitney testing was performed. ROC analysis was used for determination of the area under the ROC curve for differentiation between CSRs containing PCa upon MRGB vs. those failing to histologically diagnose PCa. Statistical analysis was performed using SPSS version 19.0 (Statistical Package for Social Sciences, Chicago, IL). Level of significance was set at P<0.05.
Figure 1  Case presentation: a 62-year-old patient with an initial PSA of 7.2 ng/ml and a PSA-D of 0.11 ng/ml/cc. Digital rectal examination revealed no abnormalities (cT1c), with a Gleason 3 + 3 = 6 PCa in 2 of 9 random TRUS-guided biopsies. MP-MRI revealed a single CSR of which MRGB was performed confirming a Gleason 3 + 3 = 6 PCa at histopathology.

Multiparametric MRI, including T2-weighted (A), dynamic contrast-enhanced (B), and diffusion-weighted (C) MR images of the presented patient showing a discrete hypointense lesion in the left peripheral zone upon T2-weighted corresponding to an area of hyperperfusion on dynamic contrast-enhanced and hypointensity on the ADC map, defined as CSR. Conventional ADC map at MRGB (D) showing a hypointense lesion in the left peripheral zone corresponding to CSR on the pre-MRGB multiparametric MRI (blue dotted outline). MRGB of CSR as identified on multiparametric MRI (E). Apparent diffusion coefficient calculation of this specific CSR (red) established a median ADC of $0.88 \times 10^{-3} \text{mm}^2/\text{s}$, with a mADC of $1.70 \times 10^{-3} \text{mm}^2/\text{s}$ for the contralateral normal ROI (green). Pathological examination of the obtained MRGB cores confirmed a Gleason 3+3=6 PCa.
Results

We included 54 consecutive patients from November 2009 to September 2011 according to the criteria for AS as stated in the Methods section. Median age in our cohort was 65.0 (interquartile range: 62.0–69.0), with a mean PSA of 6.2 ng/mL (SD: 1.85) and a mean PSA-D of 0.13 ng/mL/mL (SD: 0.05). The number of positive TRUS-guided biopsy cores was 1 in 35 participants, whereas 19 participants showed PCa in 2 cores. We were able to identify at least 1 CSR in 53 participants, with a median of 2 CSRs (range: 0–4) per patient, accounting for a total of 111 CSRs eligible for analysis. Of these, 7 CSRs were consequently excluded from the analysis because they were subject to inadequate tissue sampling by MRGB, as verified by the absence of prostate tissue on the final histopathologic examination or severe motion artifact rendering the obtained imaging not useful for analysis. From the remaining 104 CSRs, at least 1 MRGB was performed, with a median number of 2 cores taken from every CSR (range: 1–4) and a median number of 4 cores taken per patient (range: 0–6). In 5 CSRs, we were not able to identify a contralateral normal ROI. MRGB confirmed PCa in 29 of the 53 patients (54.7%) and 32 of 104 CSRs (30.8%) with no histological evidence of disease upon MRGB after MP-MRI despite a histological diagnosis of PCa upon random TRUS-guided biopsies. Six patients had 1 CSR with a high-grade Gleason component (Gleason grade 4 and/or 5) upon MRGB, of which 5 were upgraded to a Gleason 3 + 4 = 7 PCa and 1 had a Gleason 3 + 5 = 8 PCa. No statistically significant differences in PSA, PSA-D, or number of positive TRUS-guided biopsy cores were recorded for the patients with Gleason upgrading vs those without Gleason upgrading upon MRGB (see Table 1). The mean mADC for all CSRs was $1.19 \times 10^{-3}$ mm$^2$/s (SD: 0.28) compared with a mean mADC of $1.43 \times 10^{-3}$ mm$^2$/s (SD: 0.29; p<0.001) for the contralateral normal ROIs. The mean mADC in a CSR positively sampled for PCa by MRGB was $1.04 \times 10^{-3}$ mm$^2$/s (SD: 0.29), whereas the CSRs with no PCa upon MRGB displayed a mean mADC of $1.26 \times 10^{-3}$ mm$^2$/s (SD: 0.25; p<0.001). A diagnostic accuracy of mADC for predicting the presence of PCa in a CSR sampled by MRGB with an area under the ROC curve (AUC) of 0.73 was established (95% confidence interval: 0.61–0.84) (Fig. 2). Cancer-suspicious regions with a high-grade Gleason component upon MRGB displayed a mean mADC of $0.84 \times 10^{-3}$ mm$^2$/s (SD: 0.35) vs a mean mADC for the low-grade CSRs of $1.09 \times 10^{-3}$ mm$^2$/s (SD: 0.25; p<0.05; Fig. 3).

### Table 1: Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All subjects (n=54)</th>
<th>MRGB Gleason ≤3+3=6 or no PCa (n=48)</th>
<th>MRGB Gleason &gt;3+3=6 (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PSA (range)</td>
<td>6.2 (1.2-10.1)</td>
<td>6.3 (1.2-10.1)</td>
<td>6.2 (4.9-7.3)</td>
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<tr>
<td>Mean PSA-density (range)</td>
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<td>0.13 (0.02-0.28)</td>
<td>0.16 (0.09-0.19)</td>
</tr>
<tr>
<td>Mean number of positive TRUS-guided biopsy cores (range)</td>
<td>1.4 (1-2)</td>
<td>1.3 (1-2)</td>
<td>1.5 (1-2)</td>
</tr>
<tr>
<td>Mean number of CSRs identified at MP-MRI (range)</td>
<td>2.1 (0-4)</td>
<td>2.1 (0-4)</td>
<td>1.7 (1-2)</td>
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<tr>
<td>Mean number of MRGB cores taken (range)</td>
<td>3.9 (0-6)</td>
<td>3.8 (0-6)</td>
<td>4.0 (3-5)</td>
</tr>
<tr>
<td>Mean number of positive CSRs on MRGB (range)</td>
<td>0.6 (0-2)</td>
<td>0.5 (0-1)</td>
<td>1.2 (1-2)</td>
</tr>
</tbody>
</table>


Figure 2: ROC curve of mADC for discrimination between CSRs harboring no PCa vs any PCa upon MRGB (AUC: 0.73)
established at 1 year of follow-up and this might comprise a mix of true grade and/or volume progression as well as initial undergrading and/or understaging, whereas we performed restaging at inclusion, leaving true progression unlikely to occur in the presented cohort.

Stringent inclusion for AS will lead to low secondary intervention rates, however, at the cost of greatly limiting the number of candidates for such protocols. On the other hand, liberal inclusion criteria for AS will reduce the number of patients considered not eligible for AS while harboring true low-risk PCa but consequently lead to substantial higher intervention rates during follow-up. In our opinion, the delicacy of this balance is largely determined by inadequate staging and grading tools used to identify candidates for AS. Therefore, controversy persists on adequate inclusion criteria used for such protocols. The use of Gleason grade as an inclusion parameter for AS is definitely hampered by the well-known phenomenon of Gleason undergrading by TRUS-guided biopsies. This potentially leads to high “progression” rates during AS representing initial undergrading and/or understaging of PCa by TRUS-guided biopsies, which has been shown in up to 27.8% of candidates for AS undergoing radical prostatectomy. An interesting approach by Eggener et al. incorporated an immediate restaging biopsy round before inclusion in an AS protocol, showing a consequently low intervention rate of 9% at 2 years of follow-up in their cohort. Unfortunately, they did not report separately on the results of this immediate restaging biopsy and it remains unknown how many patients were not included based upon upstaging at this second biopsy round. The importance of this issue is also underlined by 2 recent series showing a 16% to 18% rate of Gleason upgrading after immediate repeat biopsy in an AS population.

Approaching the problem of Gleason undergrading by another set of TRUS-guided biopsies before inclusion in an AS protocol obviously has limitations of its own. MP-MRI of the prostate in combination with MRGB might be very well able to fill in this lacuna. T2-weighted MRI as a single entity has not been able to differentiate reliably between the low-grade and high-grade PCa, whereas T2-weighted MRI combined with DWI in a radical prostatectomy (RP) correlated series has been shown to have good sensitivity and specificity for detecting clinical significant PCa, defined as a Gleason score of 6 or greater and a tumor diameter greater than 4 mm. The discriminatory value of ADC for the low-risk group vs the intermediate-risk/
high-risk groups based upon PSA and TRUS-guided biopsy histopathology has been described. ADC-values have been established to correlate well with Gleason score in TRUS-guided biopsies and, more importantly, RP specimens. In addition, ADC has been shown to be able to predict Gleason score undergrading in patients with a Gleason grade 3+3=6 or less upon TRUS-guided biopsy and did outperform TRUS-guided biopsy Gleason grade as a predictor of low-risk Gleason grade vs intermediate/high-risk Gleason grade upon RP, suggesting that DWI might be able to identify patients who are not correctly graded by TRUS-guided biopsy.

In an AS cohort, the proportion of very low-volume/low-grade PCa is likely to be high, which might lead to a high false-negative ratio of MP-MRI for predicting the presence of PCa upon MRGB. This was confirmed by the inability of MP-MRI and MRGB to detect PCa in 45.3% of patients in our series, thus failing to diagnose PCa in a substantial number of AS patients. Potentially, TRUS-biopsy artifacts upon MP-MRI might have been contributing to the high rate of false-positive CSRs; however, in our experience, an interval of more than 4 weeks from TRUS-guided biopsies does not hamper PCa detection and should be able to limit biopsy artifacts. So far, the lack of follow-up in our described cohort does not elucidate whether the patients in whom the presence of PCa was not histologically confirmed after MP-MRI and MRGB do harbor truly low-risk disease. If this holds true after a prolonged follow-up, in our opinion, MP-MRI with MRGB remains the test of choice to confirm the low-risk character of PCa in participants eligible for AS and might even be used as a technique to identify patients who need to be subjected to further histological diagnosis in case of an elevated PSA.

Published data on the performance of DWI in AS use progression at repeat biopsy and risk of definitive treatment during follow-up as outcome parameters and do not elaborate on the issue of incorrect risk stratification at inclusion in AS protocols. Using these outcomes within an AS cohort with a PSA less than 15 and a Gleason score of 7 or less, 1 group found ADC to be a significant predictor of both adverse repeat biopsy findings and progression to definitive curative treatment. However, the criteria used for AS in these series make inclusion of a larger proportion of high-grade PCa in comparison to our series likely, reflected by a high rate of adverse repeat biopsy findings of 40% at 1 year. Most contemporary AS protocols use more strict inclusion criteria, possibly leaving the added value of ADC less impressive while evaluating a more true low-risk population upfront. We aimed to correlate the DWI features of the AS participants with histopathology obtained at inclusion. MRGB has been established to more accurately sample prostate cancer Gleason grade compared to TRUS-guided biopsies and therefore seems to be a more appropriate method to determine histopathological Gleason grade in AS candidates who are not undergoing RP. For this reason, we chose to obtain histopathological verification of our CSRs by MRGB in every participant. In the present series, we showed that ADC is able to differentiate tumor-bearing CSRs from noncancerous CSRs with reasonable accuracy and should thus be considered in any MRI protocol used for identification of CSRs and targeting of biopsies in AS candidates.

The main limitation of our series is the lack of follow-up, leaving unrevealed how patients who are confirmed to harbor low-risk PCa by MP-MRI and MRGB do fare. It is, at this point, impossible to determine whether these patients are at a lower risk for progression during follow-up. However, a substantial proportion of the participants were identified as participants who have incorrectly stratified low-risk prostate carcinoma and were referred for definitive curative treatment after the MP-MRI, including DWI, and MRGB. Another methodological limitation of our series might be that the ROIs defined as contralateral normal were not sampled histologically by MRGB to confirm their benign character and might thus be harboring foci of low-volume/low-grade cancer in some cases. However, mADC was found to be a significant predictor of high-grade PCa upon MRGB in all participants. The use of DWI as a single measure to identify and grade PCa is limited by the wide variability of ADC values between and within patients, making the identification of a threshold for (high-grade) PCa impossible. For this reason, DWI should always be part of a MP-MRI setting in which histopathological verification of the identified CSRs should be obtained. Within such a framework, DWI is a very valuable tool to guide targeted biopsies.

We conclude that DWI is a promising tool for risk stratification in patients eligible for AS upon clinical and TRUS-guided biopsy criteria and may aid in identification and targeting biopsy of PCa to determine true Gleason grade and identify patients subject to Gleason undergrading. Further prospective evaluation of our MR- PRIAS cohort will be needed to establish whether incorporation of MP-MRI and MRGB at inclusion does lower the risk for
Gleason upgrade at repeat biopsy by better risk stratification. Future series will need to address the question whether DWI does outperform or can be used in conjunction with established clinical parameters, such as PSA density and number of cores positive for PCa, in predicting adverse repeat biopsy findings. Its equivalence to an immediate restaging TRUS-biopsy session or saturation template biopsy also remains unclear. Ongoing prospective inclusion in and evaluation of our cohort will continue to further establish the value of DWI in the selection and monitoring of patients on AS for low-risk PCa through a more adequate prediction of biopathological behavior.

References


Chapter 5

PRE-OPERATIVE AND PATHOLOGICAL STAGING OF PROSTATE CANCER AT RADICAL PROSTATECTOMY
Chapter 5.1

The predictive value of endorectal 3-Tesla multiparametric MRI for extraprostatic extension in low-, intermediate and high-risk prostate cancer patients

Diederik M. Somford, Esther H. Hamoen, Jurgen J. Fütterer, Jean-Paul van Basten, Christina A. Hulsbergen-van de Kaa, Willem Vreuls, Inge M. van Oort, Henk Vergunst, Lambertus A. Kiemeneij, Jelle O. Barentsz, J. Alfred Witjes
Abstract

**Purpose** We aimed to determine the positive and negative predictive values of multiparametric MRI (MP-MRI) for extraprostatic extension (EPE) at radical prostatectomy (RP) for different prostate cancer (PCa) risk groups.

**Materials and Methods** We evaluated a cohort of 183 patients that underwent 3 Tesla (3-T) MP-MRI, including T2-weighted, diffusion-weighted MR Imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) sequences, with an endorectal coil before RP, pathological stage at RP was used as standard reference for EPE. The cohort was classified into low-, intermediate and high-risk groups according to the d’Amico criteria. We recorded prevalence of EPE at RP and determined sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of MP-MRI for EPE in each group. Uni- and multivariable analyses were performed to identify predictors of EPE at RP.

**Results** Overall prevalence of EPE at RP was 49.7% ranging from 24.7-77.1% between low- and high-risk categories. Overall staging accuracy of MP-MRI for EPE was 73.8%, with sensitivity, specificity, PPV and NPV of 58.2%, 89.1%, 84.1% and 68.3%, respectively. PPV of MP-MRI for EPE was best in the high-risk cohort with 88.8%. NPV was highest in the low-risk cohort with 87.7%. With an odds ratio (OR) of 10.3 MP-MRI is by far the best pre-operative predictor of EPE at RP.

**Conclusions** For adequate patient counselling, knowledge of predictive values of MP-MRI for EPE is of utmost importance. High NPV, important for decisions on nerve-sparing strategies at RP, is only reached in low-risk subjects.

Introduction

Surgical margin status is an important prognostic factor for biochemical recurrence following radical prostatectomy (RP) and the only factor to be influenced by surgical method and nerve-sparing strategies. Knowledge of the presence and localization of extraprostatic extension (EPE) is likely to reduce the number of positive surgical margins (PSM) since it enables the surgeon to select patients eligible for nerve-sparing procedures. Prediction of pT3 prostate cancer by digital rectal examination (DRE) and transrectal ultrasound (TRUS) is known to have low accuracy. The staging performance of MRI for prostate cancer (PCa) has been extensively reported with sensitivity and specificity rates of 40-77.8% and 76.5-98%, respectively. Traditionally, radiologists have been providing high-specificity readings to prevent unnecessary abolition of curative surgery while favouring external beam radiotherapy over RP in case of suspected pT3 PCa. While achieving good results with RP in patients with possible pT3 PCa, the focus of radiologist might have to shift to high-sensitivity readings aimed at reducing PSM rates. Clinicians are mainly concerned with the predictive values of the test, rather than its sensitivity or specificity. Using the same test in a population with higher prevalence automatically increases positive predictive value (PPV). Conversely, increased prevalence results in decreased NPV for the same test. Risk-stratified subgroup analyses for the staging performance of multiparametric MRI (MP-MRI) are scarce, while this could be an important factor influencing the predictive values for EPE at RP. In general, in low- and intermediate risk patients the urologist would be most helped by a high NPV to select candidates for active surveillance or nerve-sparing RP. In high-risk patients a high PPV is of utmost importance as knowledge of the site of EPE might help in reducing the substantial risk of a PSM. We evaluated the staging performance of endorectal coil (ERC) MP-MRI at 3-Tesla (3-T), including T2-weighted, diffusion-weighted (DWI) and dynamic contrast-enhanced (DCE) sequences. Sensitivity, specificity, PPV and NPV of MP-MRI for EPE were recorded for different d’Amico risk groups (low-, intermediate and high-risk groups). Furthermore we evaluated the predictive value of MP-MRI for EPE in a multivariable analysis incorporating other well-established predictors of EPE at RP.
Material and methods

Subjects

Between January 2007 and December 2010, 183 consecutive patients prospectively scheduled for RP underwent MP-MRI at 3-T with an endorectal coil, including T2-weighted, DWI and DCE sequences in two referral centres. Our institutional review board waived the need for an informed consent. Patients with extensive cT3 disease were not considered candidates for RP and are therefore not included in this series. MP-MRI staging results were not used to exclude patients for RP, as there is no current evidence to what extent a suspicion of EPE on MP-MRI would translate into a poor prognostic factor before RP. Only evidence of nodal metastasis upon MP-MRI would lead to exclusion for RP. For all patients age, prostate specific antigen (PSA) level, clinical stage as determined by DRE, and TRUS-guided biopsy combined Gleason score were documented. The majority of patients underwent an 8-12 core TRUS-guided biopsy procedure in their referring hospital. Patients were stratified according to the d'Amico risk groups as follows: low-risk: PSA less than or equal to 10, combined Gleason score less than or equal to 6, and clinical stage T1-2a; intermediate risk: PSA between 10 and 20 and/or Gleason score 7 and/or clinical stage T2b; high-risk: PSA more than 20 and/or combined Gleason score equal or larger than 8 and/or clinical stage T2c-3a. Within the low-risk cohort we classified a subset of patients as low-volume, low-risk PCa using a PSA less than or equal to 10, combined Gleason score less than or equal to 6, a clinical stage T1 and less than 3 positive biopsies.

MP-MRI imaging and interpretation

MP-MRI with an ERC was performed using a 3-T MR scanner (Siemens Trio Tim, Erlangen, Germany). Patients were examined in the supine position using a pelvic phased-array coil in combination with an inflatable ERC (Medrad, Pittsburgh, PA, USA). The MP-MRI protocol was consistent over time and incorporated anatomical T2-weighted imaging in the axial, sagittal and coronal plane, covering the prostate and seminal vesicles. Axial images were obtained perpendicular to the ventral surface of the rectal wall to facilitate comparison with whole-mount sectioned RP specimens. DWI was performed with b-values of 0, 50, 500, and 800 s/mm². The scanner software performed an automated calculation of ADC maps using all acquired b-values. DCE was acquired in the transversal plane (time resolution 3.5s, 45 repetitions) using intravenous injection (0.1 mmol per kilogram of bodyweight) of gadopentetate dimeglumine (Dotarem, Guerbet, Paris, France). We refer to appendix 2 for the specific MP-MRI characteristics. All MP-MRI imaging was prospectively evaluated for the presence of EPE by one of two experienced radiologists (JJF, JOB) with 8 and 18 years of experience in prostate MRI. Following PCA localization using all MP-MRI sequences, presence of EPE upon MP-MRI was scored on T2-weighted imaging, according to established criteria for EPE and based on personal training and knowledge. Both readers were not blinded to the clinical characteristics of individual cases. The MP-MRI reports were categorised by two observers (DMS, EHH) using a dichotomous scale for suspicion of EPE at MP-MRI to be used for further analysis. Explicit statements about presence or absence of EPE at MP-MRI were

Figure 1 Case example of true-positive EPE at MP-MRI with correlation of RP specimen in a high-risk patient. Patient aged 63 years, pre-operative PSA 16 ng/ml, DRE: clinical right-sided T3. TRUS-guided biopsy: bilateral Gleason 4+3=7 prostate cancer.
scored accordingly. In less explicit cases a strong suspicion of EPE was classified as positive, whereas cases for whom EPE could not be ruled out were classified as negative. For case examples, see figures 1 and 2.

Pathology processing
Following RP, prostate specimens were fixed overnight in 10% neutral buffered formaldehyde and routinely processed according to local procedure, which is similar for both pathology departments involved. In brief, after inking of the surface, the prostate specimen was cut into serial transverse
Chapter 5 Pre-operative and pathological staging of prostate cancer at radical prostatectomy

was used, incorporating all significant predictors of EPE at RP on univariable analysis, to identify independent predictors of EPE at RP. The SPSS software package version 19.0 (Statistical Package for Social Sciences™, Chicago, IL, USA) was used for statistical analysis, with the 2-tailed level of significance set at p<0.05.

Results

Patient characteristics are shown in table 2. Overall, 91 patients had EPE in their RP specimen, accounting for an overall prevalence of EPE of 49.7%. SVI was reported in 21 patients accounting for an overall 11.5% prevalence of SVI. Overall accuracy, sensitivity, specificity, PPV and NPV of MP-MRI for EPE were 73.8%, 58.2%, 89.1%, 84.1% and 68.3%, respectively.

Univariable analysis identified PSA, DRE, biopsy Gleason score, d’Amico risk group and stage at MP-MRI as significant predictors of EPE at RP, and these variables were consequently included in multivariable analysis. Logistic regression analysis identified PSA level and MP-MRI stage as significant independent predictors of EPE at RP (p<0.05), with stage at MP-MRI being the strongest predictor of EPE at RP with an odds ratio (OR) of 10.3 (see table 1).

D’Amico risk groups (see table 2)

Low-risk cohort

According to the d’Amico risk classification 73 patients were stratified as low-risk, of which 18 patients had EPE upon RP, thus accounting for a prevalence of EPE of 24.7%. SVI was present at RP in one case (1.4%) of the low-risk cohort. In this cohort sensitivity, specificity, PPV and NPV of MP-MRI for EPE were 61.1%, 90.9%, 68.8% and 87.7%, respectively. Low-volume, low-risk PCa was established in 18 patients, with 3 patients having EPE upon RP, accounting for a prevalence of EPE of 16.7% in this subset. In this subset sensitivity, specificity, PPV and NPV were 33.3%, 86.7%, 33.3% and 86.7%, respectively.

Intermediate risk cohort

Sixty-two patients had intermediate risk disease according to the d’Amico risk classification, with 36 patients diagnosed with EPE upon RP, a 58.1% prevalence of EPE. Five patients (8.1%) had SVI in this cohort. Sensitivity,
Table 1  Patient characteristics including uni- and multivariate analysis of pre-operative predictors of EPE at RP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Low-risk</th>
<th>Intermediate risk</th>
<th>High-risk</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number/statistics</td>
<td>183</td>
<td>73</td>
<td>62</td>
<td>48</td>
<td>P-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>62.4±4.9</td>
<td>61.1±6.2</td>
<td>63.4±5.2</td>
<td>63.3±6.0</td>
<td>0.158</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT1</td>
<td>95 (51.9%)</td>
<td>45 (61.6%)</td>
<td>40 (64.5%)</td>
<td>10 (20.8%)</td>
<td>&lt;0.001*</td>
<td>1.8 (0.9-3.4)</td>
</tr>
<tr>
<td>cT2</td>
<td>67 (36.6%)</td>
<td>28 (38.4%)</td>
<td>22 (35.5%)</td>
<td>17 (35.4%)</td>
<td>0.091</td>
<td></td>
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<tr>
<td>cT3</td>
<td>21 (11.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>21 (43.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA (continuous)</td>
<td>10.0±8.4</td>
<td>6.2±2.4</td>
<td>9.4±4.6</td>
<td>16.6±13.1</td>
<td>&lt;0.001*</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Biopsy combined Gleason</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3+3=6</td>
<td>102 (55.7%)</td>
<td>73 (100%)</td>
<td>17 (27.4%)</td>
<td>12 (25.0%)</td>
<td>&lt;0.001*</td>
<td>1.5 (0.8-2.8)</td>
</tr>
<tr>
<td>3+4/4+3=7</td>
<td>58 (31.7%)</td>
<td>0 (0%)</td>
<td>45 (72.6%)</td>
<td>13 (21.1%)</td>
<td>0.269</td>
<td></td>
</tr>
<tr>
<td>≥4+4=8</td>
<td>23 (12.6%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>23 (47.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D’Amico risk classification</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPE at MP-MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>120 (65.6%)</td>
<td>57 (78.1%)</td>
<td>42 (67.8%)</td>
<td>21 (43.8%)</td>
<td>&lt;0.001*</td>
<td>1.4 (0.6-3.1)</td>
</tr>
<tr>
<td>T3</td>
<td>63 (34.4%)</td>
<td>16 (21.9%)</td>
<td>20 (32.3%)</td>
<td>27 (56.3%)</td>
<td>&lt;0.001*</td>
<td>10.3 (4.4-24.2)</td>
</tr>
<tr>
<td>EPE at RP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>92 (50.3%)</td>
<td>55 (75.3%)</td>
<td>26 (41.9%)</td>
<td>11 (22.9%)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>pT3</td>
<td>91 (49.7%)</td>
<td>18 (24.7%)</td>
<td>36 (58.1%)</td>
<td>37 (77.1%)</td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

EPE: extraprostatic extension, RP: radical prostatectomy, OR: odds ratio, CI: confidence interval, PSA: prostate-specific antigen, MP-MRI: multiparametric MRI, N/A: not applicable, *significant at p<0.05

Table 2  Performance of MP-MRI for predicting EPE upon RP according to d’Amico risk groups

<table>
<thead>
<tr>
<th>D’Amico risk group</th>
<th>N</th>
<th>EPE prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All risk groups</td>
<td>183</td>
<td>49.7%</td>
<td>58.2%</td>
<td>89.1%</td>
<td>84.1%</td>
<td>68.3%</td>
</tr>
<tr>
<td>Low-risk</td>
<td>73</td>
<td>26.7%</td>
<td>61.1%</td>
<td>90.9%</td>
<td>68.8%</td>
<td>87.7%</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>62</td>
<td>58.1%</td>
<td>50.0%</td>
<td>92.3%</td>
<td>90.0%</td>
<td>57.1%</td>
</tr>
<tr>
<td>High-risk</td>
<td>48</td>
<td>77.1%</td>
<td>64.9%</td>
<td>72.7%</td>
<td>88.9%</td>
<td>38.1%</td>
</tr>
</tbody>
</table>

MP-MRI: multiparametric MRI, EPE: extraprostatic extension, RP: radical prostatectomy, N: number of cases, PPV: positive predictive value, NPV: negative predictive value.
specificity, PPV and NPV of MP-MRI for EPE were 50.0%, 92.3%, 90.0% and 57.1%, respectively.

**High-risk cohort**

High-risk disease was established in 48 patients, with EPE present upon RP in 37 patients, accounting for an EPE prevalence of 77.1%. In the high-risk cohort 15 patients (31.3%) had SVI upon RP. Sensitivity, specificity, PPV and NPV of MP-MRI for EPE in this cohort were 64.9%, 72.7%, 88.9% and 38.1%, respectively.

**Discussion**

It has been well established that prevalence of EPE in RP specimens differs greatly among risk groups for prostate cancer with a prevalence ranging from 9.4–16.5% for low-risk subjects to 44.7–53% for high-risk subjects. The prevalence of EPE is also influenced by several established parameters such as PSA, clinical stage and biopsy Gleason score. We found the overall prevalence of EPE in our series to be higher for all risk-groups compared to the literature. A contributing factor to our high rates of EPE over all risk categories might be the fact that PSA-screening was not very widespread in our country in the evaluated period, possibly leading to inclusion of an overall higher stage PCa population.

Sensitivity and specificity of multimodality MRI for detecting EPE differ among published series and are influenced by magnetic field strength, use of an ERC and MRI parameters used. Also, these are influenced by the way the radiologist is performing the interpretation, especially in equivocal or difficult cases. At present, radiologists have been focusing on high-specificity readings in order to prevent incorrectly ruling out a patient for curative surgery while having the lowest false-positive ratio for EPE possible. However, one might argue that in current clinical practice high-sensitivity readings should be the standard as patients with a suspicion of EPE on MP-MRI are not definitely ruled out for curative surgery.

To our knowledge, only two earlier series evaluated the staging performance of MP-MRI in a risk-stratified population. Wang et al. looked at the incremental value of MR staging to the Partin nomogram for prediction of EPE in clinically organ-confined disease (<cT3). The prevalence of ≥pT3 disease in their series was 27% and they found an area-under-the-ROC-curve (AUC) of 0.80 for the Partin nomograms alone and an AUC of 0.88 when augmented with the MR findings. Using the ROC-curve, they concluded that the highest incremental value was present in intermediate and high-risk groups. However, the ROC-curve does not incorporate predictive values and therefore is not likely to be influenced greatly by population prevalence of EPE. Cornud et al. found no difference between low- versus intermediate/high-risk groups. Only 10% of their patients were categorized as high-risk (PSA>20 and Gleason>7) and cT3 disease was excluded from their analysis. They reported a sensitivity of 55% and a specificity of 96% for EPE, as well as excellent PPV (81%) and NPV (89%) in their series with an EPE prevalence of 21% for the whole patient group, which is more comparable to our low risk cohort with a prevalence of EPE of 24.7%. Possibly their superior NPV is explained by their evaluation of a population at a lower risk for EPE compared to ours, which underlines our conclusion that the NPV of MP-MRI for EPE is best in a low-risk population.

When MP-MRI is used to select patients eligible for active surveillance a high NPV for EPE is of paramount importance and this series shows a very good NPV in the low-volume, low-risk subset. An acceptable NPV for ruling out EPE using pre-operative imaging should be able to strike the right balance between unneeded resection of the neurovascular bundle and the risk of PSM and is only reached in the low-risk cohort in our series. The relative high proportion of false negative MP-MRI results in intermediate risk subjects should place the emphasis on the risk of PSM while discussing the option of a nerve-sparing RP in these cases. The NPV of 57.7% for EPE in this cohort is hardly sufficient and could benefit most from an adapted high-sensitivity reading. When MP-MRI is used to exclude patients with evident EPE from curative surgery, high-specificity readings should be performed, leading to a high PPV of 88.9% in high-risk subjects. In high-risk cases the high PPV of MP-MRI for EPE might aid the urologist in decreasing the risk of PSM even when performing a non-nerve-sparing RP.

The first and foremost limitation of our series is the performance of a traditional high-specificity reading in all cases as discussed earlier. One might argue that if a tailored reading according to risk category, as promoted in our conclusion, had been performed, the overall performance of MP-MRI would have been improved.
increase, especially in the intermediate risk group. Also, the radiologist was not blinded to the patient characteristics and an interpretation bias cannot be excluded. Lastly, all MP-MRI studies and reports were from one of two very experienced readers and it remains unknown whether the presented results are reproducible in a centre with a different experience level.

Conclusions

Compared with other pre-operative parameters MP-MRI is the best predictor of EPE at RP. With the presence of EPE in one out of four patients in the low-risk cohort it is justifiable to evaluate every subject pre-operatively with MP-MRI before deciding upon nerve-sparing approaches with a NPV of 87.7% for EPE. In intermediate risk subjects the reassurance by MP-MRI for performing a nerve-sparing approach in selected cases implies a risk of PSM due to the high proportion of false-negative MP-MRI. The radiologist can deliberately influence the sensitivity and specificity of a reader-dependent test such as MP-MRI and should therefore be aware of the different clinical issues posed according to risk categories. Considering this, the radiologist will be able to provide a tailored estimation of EPE according to these implications, which warrants a high-sensitivity MP-MRI reading in low- and intermediate risk subjects, and a high-specificity MP-MRI reading in high-risk patients.

References

Chapter 5.2

Prognostic relevance of number and bilaterality of positive surgical margins after radical prostatectomy

Diederik M. Somford, Inge M. van Oort, Jean-Pierre Cosyns, J. Alfred Witjes, Lambertus A. L. M. Kiemeney, Bertrand Tombal

Abstract

**Purpose** Positive surgical margin (PSM) status following radical prostatectomy (RP) is a well-established prognostic factor. The aim of the present study is to evaluate whether number of PSMs or bilaterality of PSMs might have prognostic significance for biochemical recurrence (BCR) in the population with a PSM status following RP.

**Methods** We evaluated 1,395 RP pathology reports from the Université Catholique de Louvain, Brussels, Belgium between 1980 and 2006. All patients who underwent (neo)-adjuvant therapy were excluded, leaving a cohort of 1,009 patients, with 249 (24.7%) subjects having a PSM at RP of whom 29.4% had multiple PSMs (≥2 sites), while 13.6% had bilateral PSMs. Median follow-up was 40 months (range 0–258 months). We used BCR-free survival as the primary study outcome. BCR was defined as any rise in PSA above or equal to 0.2 ng/ml.

**Results** Of patients with a PSM status, 41% (95% CI: 33–49%) developed BCR within 5 years, compared to 12% (95% CI: 9–15%) in the population without a PSM. Multivariable analysis identified PSA at diagnosis and RP Gleason score as independent predictive factors for BCR. Increasing number and/or bilaterality of PSM did not lead to significant higher rates of BCR.

**Conclusion** In patients with a PSM, the number of positive sites or bilaterality of PSM status does not add prognostic information for risk of BCR. Survival curve slopes were different for patients with bilateral PSM, showing a significant tendency to progress to BCR earlier during follow-up than patients with unilateral PSM.

Introduction

The 5- and 10-year overall survival rates of radical prostatectomy (RP) are excellent, leading to significant survival benefit compared to watchful waiting. In the absence of extraprostatic extension (EPE) and positive surgical margins (PSM), the rates of biochemical recurrence (BCR) are low. This does not stand true for patients with a PSM, a common pathological feature following RP, with a prevalence varying between 5 and 43% in different series. Several studies have shown PSM to be one of the most important prognostic factors for BCR following RP.

The EORTC 22911 trial established that adjuvant external irradiation after RP improves biochemical recurrence (BCR)-free survival in patients with a PSM or pathological T3 stage. Whether this translates into an overall survival benefit could not be detected due to a relative short follow-up. In this trial, 43.7% of the patients in the wait-and-see arm experienced biochemical or clinical progression or death. This percentage was reduced to 26.1% in the irradiation arm. However, if all patients in this series would have received immediate radiotherapy, over fifty percent would have received intervention without ever progressing to BCR at the cost of radiotherapeutic toxicity. Therefore, characterization of patients at high risk of BCR after RP would be of great help to identify those patients benefitting most of immediate postoperative radiotherapy. Reevaluation of the EORTC 22911 data by van der Kwast et al. stressed that among patients with adverse pathological features on RP, those with PSM benefit most from immediate radiotherapy, preventing 291 BCR events for every 1,000 treated. We hypothesized that the number of PSMs or bilaterality of PSMs is an additional risk factor of BCR in patients with a PSM and may indicate who will be ideal candidates for adjuvant postoperative radiotherapy.

Patients and methods

**Study population and data retrieval**

The pathology reports of 1,395 open retropubic RP procedures performed at the Department of Urology, Université Catholique de Louvain, Brussels, between 1980 and 2006 by two surgeons were retrospectively evaluated for PSM status. Since 1999, intra-operative frozen sections were used to avoid
Pathology processing

The left and right sides of the prostate gland were identified by a longitudinal incision into the right anterior half. Following fixation in buffered 10% formaldehyde, the 5-mm thick proximal and distal transections of the prostate were serially sectioned at 2-mm intervals parallel to the urethra. The tips of the vasa deferentia were transected, and the seminal vesicles were longitudinally sectioned up to their junction with the prostate. The remaining prostate gland was then serially sectioned perpendicularly to the apical-basal axis at 5-mm intervals to perform whole mount sections. The external surface of surgical radical prostatectomy specimens was covered with ink since 1990. Surgical margins were considered as positive or negative when the malignant cells were separated without or with any amount of benign tissue from the inked edge of the surgical resection of the gland, respectively. The paraffin-embedded tissues were recut if necessary until visualization of the inked margin. When the margins had not been inked, the paraffin blocks were recut until the whole circumference of the tissue sample was mounted on the slide. The edges of the artifactual disruptions of prostatic or extraprostatic tissue were not considered as surgical margins.

Statistical analysis

For statistical analysis, we used SPSS software (SPSS, version 16.0.01, Chicago, Illinois, USA). Kaplan–Meier survival analysis was performed with BCR-free survival as outcome for both single versus multiple PSM and unilateral versus bilateral PSM. The Wilcoxon test was used to detect significant differences in BCR-free survival rates between groups. Multivariable Cox proportional hazards regression models were composed to determine prognostic factors for BCR. As multiple PSMs will represent a large subgroup of bilateral PSMs, we performed multivariable analysis for both factors separately. Statistical significance in our study was set at $P < 0.05$.
bilateral PSM did differ significantly (P = 0.029), as the bilateral PSM cohort did progress to BCR earlier during follow-up, with the curves closing in later (see figure 1).

Table 1  Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>PSM</th>
<th>Single PSM</th>
<th>Multiple PSM</th>
<th>Unilateral PSM</th>
<th>Bilateral PSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>249</td>
<td>154/218 (70.6%)</td>
<td>64/218 (29.4%)</td>
<td>165/191 (86.4%)</td>
<td>26/191 (13.6%)</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>63.8±6.9</td>
<td>63.6±6.9</td>
<td>64.7±6.1</td>
<td>63.8±6.5</td>
<td>64.0±7.0</td>
</tr>
<tr>
<td>PSA at diagnosis (mean±SD)</td>
<td>11.7±9.7</td>
<td>10.7±7.8</td>
<td>12.9±12.8</td>
<td>11.4±8.4</td>
<td>11.8±13.1</td>
</tr>
<tr>
<td>Pathological Stage</td>
<td>pT2</td>
<td>122 (49.8%)</td>
<td>82 (53.9%)</td>
<td>25 (40.3%)</td>
<td>80 (49.7%)</td>
</tr>
<tr>
<td></td>
<td>pT3</td>
<td>123 (50.2%)</td>
<td>70 (46.1%)</td>
<td>37 (59.7%)</td>
<td>81 (50.3%)</td>
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<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>RP Gleason score</td>
<td>≤6</td>
<td>173 (69.8%)</td>
<td>110 (71.4%)</td>
<td>41 (64.1%)</td>
<td>118 (71.5%)</td>
</tr>
<tr>
<td></td>
<td>≥7</td>
<td>66 (26.6%)</td>
<td>40 (26.0%)</td>
<td>18 (28.1%)</td>
<td>41 (26.8%)</td>
</tr>
<tr>
<td></td>
<td>8-10</td>
<td>9 (3.6%)</td>
<td>4 (2.6%)</td>
<td>5 (7.8%)</td>
<td>6 (3.6%)</td>
</tr>
<tr>
<td></td>
<td>missing</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5-year BCR (95% CI)</td>
<td>41% (33-49%)</td>
<td>43% (32-54%)</td>
<td>46% (31-61%)</td>
<td>45% (35-55%)</td>
<td>46% (24-68%)</td>
</tr>
</tbody>
</table>

PSM: positive surgical margin, SD: standard deviation, CI: confidence interval, RP: radical prostatectomy, BCR: biochemical recurrence rate.

Figure 1  Kaplan-Meier BCR free survival curves for unilateral and bilateral PSM

Univariable analysis identified PSA at diagnosis, pathological stage, RP Gleason score, and perineural invasion (PNI) as possible predictors of BCR after RP in this PSM series, and these factors were consequently included in the multivariable analysis. Bilateral PSM status and number of PSMs did not add prognostic information (see Table 2).

**Table 2** Univariable and multivariable analysis of prognostic factors for BCR in a PSM cohort.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable Analysis HR (95% CI)</th>
<th>Multivariable Analysis HR (95% CI)</th>
<th>p-value</th>
<th>Multivariable Analysis HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at RP</td>
<td>1.00 (0.97-1.03)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>PSA at diagnosis (ng/ml)</td>
<td>1.04 (1.02-1.05)</td>
<td>1.03 (1.01-1.05)</td>
<td>p=0.002</td>
<td>1.04 (1.02-1.06)</td>
<td>p=0.000</td>
</tr>
<tr>
<td>Pathological Stage (pT3 vs. pT2)</td>
<td>2.36 (1.47-3.79)</td>
<td>1.45 (0.82-2.58)</td>
<td>p&gt;0.05</td>
<td>1.42 (0.77-2.63)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>RP Gleason Score (per point)</td>
<td>1.42 (1.15-1.76)</td>
<td>1.34 (1.07-1.68)</td>
<td>p=0.01</td>
<td>1.32 (1.04-1.66)</td>
<td>p=0.02</td>
</tr>
<tr>
<td>PNI</td>
<td>2.20 (1.40-3.44)</td>
<td>1.22 (0.71-2.09)</td>
<td>p&gt;0.05</td>
<td>1.43 (0.82-2.50)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Multiple vs. single PSM</td>
<td>1.37 (0.72-2.64)</td>
<td>1.05 (0.63-1.74)</td>
<td>p&gt;0.05</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Bilateral vs. unilateral PSM</td>
<td>1.28 (0.79-2.07)</td>
<td>N/A</td>
<td>N/A</td>
<td>1.32 (0.66-2.62)</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

BCR: biochemical recurrence, PSM: positive surgical margin, HR: hazard ratio, CI: confidence interval, RP: radical prostatectomy, PNI: perineural invasion, N/A: not applicable.

Discussion

Data on 5-year risk of BCR for PSM patients following RP are reported between 25 and 47% [5,10–12]. No effect on prostate cancer-specific survival or overall survival has been determined for PSM status, probably because the available follow-up does not suffice to detect these differences if present. Preoperative PSA, RP Gleason score, and pathological stage are well-established predictors of BCR following RP [3,16–19]. In correspondence with other series, we identified RP Gleason score as a prognostic factor for BCR among patients with a PSM [5,7,9,11]. All these earlier reports identified pathological stage as a prognostic factor for BCR as well, which we could only confirm in univariable analysis. This might be contributed to the 370 patients that were excluded from our analysis because of (neo)-adjuvant therapy leading to a disproportional exclusion of poor-risk subjects with higher pT-stages. Furthermore, psT3 subjects were more likely to have PSM, which was included in multivariable analysis, and might, due to its profound effect on BCR rates, diminish the effect of psT3 stage on BCR rates. Much debate remains over the prognostic value of PNI in RP specimens [20, 21]. In our subset of patients with PSMs, we could not identify PNI as an independent prognostic factor for BCR on multivariable analysis.

Five studies address the number of PSMs in detail in populations that did not receive immediate postoperative therapy and yielded conflicting results. In a subset of 480 patients analyzed by Lowe and Lieberman, a significant increase in BCR for patients with multiple PSMs compared with single PSM patients was found [22], a finding confirmed in another series by Sofer et al. with 210 patients with PSM [23]. Both series did not include pathological stage in their analyses, which may have led to biased results as one might expect a higher relationship between the number of PSMs and BCR in patients with higher pathologic stages. Despite these findings, the effect of multiple PSMs on BCR is difficult to assess because of the potential influence of confounding variables such as the use of adjuvant therapy and the interplay of pT3 stage with BCR. Overall, the number of PSMs does not appear to be an independent predictor of BCR, and its prognostic value may be limited to specific subgroups of patients.
hypothesize that extraprostatic extension (pT3) is far more common in the subgroup with multiple PSM status. In our series, we could confirm that pathological T3 stage was significantly more common in the multiple and bilateral PSM cohorts compared with the single PSM cohort. This hypothesis is supported by a larger series by Blute et al. of 697 pT2 patients with a PSM in which only a slightly higher rate of BCR was found for patients with multiple PSM when compared with those with a single PSM19. Also, a more recent report on PSM status in 354 patients with extraprostatic carcinoma (pT3a/b) on RP could also not detect a significant difference in BCR between patients with single and multiple PSMs20. Therefore, we think that any report on PSM status should include pathological stage in the multivariable analysis in order to be able to assess the independent prognostic value of PSM status properly. Furthermore, as patients with multiple or bilateral PSMs tend to experience BCR earlier during follow-up with Kaplan-Meier curves closing in later on, the relative short follow-up of 22 months by Sofer et al.23 could have led to a false impression of increased BCR for multiple PSMs when processing Kaplan-Meier curves on these data. This is supported by the difference in calculated 5-year BCR rates for multiple PSMs between ours and their series, 41% versus approximately 60% (read from the Kaplan-Meier curve), respectively. A series by Jayachandran et al. reporting on 902 patients with PSM and/or pT3 disease could not identify pathological stage as an independent predictor of BCR on univariable analysis, and thus, did not incorporate this factor in their multivariable analysis24. Consequently, they found number of PSM to be significantly associated with BCR on univariable and multivariable analysis, a finding we could not confirm. In their series, they did however exclude a substantial number of patients (n = 205) with seminal vesicle invasion, which could account for a large number of BCR subjects in our series as these are relative poor-risk subjects within the pT3 subgroup.

We did not take the extent or length and site of PSM into account, and contradictory reports have been published on this issue. Some finding length of PSM as a prognostic marker for BCR25, whereas others could not identify extent of PSM as a prognostic marker4-27. Most series did not find site of PSM to be predictive of BCR21-23, while Blute et al.24 identified the prostate base as the only anatomic site of PSM predictive for recurrence at that specific anatomic site with a significant effect on 5-year risk of BCR, which increased from 15 to 44% in case of a PSM at the prostate base.

To our knowledge, no study on bilaterality of PSM status has been published before. Nevertheless, one might hypothesize that bilateral PSM status might influence BCR-free survival, as it might express more extensive tumor involvement of the prostate bed after RP. Nevertheless, we could not identify an independent prognostic value of bilateral PSM status on multivariable analysis in our series. We found patients with bilateral PSM to progress to BCR earlier during follow-up, with survival curves closing in at about 5-years of follow-up.

The main limitation of our series is the retrospective data collection, which led to a substantial number of missing data in which we could not establish the details of PSM status on number and bilaterality. Interestingly, patients with missing data did better as far as BCR rates are concerned, which might be attributed to less detailed pathological reporting on number and bilaterality of PSM in case of a single or limited multiple PSM status. Another concern is the relatively low power of our series to detect differences between groups; this is mainly an issue in the comparison of unilateral versus bilateral PSM, as only 26 subjects were documented to have bilateral PSM. Furthermore, the median follow-up of approximately 40 months could be insufficient to detect differences in long-term BCR in our series.

Conclusions

We conclude that number or bilaterality of PSM are not independent predictors of BCR, although patients with bilateral PSMs did show a significant tendency to progress to BCR earlier during follow-up compared to patients with unilateral PSMs. For conclusive evidence, future prospective series with longer median follow-up addressing this issue are needed. The search for more valid prognostic markers for disease recurrence following RP continues for better risk stratification and decision making regarding timing of adjuvant radiotherapy in post-RP subjects.
References


SUMMARY OF THESIS
NEDERLANDSE SAMENVATTING
6. Summary of thesis

Chapter 3 elaborates on current biopsy strategies and confirms the reluctance with TZB for baseline TRUS-guided biopsies as currently advocated in most (inter)national guidelines. It describes the efficacy of MRGB following repeated negative TRUS-guided biopsies. Chapter 3 also gives information on the role of MP-MRI and consequent MRGB in an AS protocol (MR-PRIAS) excluding a substantial number of undergraded and/or understaged patients from AS.

In chapter 3.1 we present a series on the added value of TZB in a baseline TRUS-guided biopsy setting. We found TZB to have little incremental value over sextant PZ biopsies with regard to the diagnosis of PCa, increasing the diagnostic yield from 40.5% to 42.2% for PCa detection. Furthermore, TZB did not increase the grading performance of PZB importantly as only 2.4% of patients had Gleason 4 and/or 5 components in their TZB cores not present in the sextant PZB cores. Interestingly, there is a persistent need for repeat biopsy procedures as 8.1% of patients not diagnosed with PCa upon baseline TRUS-guided biopsy were diagnosed with PCa during follow-up. Overall, 26.8% of consequent biopsy procedures, including repeated TRUS-guided biopsy and MRGB, were positive for PCa.

Chapter 3.2 shows that MRGB is able to detect PCa in a majority of cases suspected to have PCa following 2 or more negative TRUS-guided biopsy sessions. Overall, 59% (40/68) of MRGB procedures in this series led to a diagnosis of PCa, of which the majority were deemed clinically significant based upon PSA-characteristics, biopsy Gleason score and/or RP specimen. Within this highly selected population referred for MRGB, 57% of PCa locations were found anteriorly, an area not sampled easily by TRUS-guided biopsies. This underlines the need for focusing repeated (TRUS-guided) biopsy procedures at the anterior aspects of the prostate. The high diagnostic yield of MRGB for patients following negative TRUS-guided biopsies has now been reproduced by several larger series from different centers.

Chapter 3.3 illustrates the potential role of MP-MRI and consequent MRGB at inclusion in an AS protocol. MRGB of CSRs identified upon MP-MRI detected a Gleason 4 and/or 5 component not detected by TRUS-guided biopsies in 10.9% (7/64) of cases. Four out of 64 patients (6.3%) had a suspicion of EPE at
Gleason undergrading when evaluating their RP specimen. The slice with the lowest ADC-value, representing the most aggressive part of the tumour, was used for evaluation. DWI was able to identify those patients subject to Gleason undergrading with high accuracy with an area under the ROC-curve of 0.88.

In chapter 4.4 ADC characteristics of subjects considered eligible for AS according to PRIAS-criteria are discussed. We found patients harbouring no PCa, low-grade PCa (no Gleason 4 and/or 5 component) or high-grade PCa (any Gleason 4 and/or 5 component) upon MRGB of CSRs defined upon MP-MRI evaluation to display significantly different ADC-values of $1.26 \times 10^{-3}$ mm$^2$/s, $1.09 \times 10^{-3}$ mm$^2$/s and $0.84 \times 10^{-3}$ mm$^2$/s, respectively. With an AUC of 0.73 for prediction of PCa in a CSR the reliability of DWI to accurately rule out PCa is in our opinion too low to abolish targeted biopsies of CSRs at this point. However, DWI seems able to guide the targeted biopsies to the most aggressive part of the tumour with fair accuracy. The implications of a false-negative MP-MRI evaluation in an AS population with an earlier histological diagnosis of PCa, leading to negative MRGB in 45.3% of cases in this series, remain to be determined with prolonged follow-up.

Chapter 5 defines the possibilities of personalized decision-making based upon staging MP-MRI results and the finding of PSM status following RP. Knowledge of the predictive values of MP-MRI for EPE stratified for different PCa risk categories facilitates patient counselling on treatment options. Similarly, the appraisal of PSM status and possible subsets at high-risk of BCR provides the urologist with tools to discuss the need for immediate adjuvant radiotherapy following RP.

Chapter 4.1 presents and overview of state-of-the-art MP-MRI imaging and a review of literature providing a framework for the series presented in the consequent subchapters. This review identifies MP-MRI, combining T2-weighted MR imaging, DWI and DCE-MRI, as a reliable localization and staging tool for PCa and outlines the promises that MP-MRI, and more specifically DWI, behold for adequate grading of PCa.

Chapter 4.2 outlines the correlation between ADC and final RP Gleason score for PZ PCa, establishing an area under the ROC-curve (AUC) of 0.90 for differentiation between low-grade (Gleason $\leq 3+3=6$) and intermediate and high-grade PCa. ADC-values differed significantly ($p<0.001$) for low-, intermediate and high-grade PCa, with $1.30 \times 10^{-3}$ mm$^2$/s, $1.07 \times 10^{-3}$ mm$^2$/s and $0.94 \times 10^{-3}$ mm$^2$/s, respectively. ADC-values thus enable correct pre-treatment grading of PCa and DWI might be able to overcome the limitations of current grading of PCa by TRUS-guided biopsies. This series identifies DWI as an important adjunct for clinical decision-making.

Chapter 4.3 addresses the clinically important issue of Gleason undergrading by TRUS-guided biopsies and explores ADC as a possible tool to identify patients subject to Gleason undergrading prior to RP. In a set of patients with a TRUS-guided biopsy Gleason score $\leq 3+3=6$, 48% of patients were subject to Gleason undergrading when evaluating their RP specimen. The slice with the lowest ADC-value, representing the most aggressive part of the tumour, was used for evaluation. DWI was able to identify those patients subject to Gleason undergrading with high accuracy with an area under the ROC-curve of 0.88.

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Chapter 5.1 confirms the ability of MP-MRI to stage PCa reliably, outperforming all the other pre-operative characteristics currently available with an odds-ratio (OR) of 10.3 upon multivariate analysis. We established an overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 58.2%, 89.1%, 84.1% and 68.3%, respectively, of MP-MRI for EPE at RP. More specifically this series introduces the varying performance of staging MP-MRI in different risk-stratified PCa subsets. It identifies superior NPV in low-risk patients, suggesting that the finding of no suspicion of EPE on MP-MRI confirms the possibility of AS or a nerve-sparing RP to the urologist. On the other hand the PPV in this same
6. Nederlandse Samenvatting

Dit proefschrift omhelst de uitdagingen in de diagnostiek en gradering/stadiëring van het gelokaliseerd prostaatcarcinoom (PCa). De nadruk ligt allereerst op het optimaliseren van biopsiestrategieën om op een zo min mogelijk belastende wijze tot een adequate diagnose te komen. Verder wordt uitgebreid ingegaan op de rol van gevanceerde multiparametrische MRI-technieken om de diagnostiek rondom het PCa te verbeteren en op die wijze tot optimale therapiekeuzes te komen voor de individuele patiënt.

Hoofdstuk 3 gaat in op de huidige biopsiestrategieën voor PCa en bevestigt de terughoudendheid met transitzone biopten (TZB) voor een eerste sessie TRUS-geleide biopsieën zoals momenteel bepleit in de meeste (inter)nationale richtlijnen. Het beschrijft de effectiviteit van MR-geleide biopten (MRGB) na herhaalde negatieve TRUS-geleide biopsieën. Hoofdstuk 3 geeft ook informatie over de rol van de multiparametrische MRI (MP-MRI) en daaruit voortvloeiende MRGB in een active surveillance (AS) protocol (MR-PRIAS) met als gevolg exclusie van een aanzienlijk aantal patiënten als gevolg van ondergradering en onderstadiëring bij TRUS-geleide biopsieën.

In hoofdstuk 3.1 presenteren we een serie over de toegevoegde waarde van TZB in de context van eerste TRUS-geleide biopsieën. We stelden vast dat TZB weinig toegevoegde waarde hadden ten opzichte van sextantbiopten van de perifere zone (PZ) met betrekking tot de diagnose van prostaatcarcinoom (PCa), met een toename van PCa detectie van 40,5% tot 42,2%. Bovendien bleken TZB niet veel bij te dragen in de gradering van PCa, aangezien slechts 2,4% van de patiënten een Gleason 4 en/of 5 component in hun TZB had die niet in de sextant perifere zone biopten (PZB) gevonden werd. Er is er een duidelijke indicatie voor herhaalde biopsieën gedaan aan 8,1% van de patiënten die niet werden gediagnosticeerd met een PCa bij eerste TRUS-geleide biopsie, alsnog werd gediagnosticeerd met PCa tijdens de follow-up. Hierbij waren 26,8% van de biopsieprocedures gedurende follow-up, waaronder herhaalde TRUS-geleide biopsieën en MRGB, positief voor PCa.

Hoofdstuk 3.2 laat zien dat MRGB in staat is om PCa op te sporen in een meerderheid van de gevallen met een persisterende verdenking op PCa na 2 of meer negatieve TRUS-geleide biopsiesessies. In het algemeen leidde 59% (40/68) van MRGB procedures in deze serie tot een diagnose van PCa,
Hoofdstuk 3.3 illustreert de mogelijke rol van MP-MRI en daaruit voortvloeiende MRGB bij inclusie in een AS protocol. MRGB van cancer-suspicious regions (CSR) zoals geïdentificeerd op MP-MRI toonde een Gleason 4 en/of 5-component aan die niet was gevonden met TRUS-geleide biopsië in 10,9% (7/64) van de gevallen. Vier van de 64 patiënten (6,3%) had een vermoeden van extraprostatische extensie (EPE) bij een MRGB-positieve CSR en werden daardoor uitgesloten van AS. Binnen dit protocol werden zes patiënten uitgesloten van AS door het verwijzende uroloog in verband met multifocaal PCa. In totaal werden 23,4% van de patiënten van AS uitgesloten op basis van de MP-MRI/MRGB bevindingen. Wat betreft de herbeoordeling na 1 jaar, werden slechts 3/30 (10,0%) patiënten uitgesloten van AS op basis van de MP-MRI/MRGB bevindingen, hetgeen in overeenstemming was met de standaard evaluatie waarbij de hoogste ADC-waarde tijdens de follow-up zo mogelijk wordt gecombineerd met de standaard evaluatie met herhaalde biopsieën. Hoewel het zeer beperkte aantal patiënten die tot dusver de 1-jaar follow-up bereikte in deze serie maakt het echter moeilijk om zinvolle conclusies te trekken.

In hoofdstuk 4 exploreren we de mogelijkheden van diffusie-gewogen MRI (DWI) en de DWI-afgeleide apparent diffusion coefficient (ADC) waarden in het optimaliseren van de gradering en behandeling van PCa en het identificeren van patiënten met een risico op Gleason ondergradering door TRUS-geleide biopsieën. Deze specifieke kwaliteit van DWI heeft zijn belangrijkste verdienste in de selectie van de patiënten die in aanmerking komen voor AS en voor risicostratificatie voorafgaand aan behandeling.

Hoofdstuk 4.1 presenteert een overzicht van state-of-the-art MP-MRI beeldvorming en een review van de literatuur. Hiermee wordt een kader gecreëerd voor de daarna volgende series in dit hoofdstuk. Dit review identificeert MP-MRI, bestaande uit een combinatie van T2-gewogen MRI, DWI en dynamic contrast-enhanced (DCE) MRI, als een betrouwbare lokalisatie- en stadieringstool voor PCa en schetst de mogelijkheden die MP-MRI, en meer specifiek DWI, hebben voor een adequate gradering van PCa.

Hoofdstuk 4.2 beschrijft de correlatie tussen ADC en radicale prostatectomie (RP) Gleason score voor PCa in de PZ, met een area-under-the-ROC-curve (AUC) van 0,90 voor differentiatie tussen laaggradig (Gleason ≤ 3 +3 = 6) en intermediair en hooggradig PCa. ADC-waarden verschilden significant (p <0,001) voor laag-, intermediair en hooggradig PCa, met 1,30x10⁻³ mm²/s, 1,07x10⁻³ mm²/s en 0,94x10⁻³ mm²/s, respectievelijk. Juiste gradering van PCa middels DWI/ADC voorafgaand aan behandeling overwint dus mogelijk de huidige beperkingen voor de classificatie van PCa middels TRUS-geleide biopsieën. Als zodanig identificeert deze serie DWI als een belangrijk hulpmiddel voor klinische besluitvorming.

Hoofdstuk 4.3 behandelt de klinisch belangrijke kwestie van Gleason ondergradering middels TRUS-geleide biopsieën en verkent ADC als een mogelijk instrument om patiënten met Gleason ondergradering voorafgaand aan RP te identificeren. In een reeks van patiënten met een TRUS-geleide biopsie Gleason score ≤3+3=6, had 48% van de patiënten Gleason ondergradering bij de beoordeling van hun uiteindelijke RP specimen. Het segment met de laagste ADC-waarde, hetgeen het meest agressieve deel van de tumor identificeert, werd gebruikt voor evaluatie. DWI kon patiënten met Gleason ondergradering met hoge nauwkeurigheid identificeren met een area-under-the-ROC-curve van 0,88.

In hoofdstuk 4.4 worden de ADC kenmerken van patiënten die in aanmerking komen voor AS volgens de PRIAS-criteria besproken. We stelden vast dat patiënten die geen, laaggradig (een Gleason 4 en/of 5 component) of hooggradig PCa (Gleason 4 en/of 5 component) hadden bij MRGB van de geïdentificeerde CSR's significant verschillend ADC-vaarden hadden van 1,26x10⁻³ mm²/s, 1,09x10⁻³ mm²/s en 0,84x10⁻³ mm²/s, respectievelijk. Met een AUC van 0,73 voor het voorspellen van de aanwezigheid van PCa in een CSR is de betrouwbaarheid van DWI om PCa nauwkeurig uit te sluiten naar onze mening te laag om af te zien van gerichte biopten van de betreffende...
Hoofdstuk 5.2 richt zich op het identificeren van patiënten met een hoog risico op BCR in geval van een PSM bij RP. De uitbreiding van het aantal bekende risicofactoren voor BCR na een PSM, zoals lengte van PSM en localisatie ter hoogte van de basis van de prostaat, kan de identificatie van patiënten die baat hebben bij onmiddellijke radiotherapie na RP verbeteren. Het betreft hier een negatieve studie, waarbij we multifocale of bilaterale PSM-status niet hebben kunnen identificeren als een voorspeler van BCR. Er is wel sprake van een significante tendens tot een eerder BCR in geval van een bilaterale PSM-status.

CSR's. Daarentegen lijkt DWI in staat om deze gerichte bioten met grote nauwkeurigheid naar het meest agressieve deel van de tumor te leiden. De implicaties van een vals-negatieve MP-MRI evaluatie in een AS populatie met een eerdere histologische diagnose van prostaatkanker op basis van TRUS-geleide biopscien, hetgeen in deze serie leidt tot een negatief MRGB in 45,3% van de gevallen, zal nog moeten worden vastgesteld middels langduriger follow-up.

Hoofdstuk 5 definiert de mogelijkheden van geïndividualiseerde besluitvorming op basis van stadiëringen MP-MRI resultaten en in geval van een positief snijvlak (PSM) na RP. Kennis van de verschillende voorspellingen van MP-MRI voor EPE binnen de uiteenlopende risicogroepen faciliteert het correct voorlichten van de patiënt over de mogelijke behandelingen. Ook de constatering van een PSM en identificatie van patiënten met een hoog risico op biochemisch recidief (BCR) biedt de uroloog handvatten om de noodzaak van onmiddellijke adjuvante radiotherapie na RP te bespreken.

Hoofdstuk 5.1 bevestigt het vermogen van MP-MRI om betrouwbaar het pT-stadium van PCa vast te stellen (zie appendix 3), en presteert beter dan alle andere pre-operatieve kenmerken met een odds-ratio (OR) van 10,3 bij multivariate analyse. Wij stelden een sensitiviteit, specificiteit, positief voorspellende waarde (PPV) en negatief voorspellende waarde (NPV) van 58.2%, 89.1%, 84.1% en 68.3%, respectievelijk, vast van MP-MRI voor EPE bij RP. Meer specifiek verduidelijkt deze serie de wisselende voorspellende waarden van stadiëringen MP-MRI in de verschillende risicogroepen. In geval van laag-risico patiënten is we sprake van een hoge NPV, hetgeen de mogelijkheid van een zenuwsparende RP in geval van het ontbreken van een verdenking op EPE bij MP-MRI in deze populatie onderschrijft. Daarentegen kan de lage PPV in deze populatie leiden tot een aantal onnodige niet-zenuwsparende procedures of onjuiste uitsluiting van AS protocollen bij gebruik van MP-MRI voor deze beslissingen. Aan de andere kant van het risico-spectrum, is de PPV voor EPE zeer hoog in hoog-risico patiënten, hetgeen het nut van MP-MRI voor het verkrijgen van kennis over de exacte localisatie van EPE in geval van RP onderschrijft. Tevens onderstrept deze hoge PPV de mogelijkheid om andere therapiemodaliteiten, zoals externe radiotherapie, te exploreren in geval van zeer uitgebreide EPE, waarbij de kans op curatie middels RP beperkt wordt geacht.
7. General discussion and clinical implications

7.1 Diagnostic strategies for prostate cancer

Over recent decades the number of recommended biopsy cores for the diagnosis of PCa has increased from classical sextant biopsy to the more extended TRUS-guided biopsy protocols we use today. Current guidelines recommend extended (10–12 core) PZ sampling of the prostate in case of a suspicion for PCa due to an elevated PSA and/or an abnormal DRE. TZB is not recommended for baseline TRUS-guided biopsies, based upon several reports showing little incremental value.

Chapter 3.1 of this thesis also shows little incremental diagnostic value over of TZB over sextant PZ biopsy, thus confirming the exclusion of TZ biopsies for baseline TRUS-guided biopsies. Still, TRUS-guided biopsies have a significant false-negative rate and therefore the need for repeated TRUS-guided biopsies in case of a persistent suspicion of PCa has not been eliminated. The ideal scheme and approach for repeat TRUS-guided biopsies has not been established yet and the concept of repeating a procedure with a substantial false-negative rate obviously has limitations of its own. Different alternatives have been advocated including saturation biopsies, transperineal biopsies and targeted prostate biopsies, such as MRGB. It is clear that repeat biopsy sessions in any form induce a significant procedure burden to the patient accompanied by the prolonged insecurity whether or not harbouring PCa. Furthermore, every biopsy session, especially in case of transrectal procedures, incorporates a new risk of infectious adverse events, which seem to be increasing over recent years mainly due to antibiotic resistance of micro-organisms.

MRGB has been shown to have a high diagnostic yield in a population following 2 or more negative TRUS-guided biopsies in chapter 3.2, establishing a PCa diagnosis in 40/68 (59%) of patients of which the majority were deemed clinically significant. In the past years these results have been reproduced in larger series and a recent review of literature by Moore et al. outlined MRI in combination with targeted biopsies of CSRs to be an effective method to diagnose clinically significant PCa. Our main challenge as clinicians should be to minimise the false-negative rate of any diagnostic algorithm for PCa, obtained at the minimum number of biopsy cores needed. A recent series by Komai et al. has shown that MP-MRI misses about 14% of
significant cancers diagnosed by an extensive biopsy protocol combining 12-core transrectal PZ biopsies with 14-core sampling of the anterior aspect of the prostate using a transperineal approach. Therefore, it does not seem possible to refrain from schematic biopsies of the prostate to exclude significant PCa at this moment. In our opinion the ideal scenario might be a pre-biopsy MP-MRI to determine the need for anterior sampling and/or targeted biopsies in combination with a 10-12 core biopsy scheme sampling the PZ, as recommended by the current guidelines.

Significant PCa seems to be very unlikely in case of negative TRUS-guided biopsies sampling the PZ combined with a negative MP-MRI examination. In case of a CSR upon MP-MRI it is imminent that targeted biopsies should be performed, the role of schematic anterior prostate sampling in this context however remains to be established. This strategy is likely to reduce the rate of incidental PCa during follow-up and a series by Hoeks et al has shown that only 2.7% (9/330) of patients with a negative MP-MRI/MBRG evaluation following negative TRUS-guided biopsies were diagnosed with PCa during follow-up. On the other hand we know from AS series, like the one presented in chapter 4.4 of this thesis, that MP-MRI fails to diagnose approximately half of low-grade, low-volume cancers. As long as we are not confident that those cancers missed by MP-MRI will remain indolent over an extended period of time, MP-MRI is not ready to serve as a stand-alone PCa test. While MP-MRI does not detect a substantial number of low-risk PCa diagnosed by schematic TRUS-guided biopsy, prolonged follow-up in our AS cohort will elucidate how patients with no CSR upon MP-MRI or no PCa upon concomitant MRGB of CSRs will fare. If a negative MP-MRI evaluation will turn out to be a good predictor of true clinically insignificant disease, this could have important repercussions for diagnostic strategies for PCa in a PSA-screened population. Eventually, MP-MRI might evolve to an up-front pre-biopsy test in patients with an elevated PSA to preclude the need for TRUS-guided and/or targeted prostate biopsies. As urologists we have to identify our strength, which beholds the diagnosis of PZ PCa using TRUS-guided biopsies; however, the radiologist will probably lead in detecting and targeting anterior PCa using MP-MRI.

7.2 Role of MP-MRI in active surveillance for low-risk prostate cancer

With regard to improving inclusion in AS protocols, MP-MRI is the most promising tool currently available. We need to elucidate whether MP-MRI is able to reliably and reproducibly identify patients subject to Gleason undergrading and/or understaging at TRUS-guided biopsy. DWI-derived ADC-values correlate well with RP Gleason score and DWI is the most appropriate tool to estimate the true Gleason score following a diagnosis of low-volume, low-risk PCa. In chapter 4.2 a series on the correlation of ADC and RP Gleason score is presented, showing good accuracy, which has been confirmed by other series. Prediction of the true Gleason grade can be of great importance as decisions on treatment options are at least partially based on the biopsy-acquired combined Gleason score. By means of the ADC, DWI is able to identify patients subject to Gleason undergrading following a diagnosis of Gleason ≤3+3=6 PCa upon TRUS-guided biopsies, as outlined in chapter 4.3, and could be an important tool in AS inclusion. However, with an AUC of 0.73 for prediction of PCa in a CSR as presented in chapter 4.4 of this thesis, MP-MRI is not yet able to predict the presence of PCa with sufficient accuracy to abolish histological verification of CSR’s in an AS population.

The substantial rate of Gleason undergrading using TRUS-guided biopsies has been shown to be virtually a non-issue in case of MRGB. In case of candidates for AS chapter 3.3 and chapter 4.4 of this thesis have shown that MRGB is able to identify a substantial number of cases subject to Gleason undergrading, who are therefore not considered eligible for AS. Interestingly, in a substantial number of cases MP-MRI/MRGB evaluation was not able to confirm a diagnosis of PCa in these patients who had histologically proven PCa upon their TRUS-guided biopsies. Vargas et al. showed that a negative MRI study had a high NPV and high specificity for upgrading upon immediate confirmatory biopsy in low-risk PCa patients, whereas a positive MRI study had a very high sensitivity for upgrading. Prolonged follow-up of patients with a negative MP-MRI within AS protocols, such as MR-PRIAS, will show whether a negative MP-MRI evaluation does truly represent clinically insignificant disease, which in turn might have important implications for diagnostic strategies for PCa.
Even in a population considered eligible for AS, EPE is a rather common feature at RP. When staging MP-MRI is used to identify patients eligible for AS, a high NPV for EPE is of paramount importance. Translating the staging performance of MP-MRI as outlined in Chapter 5.1 to AS protocols, we found MP-MRI to have a high NPV of 86.7% for EPE in low-volume, low-risk PCa subjects, and therefore a MP-MRI study with no evidence of EPE in candidates for AS is very likely to rule out any significant EPE, which is considered a contra-indication for AS. In the results of MP-MRI at inclusion in MR-PRIAS, as presented in Chapter 3.3, 6.3% of patients considered eligible for AS had a suspicion of EPE, which corresponds with the reported 5-8% incidence of EPE in AS candidates undergoing RP.

Whereas evidence for the merits of MP-MRI at inclusion in AS is accumulating, the role of MP-MRI in follow-up during AS is unclear. At this point only limited reports on the use of MP-MRI for detection of progression under AS have been published indicating that there might be a role for MP-MRI during AS follow-up. Our preliminary results for the 1-year follow-up point in MR-PRIAS, as described in Chapter 3.3, suggest only limited value for MP-MRI/MRGB when compared to conventional repeated TRUS-guided biopsies but numbers are too small to draw significant conclusion. The potential benefits of DWI in this context have been published by Van As et al., establishing the potential of ADC as a marker for progression under AS.

### 7.3 Pre-treatment staging MP-MRI for prostate cancer

MP-MRI has evolved to a widely available modality to establish PCa stage before RP. Fair sensitivity and good specificity of MP-MRI for EPE at RP have been reported consistently and staging MP-MRI must now be considered a reproducible test. Interestingly, as outlined in Chapter 5.1, predictive values of MP-MRI for EPE are very wide apart in the different d’Amico risk groups, indicating the need for the radiologist and urologist alike to be aware of these differences for adequate interpretation of MP-MRI examinations and the resulting MP-MRI reports.

An acceptable NPV for ruling out EPE should be able to strike the right balance between unneeded resection of the neurovascular bundle and the risk of a PSM and is only reached in low-risk patients. In this subgroup absence of EPE upon MP-MRI reassures the surgeon to pursue a nerve-sparing approach, however, the possibility of false positive results would urge the clinician to discuss unneeded neurovascular bundle resection in cases with a suspicion of EPE upon MP-MRI. As far as the intermediate risk group is concerned, the relative high proportion of false negative MP-MRI results should place the emphasis on the risk of positive margins while counselling the patient on the options for nerve-sparing RP. On the contrary, when MP-MRI is used to exclude patients with evident EPE from curative surgery, high-specificity readings should be performed, leading to a high PPV in high-risk subjects. Even when performing a non-nerve sparing RP in these cases, staging MP-MRI might aid the urologist in decreasing the risk of PSMs. Clinical stage T3 PCa, as established by DRE, represents locally advanced disease and is a poor prognostic factor before RP. The role of RP in this subset of PCa patients is under debate and many urologists favour external beam radiotherapy over RP in this specific patient group. In this context, radiologists have been performing high-specificity readings of staging MP-MRI studies to avoid exclusion of potentially curative RP based upon a false-positive EPE call by the reporting radiologist. However, the true meaning of an MRI-established suspicion of EPE compared with the classical cT3 as determined by DRE remains unclear. It is likely that an imaging-based cT3 has a better prognosis as MP-MRI will pick up less extensive EPE than DRE, but how this should translate to clinical practice remains unclear. On the other hand, it is known that any EPE induces a significantly greater risk of BCR following RP, which is even aggravated in case of a PSM.

As outlined in Chapter 5.2, surgical margin status remains an important independent predictor of BCR following RP. In fact, it is probably the most relevant pathological predictor of BCR as it is the only factor that to a certain extent can be influenced by the operating urologist. Therefore any measure that enables us to reduce the risk of a PSM, especially in case of suspected EPE, should be considered relevant in clinical practice. Several predictors of BCR within a PSM population have been identified, such as localization at the prostate base and the length of PSM. It is evident that while performing RP in patients with suspected EPE our main focus should be on limiting the number and extent of PSM’s. Staging MP-MRI outperforms any other pre-operative characteristic for prediction of EPE, including clinical stage, as shown in Chapter 5.1 and delivers information on the presence, site and extent of EPE to the urologist performing a RP. MP-MRI thus enables us to select candidates for nerve-sparing procedures more accurately, potentially reducing the number and extent of PSM’s.
In conclusion we promote in **chapter 5.1** a high-sensitivity MP-MRI reading in low- and intermediate risk subjects, and a high-specificity MP-MRI reading in high-risk patients. Knowledge of the specific risk-stratified predictive values enables the urologist to optimize patient counselling on staging MP-MRI results and its possible consequences accordingly. The advance to risk-stratified MP-MRI interpretation based on patient and clinical characteristics illuminates the need for narrow collaboration between the radiologist, urologist and radiation oncologist, ideally taking place in a multidisciplinary consensus meeting precluding treatment decisions.

**References**

8. Future perspectives

8.1 Diagnostic strategies for prostate cancer

There is a definite need to evolve our diagnostic strategies for PCa in such a manner that we can dispose of frequent serial PSA measurements and the substantial level of uncertainty on the presence of significant PCa that are now common following negative TRUS-guided biopsy schemes. The need for our cautious approach to subjects with a negative baseline series of TRUS-guided biopsies originates in the well-documented substantial false-negative rate for significant PCa of this test. This in turn leads to high rates of repeated biopsy procedures in case of a persistent suspicion of PCa. If we could reduce the false-negative rate of our diagnostic algorithm to a minimum, we would be able to ensure that the chances of bearing significant PCa are small. This would most likely lead to a reduction of patients’ anxiety while being subjected to serial PSA-measurements and repeat biopsy procedures, while on the other hand limiting the burden of frequent outpatient consultations and repeat biopsy procedures on our health care system.

Evaluation of pre-biopsy MP-MRI

Recently several series have reported upon the performance of pre-biopsy MP-MRI in the evaluation of subjects with an elevated PSA, showing a fair to good NPV of MP-MRI for presence of clinically significant PCa. However, a substantial number of significant PCa are still missed by pre-biopsy MP-MRI. Major limitations of these series at this point are the absence of follow-up and the different criteria used for significant PCa. Furthermore, varying techniques were used as a reference diagnostic tool, including transperineal template biopsies, combined transperineal and transrectal biopsies, and MP-MRI targeted biopsies only. In any case it is far too early to consider MP-MRI as a stand-alone diagnostic tool for PCa, as validation in larger series with prolonged follow-up to determine the incidence of PCa following such an approach are absent. We think that future research on pre-biopsy MP-MRI should incorporate the current standard of 10-12 cores of TRUS-guided biopsies, enhanced with some form of anterior prostate sampling and targeted biopsy of CSRs as identified on MP-MRI for histopathological evaluation.
Future of targeted prostate biopsies
As discussed in this thesis MP-MRI is a very promising tool to detect PCa in a population with a persistent suspicion of PCa following negative TRUS-guided biopsies. In this context MRGB has been the modality of choice to sample CSRs as identified at MP-MRI and obtain a histological diagnosis of PCa. However, due to its costly and time-consuming nature the use of MRGB in clinical practice has remained limited to centres of excellence. While MRGB will remain too technically challenging to be available for every patient in every location in the short-term we have to look at alternatives integrating MP-MRI results into clinical practice. A relatively easy approach could be the implementation of fusion of MP-MRI images with real-time TRUS (MR-TRUS fusion), integrating targeted biopsies into baseline and/or repeat biopsy procedures. MR-TRUS fusion might be the perfect hybrid approach blending MP-MRI acquired CSR data within a schematic biopsy approach of the prostate delivering the best of both worlds to the urologist’s office. Future research in this field will therefore need to focus upon optimization of MR-TRUS fusion techniques and validation of these techniques in clinical practice, aiming to prove its superiority to schematic repeat TRUS-guided biopsy protocols and equivalence to MRGB.

8.2 The role of MP-MRI in risk-stratification of PCa and identifying candidates for active surveillance
It has now been established that DWI-derived ADC-values correlate well with PCa Gleason score, and this makes it an extremely useful tool in the evaluation of patients considered candidates for AS, while harbouring low-grade, low-volume PCa based upon DRE, PSA and TRUS-guided biopsies. Several series on the impact of MP-MRI, and in this context especially DWI, have now been published and without exception have shown ADC-values to be of great help in detecting patients subject to Gleason undergrading following TRUS-guided biopsies in AS candidates. In the future it might not be necessary to obtain histopathological sampling of every CSR in AS candidates, limiting the need for immediate repeat (targeted) biopsies to those subjects revealing an ADC-value suspicious for a high-grade Gleason component. Prolonged follow-up in our MR-PRIAS cohort will show whether a negative MP-MRI evaluation following a diagnosis of low-risk PCa correlates with true clinically insignificant disease and prolonged high progression-free rates in AS protocols.

Impact of negative MP-MRI evaluation of patients with (a suspicion of) low-risk PCa
Recently some series have been published that identify a negative MP-MRI evaluation indeed as an important predictor of insignificant PCa. Most series used a biopsy-based definition of insignificant PCa for this and are therefore limited by the well-known phenomenon of undergrading of PCa by TRUS-guided biopsies. At this point RP correlated studies remain scarce while being most suitable to evaluate the true rate of clinically insignificant PCa in a population with a negative MP-MRI. However this approach is also likely to introduce a bias as the decision to pursue a RP is also initiated by the diagnosis and characteristics of PCa by TRUS-guided biopsies in most cases. Ideally, we would follow-up on patients with a negative MP-MRI evaluation, for example in AS protocols, to establish the number of patients that would progress to more aggressive disease after all and would be in need of radical treatment. This approach would elucidate how patients with a negative MP-MRI evaluation would fare and could ultimately have important repercussions for diagnostic strategies for PCa. For example, if a negative MP-MRI evaluation with TRUS-guided biopsies showing no or low-grade PCa would be a reliable predictor of insignificant disease, MP-MRI could evolve to be an important adjunct tool for identifying patients not likely to display progressive PCa during follow-up, who would be ideal candidates for AS.

MP-MRI as a follow-up tool in active surveillance
While MP-MRI has been shown to be a very promising tool at inclusion in AS protocols, its role in follow-up of those patients remains unclear. Our preliminary results shows only limited added value of MP-MRI/MRGB evaluation at 1-year of follow-up in an AS protocol, however numbers are far too low to draw significant conclusions and many more subjects have to reach the 1-year follow-up timepoint to be able to evaluate the real (in) significance of MP-MRI at this point. There is a burning need for more series using MP-MRI as a follow-up tool within AS and we think that any new research endeavour in AS should at least consider including MP-MRI as a tool at inclusion and during follow-up. Future validation of MP-MRI in AS protocols is of great importance and its reproducibility outside centres of excellence remains to be determined.
Reduction of PSM rates using MP-MRI
While evidence for the performance of MP-MRI as a staging tool for localized PCa is accumulating, its role in reducing the number of PSM remains unclear. The knowledge of presence and localization of EPE is likely to reduce the number of PSM at RP, but its ability to do exact so has not been studied thoroughly. Comparing pre-operative planning with or without staging MP-MRI results is a challenge and randomizing patients to staging MP-MRI before RP seems unethical now. Ideally, a decision-aid using MP-MRI results in deciding upon nerve-sparing techniques should be validated in a clinical setting.

8.3 The individualization of staging MP-MRI and its impact on surgical margin status
Currently, in everyday clinical practice staging MP-MRI is evaluated in a standardized manner, regardless of risk of EPE of the individual patient. This simply means that the available criteria for EPE are used to provide the urologist with staging results obtained from MP-MRI, whereas the information could be more valuable should it be interpreted in its correct context. For example, when nerve-sparing strategies are considered, the urologist and patient would benefit most from a high NPV to minimize the risk of PSM at RP, resulting from a high-sensitivity reading. On the other hand, when patients with extensive EPE are to be excluded from RP and referred for external beam radiotherapy, a high PPV is warranted to exclude incorrect exclusion of potentially curative RP. A high PPV is obtained by high-specificity readings of staging MP-MRI, the type of reading most radiologists are performing at this point. While staging MP-MRI does not represent a ‘black-or-white’ test, the interpreting radiologist should be aware of the clinical consequences of his call. Therefore, communication between the disciplines, ideally in a consensus meeting, might be the crux for correct individualized interpretation of a staging MP-MRI.

Individualized staging MP-MRI reports
From a clinical point of view it is very important to discuss the influence of MP-MRI reports on impending treatment with the radiologist, who is then able to provide the urologist with a tailored high-sensitivity or high-specificity reading. All currently published series on staging performance MP-MRI have shown fair to good sensitivity for EPE, while at the same time establishing superior specificity. This is in concordance with our earlier statement that high-specificity readings are now the standard. However, with the increase of patients diagnosed with low-risk PCa, the emphasis for this specific population might have to shift to high-sensitivity readings. One could postulate that incorrect exclusion from AS or an unneeded excision of the neurovascular bundle in an individual case is to be preferred above an inclusion in AS of a patient with EPE or a PSM following RP. We suggest therefore that future series on staging MP-MRI will report upon the different risk subsets categorically to be better able to determine its value for an individual PCa case.
9. Conclusions

- PCa diagnosis, treatment and follow-up remain the urologist’s domain, who needs to call in the radiologist’s help in time to provide him with the relevant data from MP-MRI evaluation to be used in the process.

- Grading of PCa is evolving from a biopsy-based feature to a MR imaging-based prospect, greatly facilitated by advanced MP-MRI techniques such as DWI.

- PCa staging is teamwork, including the urologist, radiologist and radiation oncologist, who in consensus are able to determine the most adequate management options for an individual patient.

- Ultimately, a well-informed patient, facilitated by his urologist who is able to discuss and explicate the biopsy and MP-MRI results, should take his personal management decisions when confronted with localized PCa.
10. Curriculum Vitae

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Chapter 12

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Chapter 13

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DANKWOORD
Chapter 13

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Christina Hulsbergen-van de Kaa, je bent voor alle prostaatkankeronderzoekers in het Radboud de pathologische rots in branding. Voor zowel de radiologen als urologen fungeer je als aanspreekpunt en bij de behandeling Pathologie en zorg je voor een gedegen gouden standaard waartegen wij al onze resultaten moeten afzetten. Je hebt mij in den beginne veel geleerd over de achtergronden van de prostaatpathologie en daarmee een kader geschapen voor alle artikelen in dit proefschrift.

Collega’s urologen in het CWZ, Herbert Karthaus, Henk Vergunst, Jean-Paul van Basten en Judith Schaafstra. Jullie wil ik bedanken voor het in mij gestelde vertrouwen hetgeen mij een plek in jullie midden heeft opgeleverd. Ik werk dag in dag uit met veel plezier met jullie samen en prijs me gelukkig te mogen werken in een ambitieuze vakgroep Urologie, waarbinnen ik het gevoel heb me volledig te kunnen ontwikkelen. Van jullie allen heb ik veel geleerd en ik heb jullie steun aan mijn wetenschappelijke activiteiten altijd als onvoorwaardelijk ervaren. Herbert, jij hebt een bijzondere rol gehad in mijn vorming tot uroloog en ik ben er trots op de laatste assistent te zijn die je hebt opgeleid. Ook na mij opleiding heb je mij in mijn eerste stappen als staflid met hart en ziel bijgestaan en ik leer ook nu nog elke dag van jullie kritische houding en chirurgisch-technische vaardigheden.

Alle pathologen in het CWZ en in het bijzonder Willem Vreuls, jij bent onze prostaatkankerman en geen moeite is teveel als het de ondersteuning op pathologisch gebied betreft. Veel van het pathologisch werk uit het CWZ in mijn proefschrift is van jouw hand en dat heeft geleid tot meer dan verdiende co-auteurschappen. Je draagt de wetenschap een warm hart toe en ik hoop nog vele malen met je te filosoferen over het optimaliseren van de zorg voor onze prostaatkankerpatiënten.

Paranimfen, Sander en Martijn, jullie zijn mijn beste maatjes en onze vriendschap gaat ver terug en is onvoorwaardelijk. Sander, je ongezouten mening staat garant voor pittige discussies en je kent mij beter dan wie dan ook. Ik ben dan ook vereerd dat je mij op deze dag wilt bijstaan. Tinus, wij hebben aan één woord genoeg, hoewel in jouw geval toch vaak vele woorden gebruikt worden. Ik weet dat ik altijd op je kan terugvallen en ben blij dat je op deze dag mijn paranimf wilt zijn.

Jerry, Janneke, Bart, Arno, studievrienden van het eerste uur. Jullie begrijpen wat mij de afgelopen jaren heeft beziggehouden en met jullie kan ik sparen over de ziekenhuis- en wetenschappelijke kwakzalverijen die op ons pad komen. Ook persoonlijke hoogte- en dieptepunten delen wij en ik reken jullie tot mijn beste vrienden.

Oud-huisgenoten van de Monseigneur en later Lauwerek, de afgelopen periode heb ik jullie veel minder gesproken dan mij lief was en met de voltooiing van dit soms eindeloos lichtende project kijk ik uit naar de vele biertjes die nu weer kunnen volgen. Ik koester de gesprekken die wij kunnen voeren over de meest zinnige en zinloze onderwerpen en jullie zijn voor mij een klankbord.
Jaarclubgenoten, ik spreek jullie niet altijd regelmatig, maar als we bij elkaar zijn, komen direct de oude gewoontes en grappen weer bovendrijven. Nu is er dus geen excuus meer voor afwezigheid op zomibo’s, bvdmbo’s en wat dies meer zij.

Lieve Papa en Mama, Reinier en Miep, zonder jullie...!? Altijd staan jullie voor mij klaar en met weinig woorden weet ik me verzekerd van jullie steun. Van jullie heb ik geleerd te denken in oplossingen en niet in problemen en jullie hebben mij de bagage gegeven om deze en vele andere ambities te verwezenlijken. Het doktersvak is mij door jullie met de papplepel ingegoten.

Koos en Marlou, in raad en daad hebben ook jullie ons terzijde gestaan en jullie weten als geen ander hoe het is om een promotie naast werk en gezin te voltooien. Dank voor jullie steun en inzet, de geïnvesteerde uren van jullie kant betalen zich nu dus in papier terug. Marlou, ik hoop je na het voltooien van dit proefschrift nog vaak bij ons thuis te mogen verwelkomen, maar nu gewoon voor koffie en een goed gesprek.

Matthijs en Joost, broertjes, onze vriendschap is vanzelfsprekend en ik ben blij met de vele familiemomenten die wij delen. We wonen ver uit elkaar, maar toch voelt dat niet zo. We grijpen gelukkig elke gelegenheid aan om iets te vieren of elkaar weer te spreken of te zien. Ik waardeer het zeer dat jullie dit project met toenemende belangstelling hebben gevolgd.

Lieve Maxime en Loek, hoewel jullie te klein zijn om te beseffen waarom papa altijd moest schrijven, laat staan te weten wat een prostaat is, zijn jullie voor mij steeds een bron van vreugde en motiatie geweest. Jullie geven mij steeds weer de energie die ik nodig heb en jullie kinderwijsheden zijn onmisbaar. Ik geniet elke dag van jullie bestaan!

Willemijn, tsja, dit valt eigenlijk niet in woorden uit te drukken. Ik ben me bewust van de druk die dit proefschrift op ons heeft gelegd. Onze momenten samen zijn goud waard, hoewel ze te vaak moesten sneuvelen voor de wetenschap. Toch heb je me altijd gesteund en ben je mijn geweten én beste raadgever. Je attendeert mij op zaken die ik zelf nog niet eens gesignaleerd heb en bent mijn steun en toeverlaat. Zonder jou had ik dit nooit kunnen volbrengen en daarvoor ben ik je eeuwig dankbaar. Ik houdt zielsveel van je en hoewel je er misschien niet aan zult willen is dit ook jouw feestje.
Appendix 1

Inclusion and exclusion criteria used in the PRIAS/MR-PRIAS study

Inclusion criteria
- Histopathologically proven adenocarcinoma of the prostate
- Men should be fit for curative treatment
- PSA level at diagnosis ≤10.0 ng/mL
- PSA density <0.2 ng/mL/mL
- Clinical stage T1c or T2
- Gleason score ≤3+3=6
- ≤2 biopsy cores invaded with prostate cancer
- Participants must be willing to attend the follow-up visits

Exclusion criteria
- Men who cannot or do not want to be operated or irradiated
- A former therapy for prostate cancer
- Contra-indications to MRI or gadolinium based contrast agents (MR-PRIAS only)
### Appendix 2

**MP-MRI parameters**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Sequence</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Flip angle (degrees)</th>
<th>Slice thickness (mm)</th>
<th>Field of view (mm ´ mm)</th>
<th>Matrix size (mm ´ mm)</th>
<th>Voxel size (mm ´ mm ´ mm)</th>
<th>b-values (s/mm²)</th>
<th>Temporal resolution (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MR imaging lymph nodes and bone structures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D T2WI</td>
<td>TSE coronal</td>
<td>1390</td>
<td>100</td>
<td>100</td>
<td>1.0</td>
<td>320x320</td>
<td>320x320</td>
<td>1.0x1.0x1.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>T1WI</td>
<td>TSE coronal</td>
<td>500</td>
<td>11</td>
<td>120</td>
<td>3.0</td>
<td>384x384</td>
<td>320x256</td>
<td>1.5x1.5x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>WBDWI</td>
<td>EPI</td>
<td>6500</td>
<td>71</td>
<td>n.a.</td>
<td>3.0</td>
<td>385x385</td>
<td>154x154</td>
<td>2.5x2.5x3.0</td>
<td>600</td>
<td>n.a.</td>
</tr>
<tr>
<td>WBDWI</td>
<td>EPI</td>
<td>6200</td>
<td>66</td>
<td>n.a.</td>
<td>3.0</td>
<td>385x385</td>
<td>154x154</td>
<td>2.5x2.5x3.0</td>
<td>50</td>
<td>n.a.</td>
</tr>
<tr>
<td><strong>ERC MP-MRI prostate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2WI axial (TSE)</td>
<td>4280</td>
<td>99</td>
<td>120</td>
<td>3.0</td>
<td>180x178</td>
<td>448x448</td>
<td>0.4x0.4x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>coronal</td>
<td>3590</td>
<td>98</td>
<td>120</td>
<td>3.0</td>
<td>192x96</td>
<td>384x384</td>
<td>0.5x0.5x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>sagittal</td>
<td>4290</td>
<td>98</td>
<td>120</td>
<td>3.0</td>
<td>192x134</td>
<td>384x384</td>
<td>0.5x0.5x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>DWI SSEPI Axial</td>
<td>2600</td>
<td>90</td>
<td>n.a.</td>
<td>3.0</td>
<td>204x204</td>
<td>136x136</td>
<td>1.5x1.5x3.0</td>
<td>0/50/500/800</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>PD GE Axial 3D</td>
<td>800</td>
<td>1.51</td>
<td>14</td>
<td>3.0</td>
<td>192x192</td>
<td>128x128</td>
<td>1.5x1.5x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>DCE-MRI Spoiled GE Axial 3D</td>
<td>36</td>
<td>1.4</td>
<td>10</td>
<td>3.0</td>
<td>192x19</td>
<td>128x128</td>
<td>1.5x1.5x3.0</td>
<td>n.a.</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td><strong>MRGB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2WI TSE Axial</td>
<td>3620</td>
<td>103</td>
<td>120</td>
<td>4.0</td>
<td>256x256</td>
<td>320x320</td>
<td>0.8x0.8x4.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>DWI EPI Axial</td>
<td>3300</td>
<td>60</td>
<td>n.a.</td>
<td>3.6</td>
<td>260x211</td>
<td>160x120</td>
<td>2.2x1.6x3.6</td>
<td>0/100/400/800</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>SSFP GE Axial and Sagittal</td>
<td>4.48</td>
<td>2.24</td>
<td>70</td>
<td>3.0</td>
<td>280x280</td>
<td>256x256</td>
<td>1.1x1.1x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

### Appendix 3

#### 2002 TNM Classification for Prostate Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Substage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1a</td>
<td>Incidental histological finding; ≤5% of tissue resected during TUR-P</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>Incidental histological finding; &gt;5% of tissue resected during TUR-P</td>
</tr>
<tr>
<td></td>
<td>T1c</td>
<td>Tumor identified by needle biopsy</td>
</tr>
<tr>
<td>T2</td>
<td>T2a</td>
<td>Tumor involves half of the lobe or less</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>Tumor involves more than one half of one lobe but not both lobes</td>
</tr>
<tr>
<td></td>
<td>T2c</td>
<td>Tumor involves both lobes</td>
</tr>
<tr>
<td>T3</td>
<td>T3a</td>
<td>Extraprostatic extension (unilateral or bilateral)</td>
</tr>
<tr>
<td></td>
<td>T3b</td>
<td>Tumor invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td>T4a</td>
<td>Tumor invades bladder neck and/or external sphincter and/or rectum</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Tumor invades levator muscles and/or is fixed to pelvic wall</td>
</tr>
<tr>
<td>N</td>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td>M</td>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1a</td>
<td>Non-regional lymph node(s)</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td>Bone(s)</td>
</tr>
<tr>
<td></td>
<td>M1c</td>
<td>Metastasis at other site(s)</td>
</tr>
</tbody>
</table>

**TUR-P:** Transurethral resection of the prostate.
Appendix 4

Crosstabs used for establishing prevalence, accuracy, sensitivity, specificity, PPV and NPV of MP-MRI for EPE at RP

<table>
<thead>
<tr>
<th></th>
<th>No EPE at RP</th>
<th>EPE at RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP-MRI positive for EPE</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>MP-MRI negative for EPE</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Prevalence = (b+d)/(a+b+c+d)
Accuracy = (b+c)/(a+b+c+d)
Sensitivity = b/(b+d)
Specificity = c/(c+d)
PPV = b/(a+b)
NPV = c/(c+d)
