MULTIPARAMETRIC MR IMAGING AND MR GUIDED BIOPSY:

PROSTATE CANCER
DIAGNOSIS AND RISK-STRATIFICATION

Caroline M.A. HOEKS
Multiparametric MR imaging and MR guided biopsy: prostate cancer diagnosis and risk-stratification

Caroline M.A. Hoeks
The cover of this thesis depicts Janus, who in Roman religion was a god of transitions, of beginnings, of endings and of time. Janus is usually depicted with two faces: the past and the future.

Prostate cancer has been described as “a disease with the two faces of Janus: having one benevolent face of small, indolent tumours, abundant among middle-aged and elderly men, it also has the grim face of a great killer. This constitutes a veritable dilemma for urologists and oncologists when counseling patients with localised prostate cancer. For which patient will Janus show his benevolent smile throughout life and for which patient will he turn around and show the ruthless face of painful skeletal metastases and death?” (Ola Bratt European Urology, 2006).

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Multiparametric MR imaging and MR guided biopsy: prostate cancer diagnosis and risk-stratification
Promotor:
Prof. dr. J.O. Barentsz

Copromotoren:
Dr. J.J. Fütterer
Dr. C.A. Hulsbergen- van de Kaa
Dr. I.M. van Oort

Manuscriptcommissie:
Prof. dr. M. M. Rovers
Prof. dr. G. Villeirs (Universiteit Gent)
Dr. J.P.M. Sedelaar
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Introduction
Prostate cancer diagnosis

The first question a man with recently diagnosed prostate cancer is advised to ask his urologist is ‘What type of cancer do I have?’ (www.cancer.org), while the first questions most patients have is ‘Will I survive?’ And ‘What are my chances of losing my sexual potency?’ (www.prostate-cancer.com). All these questions pertain to aspects of prostate cancer diagnosis. This thesis focuses on the value of multiparametric magnetic resonance (MR) imaging and MR guided biopsy in prostate cancer diagnosis and its corresponding risk stratification.

On a global level, prostate cancer is, after skin cancer, the most frequently diagnosed cancer of men and the fifth most common overall cancer. Nearly seventy-five percent of the global prostate cancer incidence is registered in developed countries due to the use of prostate specific antigen (PSA) (1). Based on data from the United States 1 out of every 6 men will be diagnosed with prostate cancer during his lifetime, while 1 out of every 35 men will eventually die from it (2). These numbers imply a high disease burden for society due to high prostate cancer prevalence. Also worldwide, prostate cancer prevalence highly exceeds mortality rates as depicted in Figure 1.

When considering prostate cancer diagnosis, there are two important questions to ask. Firstly “how accurate can prostate cancer be detected using current diagnostic tools?” and, secondly “is this prostate cancer diagnosis relevant for this particular patient?”.

Prostate cancer is diagnosed based on a combination of PSA blood serum concentrations, digital rectal examination and random systematic transrectal ultrasound (TRUS) biopsies. Prostate cancer detection using these tools is subject to false-positive as well as false-negative results. False positive results are mainly caused by the PSA test. The blood-PSA level is often false-positively elevated due to benign conditions, such as i.a. prostatitis or benign prostatic hyperplasia, its specificity is therefore only 36% (3). However, false-negative PSA results also occur, even in the lower PSA ranges (2.0-3.9 ng/mL), where prostate cancer detection rates are 21%, with 24% of cancers containing a Gleason score equal or higher than 7 (4). False-negative results are also caused by prostate cancer undersampling in random systematic TRUS biopsies. Around 25% of cancers are missed in the first TRUS biopsy session (5).

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**Figure 2.** Relation between prevalence of prostate cancer at autopsy, clinically diagnosed prostate cancer, and prostate cancer deaths as presented by Damber, Lancet 2008.
CHAPTER 1

When prostate cancer has been diagnosed in a patient, the next question to ask is whether this prostate cancer diagnosis is clinically relevant for this particular patient. A diagnosis of prostate cancer in a patient, who would have never developed clinical symptoms during his life-time is defined as overdiagnosis (6). The ‘life-time’ part of this definition is influenced by patient factors like age and co-morbidities. Overdiagnosis has negative psychological, socio-economical and physical (overtreatment) effects (7).

Another clinical term for overdiagnosed low-risk cancer is clinically insignificant cancer. A cancer diagnosed during autopsy, which did not cause symptoms during a patient’s life, is called indolent cancer. Figure 2 shows the iceberg of indolent cancer in relation to the amount of currently clinically diagnosed prostate cancer. This figure illustrates the high prevalence of indolent prostate cancer in men. A consequence of the widespread use of PSA testing, is the unwanted diagnosis of parts of this “indolent cancer iceberg” (8).

Active surveillance of low-risk prostate cancer

In order to prevent harmful side-effects due to “whole gland” treatment of clinically insignificant cancers, studies that investigate whether radical treatment can be delayed without a simultaneous decrease of curability, were performed (9,10). These studies showed that risks to the patient by delaying surgical intervention (up to a median of 26.5 months) were minimal. In a recent study from 2012, 731 men with clinically stage T1-T2NxM0 cancer were randomly assigned to radical prostatectomy or to observation (11). It was found that radical prostatectomy did not significantly reduce all-cause or cancer-specific mortality during a median follow-up of 10 years. These results suggest that well-differentiated early-stage tumours do not progress rapidly and that patient outcome is unchanged by deferring radical treatment.

These findings have led to the increasing popularity of active surveillance of low-risk prostate cancer as an alternative treatment to “whole gland” treatments like radical surgery and radiotherapy. Patients are selected upon clinical and histopathological criteria for low-risk prostate cancer which may vary across studies. In general, a prostate specific antigen ≤10 ng/mL with a density <0.20 ng/mL/mL, a clinical stage ≤T1c or T2, a maximum of 2 cancer-positive TRUS biopsy cores with a Gleason score ≤3+3 to in some studies 3+4 (12,13). Subsequently, surveillance is performed.
Introduction

by repeated PSA measurements, digital rectal examinations and repeated random systematic TRUS or transperineal saturation biopsies (14,15).

During median follow-up ranging from 24 months to 6.8 years, 20-30% of active surveillance patients develop progressive disease which needs radical treatment (15-17). Recent results indicate that most “progression” in active surveillance occurs within 1-2 years after diagnosis as a result of prostate cancer undersampling with subsequent understaging or “understaging” by initial TRUS biopsy rather than the actual progression of clinically insignificant cancer (18). Suboptimal active surveillance patient selection due to inaccurate initial prostate cancer risk-stratification is also expressed in high biochemical recurrence rates after delayed treatment in active surveillance (50.4%) (15).

Multiparametric MR imaging of the prostate

During the last three decades, prostate MR imaging techniques have improved significantly. In the eighties, prostate anatomy was visualized using 0.5-1.5 tesla MR imaging, which was a promising technique thanks to its high spatial resolution and soft tissue contrast (19). Current state-of-the-art prostate MR imaging examination includes a multiparametric approach, in which combinations of anatomical T2-weighted MR imaging and functional MR imaging techniques, like diffusion weighted MR imaging, dynamic contrast-enhanced MR imaging and proton MR spectroscopy, are used. Using multiparametric MR imaging, a higher accuracy for detection, localization and staging of prostate cancer is achieved compared to T2-weighted anatomic imaging alone. These functional MR imaging techniques allow for visualization of cellular and/or molecular changes, and thus identify tissue characteristics, which can be used to determine prostate cancer aggressiveness. With diffusion-weighted MR imaging tissue cellular density is indirectly shown using the restricted motion range of hydrogen protons due to increased cellular density in prostate cancer (20). In dynamic contrast-enhanced MR imaging, prostate cancer neo-angiogenesis is evaluated by observing the behaviour of intravascular administered contrast (21). Finally, proton MR spectroscopy allows for evaluation of changes in metabolite concentrations due to prostate cancer (22).
MR guided prostate biopsies

Multiparametric MR imaging prostate cancer localization accuracies range from 70-90% (23-25). MR guided biopsy uses accurate multiparametric MR imaging prostate cancer localization to direct the biopsy needle towards (the most aggressive part of) the prostate cancer. MR guided biopsy has resulted in prostate cancer detection rates ranging from 38-59% using far less cores (median 4) compared to random systematic TRUS biopsies (8-12 cores) (26-30).

Multiparametric MR imaging and MR guided biopsy as diagnostic tests for prostate cancer and prostate cancer risk-stratification

Assessment of multiparametric MR imaging and MR guided biopsy as diagnostic tests for prostate cancer diagnosis and risk-stratification is performed by their evaluation on six levels of evidence in a hierarchical model of Fryback and Thornbury, as is depicted in Table 1 (31,32).


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<th>Parameters under investigation</th>
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<td>6. Societal impact</td>
<td>Benefit–cost and cost-effectiveness analysis from a social perspective</td>
</tr>
<tr>
<td>5. Patient outcomes</td>
<td>Fraction of patients improved with the test compared with that of those improved without the test; difference in morbidity between the patients with the test and those without the test; gain in quality-adjusted life years (QALYs) obtained by the patients with the test compared with those without the test</td>
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<tr>
<td>4. Therapeutic impact</td>
<td>Fraction of patients for whom the test is judged useful for treatment planning or for whom the treatment planning is modified on the basis of the information supplied by the test</td>
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<tr>
<td>3. Diagnostic impact</td>
<td>Fraction of patients for whom the test is judged useful for rendering the diagnosis or for whom the diagnosis is substantially modified after the test; positive and negative likelihood ratios</td>
</tr>
<tr>
<td>2. Diagnostic performance</td>
<td>Sensitivity, specificity, accuracy, positive predictive value, negative predictive value and receiver operator characteristic (ROC) analysis; intraobserver, interobserver and interstudy reproducibility</td>
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<td>1. Technical performance</td>
<td>Grey-scale range; modulation transfer function; sharpness; spatial resolution, in-plane (line pairs per mm, pixel size) and through-the-plane (slice thickness), integrated in voxel size; signal-to-noise ratio; contrast resolution (contrast-to-noise ratio); time resolution (images/s) etc.</td>
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Most scientific evidence on MR imaging and MR guided biopsy in prostate cancer diagnosis and risk-stratification has been acquired on levels 2-4. In the prostate peripheral zone, multiparametric MR imaging, including T2-weighted MR imaging, diffusion-weighted MR imaging and dynamic contrast-enhanced MR imaging improved sensitivity for prostate cancer detection to 79-81% versus 63% for T2-weighted MR imaging (level 2) (25). In the transition zone, multiparametric MR imaging improved prostate cancer detection accuracy from 64% to 79% (level 2) (33). As mentioned, targeting cancer suspicious regions on multiparametric MR imaging with MR guided prostate biopsy results in prostate cancer detection rates varying from 38-59% (level 1-2) (26-30).

Once prostate cancer is diagnosed, patient risk re-stratification can be performed according to the d’Amico risk stratification criteria (PSA level, Gleason score and clinical stage) (34). Prostate cancer staging using T2-weighted MR imaging with and without endorectal coil had accuracies of 72%-94% and 83-85% to predict extracapsular extension at 3T (level 2) (35-38). For seminal vesicle invasion accuracies were 94% and 98% respectively (level 2) (35-38). One study reported a change in surgery in 44% of patients scheduled for radical prostatectomy by pre-surgery endorectal multiparametric MR imaging (39). The MR imaging findings led to preservation of the neurovascular bundle in 67% of patients with a high clinical probability of extracapsular extension, and prevented neurovascular bundle preservation in 33% of patients with a low clinical probability of extracapsular extension (level 4). Another parameter in risk stratification of prostate cancer patients is determination of the prostate cancer Gleason score. With random transrectal ultrasound biopsy techniques, the most aggressive part of the prostate cancer is not being targeted, and this can lead to under-assessment of the aggressiveness and risk category of a particular tumour. A recent study presented upgrading from a Gleason score 6 in the initial TRUS biopsy specimen to a Gleason score ≥7 in the radical prostatectomy specimen in 201 out of 298 patients (67.4%) (40). Diagnostic accuracy for MR imaging techniques to determine prostate cancer Gleason score has mainly been evaluated in the prostate peripheral zone. Diagnostic accuracies for apparent diffusion coefficient values of diffusion weighted MR imaging, expressed as areas under the receiver operating characteristic curve (AUC), ranged from 0.78-0.80 to differentiate prostate cancers with Gleason grades ≤3 from cancers with Gleason grades ≥4 in the prostate peripheral zone (level 2) (41-43). MR spectroscopy choline-to creatine
ratios had an AUC of 0.67 and 0.90 for a similar differentiation in the prostate peripheral and transition zone respectively (level 2) (43).

Finally, tumour volume is a prognostic parameter for prostate cancer risk stratification (44,45). Although correlation coefficients of MR imaging tumour volume to histopathology tumour volume vary from 0.60-0.94, under- or over-estimation of tumour volume by MR imaging is present in 23% and 47% (level 2) (46-48). Inaccuracy of MR imaging tumour volume estimations are mainly caused by inaccurate tumour delineation due to false-positive MR imaging conditions like prostatitis or benign prostatic hyperplasia and due to irregular tumour shape (49). Furthermore, decreased detection of lower tumour Gleason grade components may result in underestimation of tumour volume on MR imaging (50).

In conclusion, most of the current evidence on MR imaging and MR guided biopsy in prostate cancer diagnosis and risk-stratification was acquired on levels 2-4. The studies, which are presented in this thesis were also performed on levels 2-4.

Aims of this thesis

Current prostate cancer epidemiology comprises a high prevalence of clinically insignificant prostate cancers, which behave as a chronic disease rather than as a lethal cancer. It is a recognized fact that most patients will rather die with than of their prostate cancer.

The high prevalence of low-risk prostate cancer requires accurate diagnostic tools, which involve accurate patient risk-stratification as part of a prostate cancer diagnosis. Random systematic TRUS biopsies undersample (the most aggressive part of a) prostate cancer and may therefore fall short in prostate cancer diagnosis and/or may result in an incorrect patient risk stratification, once prostate cancer is diagnosed.

This thesis aims to evaluate multiparametric MR imaging and MR guided biopsy for prostate cancer diagnosis and risk-stratification.
Outline of this thesis

In chapter 2 a State-of-the-Art review on multiparametric MR imaging for detection, localization, characterization, staging, biopsy guidance and active surveillance of prostate cancer is presented. Technical requirements and clinical indications are discussed.

Results of a multireader study on the added value of multiparametric MR imaging to T2-weighted MR imaging for the detection and localization of transition zone prostate cancers are described in chapter 3.

In chapter 4, diffusion-weighted MR imaging apparent diffusion coefficient values of the prostate transition zone are related to histopathology outcomes using MR guided biopsy specimens as a reference standard.

Chapter 5 describes MR guided biopsy prostate cancer detection rates in a large prospective population of patients with an elevated PSA and one or more previous negative TRUS biopsy session(s).

Chapter 6 compares radical prostatectomy specimen Gleason grade concordance of the highest Gleason grade in MR guided biopsies versus the highest Gleason grade in random systematic 10 core TRUS biopsies.

Advantages of MR guided biopsy as discussed in chapters 5 and 6 are clinically applied in chapter 7. This chapter describes the value of three-tesla multiparametric MR imaging and MR guided biopsy in early risk-re-stratification of prostate cancer patients on active surveillance.

Using the design of the latter study, a quantitative parametric analysis was performed to evaluate median apparent diffusion coefficient values of diffusion weighted MR imaging for differentiation of prostate cancer in patients on active surveillance in chapter 8.

In chapter 9 the main findings of this thesis are discussed. Clinical implications and recommendations for future research are provided.
References

CHAPTER 1


Caroline M. A. Hoeks, MD
Jelle O. Barentsz, MD PhD
Thomas Hambrock, MD
Derya Yakar, MD PhD
Diederik M. Somford, MD
Stijn W. T. P. J. Heijmink, MD
Tom W. J. Scheenen, PhD
Pieter C. Vos, MSc PhD
Henkjan Huisman, MSEE PhD
Inge M. van Oort, MD PhD
J. Alfred Witjes, MD PhD
Arend Heerschap, PhD
Jurgen J. Fütterer, MD PhD

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Abstract

This review presents the current state of the art regarding multiparametric magnetic resonance (MR) imaging of prostate cancer. Technical requirements and clinical indications for the use of multiparametric MR imaging in detection, localization, characterization, staging, biopsy guidance, and active surveillance of prostate cancer are discussed. Although reported accuracies of the separate and combined multiparametric MR imaging techniques vary for diverse clinical prostate cancer indications, multiparametric MR imaging of the prostate has shown promising results and may be of additional value in prostate cancer localization and local staging. Consensus on which technical approaches (field strengths, sequences, use of an endorectal coil) and combination of multiparametric MR imaging techniques should be used for specific clinical indications remains a challenge. Because guidelines are currently lacking, suggestions for a general minimal protocol for multiparametric MR imaging of the prostate based on the literature and the authors’ experience are presented. Computer programs that allow evaluation of the various components of a multiparametric MR imaging examination in one view should be developed. In this way, an integrated interpretation of anatomic and functional MR imaging techniques in a multiparametric MR imaging examination is possible. Education and experience of specialist radiologists are essential for correct interpretation of multiparametric prostate MR imaging findings. Supportive techniques, such as computer-aided diagnosis are needed to obtain a fast, cost-effective, easy, and more reproducible prostate cancer diagnosis out of more and more complex multiparametric MR imaging data.
Introduction

The most recent estimation by the International Agency for Research on Cancer revealed 679,000 new cases of and 221,000 deaths related to prostate cancer on a global level in 2002 (1). With an estimated 5-year prevalence of 2.3 million patients in the world, prostate cancer is a major global health problem.

Prostate cancer diagnostics are initiated on the basis of prostate-specific antigen (PSA) measurements and determination of clinical stage by means of digital rectal examination. Definite diagnosis is usually obtained by means of transrectal ultrasonography (US)-guided systematic random prostate biopsies. Histopathologic analysis of these biopsy samples provides the clinician with information on the Gleason score. This is a histopathologic score that correlates with prostate cancer prognosis (2,3).

Nomograms (4) based on the combination of PSA level, digital rectal examination findings, and systematic random biopsy–based Gleason score are used to determine the choice of therapy and prognosis. However, each of these tests has its shortcomings: Digital rectal examination has a low overall sensitivity (37%) and low positive predictive value when lower PSA ranges of 0–3 ng/mL are encountered (5). PSA measurement has yielded higher detection rates than has digital rectal examination (6), but its specificity is low (36%) owing to false-positive PSA elevation under benign circumstances, such as inflammation or benign prostatic hyperplasia (BPH) (7). When digital rectal examination results are positive or when the PSA level is elevated, systematic random sextant biopsy with acquisition of a minimum of four extra cores from lateral peripheral zones or from a region that is suspicious for cancer is generally recommended to be performed initially (8). Systematic random biopsy is prone to undersampling (35% cancers missed on first biopsy (9)) and underestimation Gleason grade in 46% of cases (10). These inaccurate tools often lead to incorrect diagnoses, inaccurate risk assessments, and less optimal therapy choices. Because these diagnostic methods all have their limitations, there is a need for improved prostate cancer diagnosis with improved detection, localization, and sampling.

In the mid 1980s, the first prostate magnetic resonance (MR) imaging examinations were performed. Since then, MR imaging has evolved from a promising technique into a mature prostate imaging modality (11,12). MR imaging can provide functional tissue information along with anatomic information. To increase the accuracy, anatomic T2-weighted MR imaging and functional MR imaging techniques such as
dynamic contrast agent–enhanced MR imaging, diffusion-weighted (DW) imaging, and hydrogen 1 MR spectroscopic imaging should be combined in an integrated multiparametric MR imaging examination. These multiparametric MR techniques will contribute to prostate cancer diagnostics, although results for detection, localization, and local staging of prostate cancer vary greatly among the studies performed.

This article will describe the fundamentals of multiparametric MR imaging of prostate cancer. We will provide an overview of the individual MR imaging techniques with their combined merits and limitations for clinical challenges such as detection, localization, local staging, and active surveillance of prostate cancer.

**MR imaging techniques**

**Anatomic T2-weighted MR Imaging**

T2-weighted MR imaging is the workhorse of prostate MR imaging. T2-weighted MR images have high spatial resolution and, thus, can clearly differentiate the normal intermediate- to high-signal-intensity peripheral zone from the low-signal-intensity central and transition zones in young male subjects (13). In the aging man, owing to variable extension of the transition zone due to BPH, the size and signal intensity of the prostate transition zone may vary. BPH itself is a round, well-defined, inhomogeneous area with (variable) intermediate signal intensity and a low signal-intensity rim that surrounds the expanded transition zone (12). Because of transition zone expansion, the remainder of the compressed central zone is often indefinable on MR images.

High-spatial-resolution T2-weighted rapid acquisition with refocused echo sequences with a small field of view, performed with endorectal and/or external body phased-array coils, are generally used to depict prostate anatomy. T1-weighted contrast in the prostate is very low. Therefore, it is not possible to appreciate the different anatomic zones on T1-weighted images. On T2-weighted images, prostate cancer can appear as an area of low signal intensity within the high signal intensity of a normal peripheral zone. An example of this finding is shown in Figure 1a. The degree of signal intensity decrease may differ with the Gleason score: Higher Gleason score components 4 or 5 have shown lower signal intensities than do lower Gleason score components 2 and 3 (14). The density and the growth pattern of the cancer may also influence T2-weighted signal intensity.
Cancers in the peripheral zone, which grow thinly scattered into the surrounding normal tissue, have shown no significant difference in quantitative T2 values with normal peripheral zone. On the other hand, densely growing cancers do show lower quantitative T2 values (15).

A limitation of T2-weighted imaging is that focal areas of low signal intensity in the peripheral zone do not always represent cancer. Benign abnormalities such as chronic prostatitis, atrophy, scars, postirradiation or hormonal treatment effects, hyperplasia, and postbiopsy hemorrhage may mimic tumor tissue (16). Low-signal-intensity lesions with a wedge shape and a diffuse extension without mass may be reliable signs of benignity (17). Hemorrhage may be differentiated on the basis of its high signal intensity on T1-weighted images. When methemoglobin is present in hemorrhagic regions, its paramagnetic characteristics result in high signal intensity on T1-weighted MR images. Preferably, MR imaging of patients suspected of having prostate cancer should be avoided for 8 weeks after prostate biopsy to allow reduction of artifacts due to postbiopsy hemorrhage (18).

Figure 1. Axial T2-weighted turbo spin-echo MR images (repetition time msec/echo time msec, 4260/99; flip angle 120°) of prostate cancer. (a) At level of midprostate to apex, a low-signal-intensity lesion is present on the right side of the prostate, within the high signal intensity of the peripheral zone (outline), with signs of minimal capsular invasion (arrow). At prostatectomy, this lesion, which was suspicious for prostate cancer, corresponded to stage T3a (extracapsular extension of 5 mm), Gleason score 7 (4+3) prostate cancer. (b) At midprostate level, a homogeneous low signal intensity area in the ventral transition zone is seen (outline), with loss of visibility of healthy BPH structures (“charcoal sign”), Invasion of anterior fibromuscular stroma at the ventral prostate can be seen (arrows). This lesion was suspicious for transition zone cancer. At prostatectomy, stage T2c, Gleason score 6 (2+4) prostate cancer was found.

Owing to the presence of BPH, cancer in central and transition zones is more difficult to discern. BPH may have signal intensity similar to that of prostate cancer.
on T2-weighted images. However, it has been reported that features such as homogeneously low T2-weighted signal intensity (Fig 1b), ill-defined irregular edges of the suspicious lesion, invasion into the urethra or the anterior fibromuscular stroma (Fig 1b), and lenticular shape are helpful signs for detection of malignancy in the transition zone (19).

Combined T1-weighted and T2-weighted MR imaging should be used for all clinical prostate cancer indications to evaluate anatomy and possible postbiopsy hematoma artifacts.

**Dynamic Contrast-enhanced MR Imaging**

Angiogenesis in prostate cancer tissue is induced by secretion of vascular growth factors in reaction to the presence of local hypoxia or lack of nutrients (20). Resultant changes in vascular characteristics can be studied well with dynamic contrast-enhanced MR imaging (Fig 2). This technique exploits the dynamic uptake and rapid washout of a gadolinium chelate contrast agent to show the typical pharmacokinetics of cancerous tissue. Because the prostate as a whole is highly vascularized, a simple comparison of pre- and postgadolinium images is usually insufficient to discern prostate cancer (21,22).

A fast and direct method to characterize prostatic vascular pharmacokinetic features is high-temporal-resolution dynamic contrast-enhanced MR imaging. Dynamic contrast-enhanced MR imaging consists of a series of fast T1-weighted sequences covering the entire prostate before and after rapid injection (2–4 mL/sec) of a bolus of a low-molecular-weight gadolinium chelate such as gadoterate meglumine or gadopentetate dimeglumine (concentration, 0.1–0.2 mmol/kg) (23,24). In addition to the most frequently used fast sequences, which have a high temporal resolution (a short period of 1–4 seconds between measurements), slow sequences (temporal resolution, 30 seconds with higher spatial resolution) have also been used. Depending on the area of anatomic coverage, the acquisition times, potential susceptibility artifacts, and desired T1 sensitivity, a choice for a faster or slower sequence must be made (25). On one hand, fast sequences may improve tissue characterization because the prostate enhances quickly with T1-weighted dynamic contrast-enhanced MR sequences. With fast sequences, accurate quantification of different pharmacokinetic enhancement parameters is possible. On the other hand, fast T1-weighted sequences have trade-offs, including reduced spatial resolution and/or anatomic coverage. Optimal spatial and temporal resolutions based on clinical indications remain subjects of future research.
Figure 2. Dynamic contrast-enhanced MR imaging of prostate cancer in 65-year-old man with PSA level of 8.3 ng/mL, clinical stage T2c cancer, and Gleason score of 7 (3+4) in 80% of the volume of systematic random biopsy specimens. (This patient is also in Fig 7). (a, b) Axial dynamic contrast-enhanced T2-weighted MR images (38/1.35; flip angle, 14°) obtained at midprostate level, with superimposed $K_{trans}$ (volume transfer constant) parametric map on a and washout parametric map on b.

(a) Right peripheral zone (outline) shows contrast enhancement (red) that is suspicious for prostate cancer.

(b) In addition to the transition zone (arrow), right peripheral zone (outline) shows increased washout.

(c) Relative gadolinium concentration (y-axis)-time (x-axis) curve of tumor shows a type 3 curve with fast increase, fast time to peak, and washout, which are suspicious for cancer.
Prior to post-processing of dynamic contrast-enhanced MR imaging data, estimation of the arterial input function can be performed. In the Tofts model, the arterial input function can be calculated with a formula that uses values of plasma concentration after administration of a bolus in healthy subjects (26). In addition to the Tofts model, automatic derivation of the arterial input function from reference tissues can be performed (27). The latter method has the advantages that it needs only T1-weighted MR images and that the arterial input function is estimated accurately in a large reference tissue volume.

Assessment of signal intensity changes on T1-weighted dynamic contrast-enhanced MR images in order to estimate contrast agent uptake in vivo can be performed qualitatively, semi-quantitatively or quantitatively. Qualitative analysis of signal intensity changes can be achieved by assessing the shape of the signal intensity–time curve. Quantification of signal intensity changes, which are generally represented by gadolinium concentration–time curves, requires semi-quantitative assessment of contrast agent concentration or calculation of different quantitative physiologic parameters by using pharmacokinetic compartmental modelling. Washout is a semi-quantitative parameter that captures the curve pattern after the first peak of enhancement. Other semi-quantitative parameters are (a) integral area under the gadolinium-concentration–time curves, (b) wash-in gradient (upward slope of first pass), maximum signal intensity, (c) time-to-peak enhancement, and (d) start of enhancement. Semi-quantitative parameters have the advantages of being fast, relatively simple to calculate, and of being available on current MR systems. They may, however, be influenced by MR unit settings (22).

In quantitative pharmacokinetic analysis, the behavior of a volume of contrast agent in the intravascular space versus that in the extravascular extracellular space is estimated in volume units for a certain period of time. The return of the contrast agent to the extracellular extravascular space can be limited by flow, by permeability of the endothelium, or by a combination of flow and endothelium permeability. The flow-limited Kety model (28), the permeability-limited Tofts model (29) and mixed models (30,31) are applicable under these respective circumstances. Tofts et al (32) suggested the following standard pharmacokinetic quantitative parameters: $V_e$ which represents the volume fraction of extravascular extracellular leakage space and $k_{ep}$ which represents the exchange rate constant of contrast agent between the extracellular extravascular leakage space and the blood plasma (in units per minute). $V_e$ and $k_{ep}$ are related with the following equation in the Tofts
model: $k_{ep} = \frac{K_{trans}}{V_e}$. When flow is limited, the volume transfer constant $K_{trans}$ equals the blood plasma flow per unit volume of tissue. Under permeability-limited conditions, $K_{trans}$ equals the permeability surface area product per unit volume of tissue, which is the case in prostate cancer. Prostate cancer tends to enhance earlier, faster, and to a greater extent and shows earlier contrast agent washout, as compared with healthy prostate tissue (23,33). This characteristic makes dynamic contrast-enhanced MR imaging a sensitive technique for prostate cancer localization. Estimated quantitative parameters can be presented to the radiologist as color-overlay maps on anatomic T2-weighted MR images to relate dynamic contrast-enhanced MR images to prostate anatomy. Prostate cancer diagnostics for clinical indications such as local staging can then be improved by better prostate cancer localization characteristics obtained with dynamic contrast-enhanced MR imaging. This advantage will be addressed in the Clinical Questions section.

One of the limitations of dynamic contrast-enhanced MR imaging is related to discrimination of cancer from prostatitis in the peripheral zone and from highly vascularized BPH nodules in the transition zone (34). Other shortcomings are a limited use of standardized approaches for calibration and analysis, the shortage of uniform commercially available tools for pharmacokinetic analysis, and the lack of consensus in acquisition protocols.

Correlation of dynamic contrast-enhanced MR images with prognostic histopathologic markers of prostate cancer angiogenesis has rarely been performed. This remains an important area for future research (35).

Dynamic contrast-enhanced MR imaging is an accurate functional MR imaging technique that can be used for all clinical indications discussed in this article. In a multiparametric MR imaging examination, the high sensitivity of dynamic contrast-enhanced MR may be used for initial evaluation of potential tumor locations. Other functional MR imaging techniques may subsequently be added to increase specificity for prostate cancer localization, because sensitivity of dynamic contrast-enhanced MR imaging is low. Little standardization exists in acquisition protocols and analytic models for dynamic contrast-enhanced MR imaging.

**DW Imaging**

In DW imaging, proton diffusion properties in water are used to produce image contrast. Images that reflect proton diffusion are acquired by applying motion encoding gradients, which cause phase shifts in moving protons, depending on the direction and quantity of their movement (36). The attenuation of the MR signal
in DW imaging is expressed with the Stejskal-Tanner equation (36). The $b$ value and the apparent diffusion coefficient (ADC) are components in this equation. While the $b$ value expresses the amount of diffusion weighting, ADC reflects the movement of the water molecules within the interpulse-time. Because ADC quantifies the flow as well as the distance a water molecule has moved, it represents both capillary perfusion and diffusion characteristics (37). Fitting the Stejskal-Tanner equation for every pixel on two or more DW images acquired with different $b$ values results in an ADC map. For prostate cancer, DW imaging $b$ values between 500 and 800 sec/mm$^2$ are typically used (38). $b$ Values of 1000 and even 2000 sec/mm$^2$ may increase the accuracy of prostate cancer detection (39). Especially within the transition zone, high $b$ values may help improve differentiation of BPH from prostate cancer (40).

Healthy prostate tissue in the peripheral zone, which is rich in tubular structures, allows extensive diffusion of water molecules within the gland tubules. Consequently, ADCs in healthy peripheral zone tissues can be high. Prostate cancer tissue destroys the normal glandular structure of the prostate and replaces ducts. It also has a higher cellular density than does healthy prostate peripheral zone tissue (38). On ADC maps, therefore, prostate cancer often shows lower ADCs in comparison to surrounding healthy peripheral zone prostate tissue (41). Examples of this are presented in Figure 3. Recently, 3 T DW imaging ADCs were shown to correlate significantly with the cellular density of prostate cancer in radical prostatectomy specimens (42).

Because the acquired ADC depend on the specific pulse sequence parameters (especially the $b$ values), the specific MR systems used, and the magnetic field strength, the ADCs of healthy and cancerous tissue have varied among reported studies. Furthermore, there is an overlap in the ADCs of healthy tissue and those of prostate cancer, within and between subjects, which limits the determination of a single threshold ADC for malignancy (4).

Mean ADCs for prostate cancer versus those for healthy prostate tissue obtained at different field strengths, with or without the use of an endorectal coil in different anatomic regions are shown in Table 1. Owing to variation in ADCs of benign prostate tissue in the peripheral and transition zones, the area under the receiver operating characteristic curve (AUC) for differentiation of prostate cancer from benign tissue can vary by anatomic location within the prostate gland and are found to be lower in the prostatic base (AUC of 0.725 in prostate base vs 0.952 and 0.906 for overall peripheral and transition zones, respectively) (44). The reported differences in detection accuracies with DW imaging might be explained by the different tissue composition in different anatomic zones of the prostate. It has been
hypothesized that a higher degree of proton motion in the extracellular water compartment occurs as opposed to that in intracellular water, where movement is restricted by cell membranes or other intracellular structures (38). As a result of variation in glandular tissue within a healthy peripheral zone to muscular or fibrous tissue within the transition zone, the ratio of intracellular versus extracellular water also differs. This variation might also explain the variability of ADCs in healthy prostate tissue that have been reported. Relative ADC thresholds calibrated to an individual gray-scale value may be a way to overcome intra- and inter-individual variation and overlap of ADCs of cancer and healthy prostate tissue (45).

DW imaging is a fast, simple, and readily available MR imaging technique for prostate cancer. Nevertheless, DW imaging of the prostate has the limitation of low in-plane spatial resolution, even at 3 T. Consequently, DW imaging is not a preferred technique for prostate cancer staging. However, DW imaging does reflect cellular density, which makes the technique potentially suitable to determine tumor aggressiveness. DW imaging, being a technique for measuring proton motion, is very sensitive to motion artifacts. Single-shot echo-planar MR imaging is used to decrease motion artifacts by acquiring images in less than 1 second. Because the phase-encoding bandwidth per pixel is very small, echo-planar imaging is very sensitive to magnetic field inhomogeneities. As a result, artifacts occur in areas with large variations in magnetic susceptibility, such as in tissue-air interfaces (air in the rectum or endorectal coil) or in chemical shift in areas with water-fat interfaces. Parallel imaging and short-imaging-time protocols are used to overcome these off-resonance artifacts (46).

Correlation of DW imaging results and histopathologic findings as well as to prognostic histologic prostate cancer markers such hypoxia-inducible factors, should be another area for future research. Of all functional MR imaging techniques DW imaging is the most practical and simple in its use. Within a multiparametric MR imaging examination DW imaging may be used for all clinical indications discussed in this article. DW imaging has the disadvantages of being susceptible to motion and to magnetic field inhomogeneities.

**Proton MR Spectroscopic Imaging**

In MR spectroscopic imaging, spectral profiles are measured in two or three spatial dimensions. These spectral profiles reflect resonance frequencies that are unique for protons in different metabolites present at the sampled location. The specific resonance frequencies or chemical shifts are given relative to a reference frequency
in parts per million (ppm). In human prostate examinations, MR spectroscopic imaging is usually performed in a volume that covers the whole prostate, which is subdivided up into a three-dimensional grid of multiple voxels. With the introduction of the endorectal coil for prostate MR examinations, it became possible to obtain in vivo MR spectroscopic imaging spectra of small voxels in the prostate (less than 1 cm$^3$) with sufficient signal to noise (47–49). The dominant peaks observed in these spectra are from protons in citrate (approximately 2.60 ppm), creatine (3.04 ppm) and choline compounds (approximately 3.20 ppm).

**Figure 3.** DW imaging of prostate cancer. Axial ADC maps (2400/81; $b = 0, 50, 500$ and 800 sec/mm$^2$) obtained at midprostate level in same patients as in Figure 1a (a) and 1b (b).

(a) Lesion with low DC (mean ADC = 0.8×10$^{-3}$ mm$^2$/sec), is suspicious for cancer in right peripheral zone (arrows). This indicates intermediate to high cancer aggressiveness. At prostatectomy, the lesion was determined to be stage T3a, Gleason score 7 (4+3) prostate cancer.

(b) Comma-shaped area with low ADC (mean ADC = 0.6×10$^{-3}$ mm$^2$/sec) is seen in ventral transition zone (arrows). This indicates intermediate to high cancer aggressiveness. At prostatectomy, lesion was determined to be stage T2c, Gleason score 6 (2+4) prostate cancer.

Polyamine signals (mostly from spermine) also may be observed (approximately 3.15 ppm) at various relative intensities, depending on the acquisition conditions. Compared with healthy peripheral tissue or BPH tissue, citrate signals are reduced and those of choline compounds are often increased in prostate cancer tissue (Fig 4) (50). Citrate is produced in epithelial cells as an intermediate product in the Krebs cycle due to aconitase inhibition. It then accumulates in the luminal space of the prostate. The lower citrate peak in cancer tissue may thus be caused by altered metabolism, as well as by a reduction of luminal space, which commonly occur in prostate cancer. Choline compounds are involved in the biosynthesis and
degradation of phospholipids, which are required for the build-up and maintenance of cell membranes. An increased cell-turnover in prostate cancer results in an increased concentration of free choline-containing molecules within the cytosol and the prostate interstitial tissue.

Table 1. Mean ADCs for Prostate Zones at Different Field Strengths with or without an Endorectal Coil

<table>
<thead>
<tr>
<th>Magnetic Field Strength (T)</th>
<th>Peripheral zone ADC</th>
<th>Transition zone ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy Tissue (x 10^{-3} mm^2/sec)</td>
<td>Prostate cancer (x 10^{-3} mm^2/sec)</td>
</tr>
<tr>
<td>1.5 without ERC</td>
<td>1.72-1.85 (19,133,135)</td>
<td>0.96-1.02</td>
</tr>
<tr>
<td>1.5 with ERC</td>
<td>1.51-1.69 (136,137)</td>
<td>1.39 (136)</td>
</tr>
<tr>
<td>3.0</td>
<td>1.86-2.61 (39,138,139)</td>
<td>1.19-1.138 (39,138,139)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are reference numbers. ERC = endorectal coil.

Because differentiation of choline peaks from creatine peaks on spectra obtained at common clinical field strengths is often hampered by their bandwidths and by weaker signals from polyamines between them, the choline plus creatine–to-citrate ratio is mostly used as a metabolic biomarker for prostate cancer. An example of this is presented in Figure 4. In the analysis of patient data, it should be taken into account that different anatomic zones of the healthy prostate have different amplitudes for citrate, creatine, and choline, which are reflected in different choline plus creatine–to-citrate ratios. High citrate concentrations are found in the glandular tissues of the prostate such as the peripheral zone, which contains epithelial cells and secretory ducts. Therefore, citrate concentrations are highest in the peripheral zone and lower in the central zone. In the transition zone, the citrate concentration may be higher in case of glandular proliferation and lower in the case of stromal proliferation (51). Furthermore, because of the sensitivity profile of the surface coil, the spectral signal intensity will drop the farther away the tissue is from the ERC. Since the prostate is relatively small and embedded in adipose tissue, much effort has been put into suppressing spectral contamination, not only of the high water signal, but also of strong lipid signals. Therefore, radiofrequency pulse schemes that selectively invert and dephase water and lipid signals have been developed (52,53). Frequency selective suppression methods, such as Mescher-Garwood (or MEGA)
pulses (52) or later band selective inversion with gradient dephasing (or BASING) are generally applicable because no high-performance gradients are necessary. Spectral-spatial pulses have the advantage of increased bandwidth, which results in decreased chemical shift–dependent localization errors. Three-dimensional MR spectroscopic imaging sequences are currently preferred over two-dimensional sequences because of the possibility of complete coverage of the entire prostate gland (47,54). Three-dimensional acquisitions can be performed in approximately 10–15 minutes with a resolution as low as 0.4 cm³ with sufficient signal-to-noise ratio at 1.5 T (54).

MR spectroscopic imaging has several limitations. Spectral quality depends on magnetic field homogeneity, which must be optimized for each patient by shimming. Considerable local magnetic field distortions may occur due to hemorrhage, which is why the examination should be performed with sufficient delay from the time of biopsy. The clinical performance of MR spectroscopic imaging of the prostate can be improved by optimizing field shimming or by means of correction procedures, in addition to better signal-to-noise ratio and chemical shift dispersion, by using stronger magnetic fields (55). Currently, the interpretation of MR spectroscopic imaging results requires special expertise and is time consuming. Automated measurement procedures, rapid display of examination results, and proper training of clinical users are important to transform MR spectroscopic imaging into a practical and widespread clinical tool. To this day, these requirements are generally not met.

MR spectroscopic imaging is an accurate technique that may be used for all clinical indications mentioned in this article. MR spectroscopic imaging needs, however, relatively more time and expertise than do other functional MR imaging techniques, which limits its clinical applicability.

Because the functional MR imaging techniques we have discussed all have their strengths and shortcomings, they are combined in a multiparametric MR imaging prostate examination to increase accuracy. A multiparametric MR imaging prostate examination consists of T1- and T2-weighted imaging combined with one or more functional MR imaging techniques.
Combined Multiparametric MR Imaging

Within the variety of possible MR imaging protocols and combinations of different techniques, consensus guidelines are needed to increase accuracy and unity in the field (56). Because formal practice guidelines for multiparametric prostate imaging are currently unavailable, the following suggestions for possible prostate multiparametric MR imaging protocols for different clinical indications can be recommended. Patients with a clinical indication of prostate cancer detection, who often have previously undergone one or more systematic random biopsies with negative results, may have a high a priori risk for transition zone cancer (57). In these patients, it is essential not only to use techniques such as T2-weighted and dynamic contrast-enhanced MR imaging, which may yield false-positive or false-negative results within the transition zone, but also DW imaging (with a high $b$ value), which may be a valuable technique in difficult detection cases. In patients referred for pre-treatment staging, it is important to use an endorectal coil in combination with anatomic T2-weighted MR imaging. Because accurate localization may improve accurate staging it may be important to add at least one multiparametric MR imaging technique (Fig 5). Patients with a clinical indication for active surveillance or focal therapy need evaluation of the stage of the cancer and its aggressiveness. Preferably, an endorectal coil could be used in combination with more than one multiparametric technique that yields findings related to prostate cancer Gleason score (DW imaging and/or MR spectroscopic imaging) (Fig 6).

The optimal strength of multiparametric MR imaging is achieved by combining the information obtained with the various techniques. Computer programs, which allow evaluation of two or more multiparametric images in one view, need to be developed for the integrated interpretation of anatomic and functional findings. An example of how this could be accomplished is presented in Figure 7. Development of supportive techniques like computer aided diagnosis (58–60) is needed to achieve fast and reproducible diagnostics from large quantities of complex data. Furthermore, the education, experience, and dedication of radiologists are essential for correct interpretation of findings from multiparametric MR imaging of the prostate (61). Minimal requirements for a multiparametric MR imaging protocol include a combination of T1- and T2-weighted MR imaging with DW and dynamic contrast-enhanced MR imaging. For detection and localization indications, the use of a phased-array coil is sufficient; for staging indications, combination with an endorectal coil may be preferred.
Figure 4. MR spectroscopic imaging in a 70-year-old man (same as in Fig 11) with a PSA level of 12 ng/mL and well-differentiated prostate cancer. (a) Axial T2-weighted turbo spin-echo MR image (4260/99; flip angle, 120°) shows stage T3a prostate cancer. Radical prostatectomy revealed a solitary Gleason score 7 (3+4) adenocarcinoma with extraprostatic extension. Red voxel has been placed in low-signal-intensity lesion in left peripheral zone, which is suspicious for cancer; blue voxel has been placed in benign-appearing region in right peripheral zone. (b) MR spectrum (750/145; flip angle, 90°) from red voxel shows choline peak that is increased relative to citrate peak. The choline plus creatine–to-citrate ratio, calculated from the integrals of the spectral peaks from choline, creatine, and citrate, is 0.80, which is suspicious for prostate cancer. (c) MR spectrum (750/145; flip angle, 90°) from blue voxel demonstrates low choline peak and high citrate peak, consistent with benign peripheral zone tissue. The choline plus creatine–to-citrate ratio is 0.32.
Figure 5. Multiparametric MR imaging for prostate cancer localization in the transition zone in a 67-year old man with a PSA level of 17.6 ng/mL and Gleason score 7 prostate cancer shows the added value of multiparametric MR imaging for localization. While T2-weighted images yielded indeterminate findings for localization, and dynamic contrast-enhanced images yielded false-positive findings in another area, DW images were used to correctly localize this high-grade prostate cancer. (a) Axial T2-weighted turbo spin-echo image (4260/99; flip angle, 120°) obtained at the level of the base of the prostate shows area of lower signal in the right ventral prostate (outline), which is suspicious for prostate cancer. Bulging is present as a sign of stage T3 disease (arrows). (b) Axial MR image with superimposed $K_{trans}$ parametric map (38/1.35; flip angle, 14°) at same level as a. Mediodorsal part of the prostate shows early enhancement (outline) but no increased $K_{trans}$ at low-signal-intensity area in a. (c) On axial ADC map (2400/81; $b = 0, 50, 500, 800$ sec/mm$^2$) obtained at same level as a, the right ventral transition zone (outline) shows restriction (mean ADC = 606×10$^{-6}$ mm$^2$/sec), which suggests highly aggressive cancer. (d) Axial whole-mount histopathologic slice from level corresponding to a–c shows stage T3b (Gleason score, 9 [4+5]) prostate cancer in right ventral prostate (outline).
Figure 6. Multiparametric MR imaging in a 69-year-old man undergoing active surveillance of Gleason score 6 (3+3) prostate cancer, found in 5% of the volume of one (left-sided) of nine systematic random biopsy core specimens. The patient had a PSA level of 6.7 ng/mL, PSA density of 0.9 ng/mL/mL, and clinical stage T2 disease. Multiparametric MR imaging findings obtained with an endorectal coil were suspect for stage T3a cancer in the left peripheral zone at the midprostate level. DW imaging findings indicated tumor intermediate to highly aggressive tumor at the same location. Subsequent MR-guided biopsy of this patient is depicted in Figure 8. (a) Axial T2-weighted turbo spin-echo MR image obtained with endorectal coil (4260/99; flip angle, 120°) at midprostate level shows small area of lower signal intensity in left peripheral zone (outline) with signs of extracapsular extension (arrows). (b) Axial MR image with superimposed $K^{\text{trans}}$ parametric map (38/1.35; flip angle, 14°; same level as a and b) at the same level as a. Early enhancement occurs in multiple areas. The region suspicious for tumor is also enhanced (outline). (c) ADC map (2400/81; $b = 800$ sec/mm$^2$) shows restriction at the suspicious region in the left peripheral zone (outlined), indicating intermediate to highly aggressive tumor. Analysis of MR-guided biopsy specimen from the suspicious lesion resulted in Gleason score of 8 (3+5) in 80% of the specimen volume, with extension into periprostatic fat (stage T3a).

Figure 7.
Figure 7. Multiparametric MR imaging of the prostate (same patient as in Fig 2: 65-year-old man, PSA level of 8.3 ng/mL, clinical stage T2c, Gleason score of 7 [3+4]) in screenshot generated by a computer-program, which can be used for image interpretation in multiparametric MR imaging. In addition to related views of multiplanar multiparametric images (A–E), quantitative information (F) is also displayed. A–E show tumor with bulging, suspicious for minimal stage T3A disease, in right peripheral zone at level of midprostate to apex (arrow). A, Axial $K_{\text{trans}}$ map from dynamic contrast-enhanced MR imaging projected over T2-weighted image (see Fig 2 for parameters). B, Sagittal T2-weighted image (4290/98; flip angle, 120°) with color overlay showing washout (from dynamic contrast-enhanced MR imaging). C, Axial ADC map (2900/81; flip angle, 90°). D, Axial DW trace image ($b = 800 \text{ sec/mm}^2$; 2900/81; flip angle, 90°). E, Axial T2-weighted image. F, Relative gadolinium concentration–time curve (left) and MR spectrum (right) from chosen point of interest in tumor (+). In MR spectrum, choline ($\text{chol}$) and citrate ($\text{cit}$) peaks can be evaluated. The low-signal-intensity lesion on E shows increased $K_{\text{trans}}$ (on A), restriction on C, high signal intensity on D, gadolinium concentration–time curve type 3 and high choline peak on F. On a five-point scale, this can be scored 5/5 on T2-w, dynamic contrast-enhanced, DW, and MR spectroscopic images, for total score of 20/20, indicating intermediate to highly aggressive tumor.

MR Imaging–guided Biopsy
As mentioned earlier, systematic random biopsy is prone to sampling error, which often results in inaccurate prostate cancer detection and Gleason score grading (10). MR-guided prostate biopsy can potentially improve prostate cancer detection, because multiparametric MR imaging–guided biopsy can be targeted toward previously determined regions that are suspicious for cancer. MR-guided biopsy is technically feasible and be performed on a routine basis (Fig 8). Owing to its limited availability and long examination time, this technique is typically used in patients with one or more previous negative systematic random biopsy sessions. Transrectal MR guided biopsy performed at 1.5 T has shown promising cancer detection rates of 38%–59% (57,62–64). These detection rates are promising in comparison to those of systematic random biopsy rates of 22%–29% (9,65) after one session and 10%–17% after two sessions (9,65).
Figure 8. (a, b) Sagittal and (c) axial gradient-echo MR images (4.48/2.24; flip angle, 70°) of MR-guided biopsy in a case of active surveillance of prostate cancer in a 69-year-old man (same patient as in Fig 6) with Gleason score 6 (3+3) disease. Multiparametric staging MR imaging (not shown) with an endorectal coil resulted in suspicion of stage T3A cancer in left peripheral zone at midprostate. DW imaging (not shown) findings indicated intermediate to highly aggressive tumor in left peripheral zone. (a) Needle guide (arrows) is positioned toward target in left peripheral zone at midprostate (outline). To accurately hit the target, the needle guide should be moved slightly caudal in sagittal plane; in position shown (red line), needle will miss the target. (b, c) Needle guide (arrows) is now accurately positioned and biopsy needle (line) has been inserted. MR guided biopsy of this suspicious lesion resulted in a Gleason score of 8 (3+5) for a volume percentage of 80% with extension into periprostatic fat (stage T3A). This patient was subsequently excluded from the active surveillance protocol.

Use of multiparametric MR imaging in MR-guided biopsy planning has been studied by Franiel et al (66) in a prospective study of 1.5-T MR imaging in 54 patients with a median of two previous negative random systematic transrectal US-guided biopsies. Their ground truth was based on MR-guided biopsy of suspicious
identifiable lesions from at least one multiparametric MR imaging technique only. They concluded that a combination of T2-weighted with DW MR imaging and either dynamic contrast-enhanced MR imaging or MR spectroscopic imaging reduced the number of areas that need to be subject to biopsy by 13%–15% while only missing 6% of cancers, in comparison to multiparametric MR imaging with all three techniques.

A limitation of MR-guided biopsy is that a multiparametric MR imaging and the MR-guided biopsy need to be performed in separate sessions because image post-processing and exact tumor localization demand time. Another disadvantage is movement of the prostate during the biopsy procedure (67). MR imaging findings have also been used to help direct biopsies under transrectal US guidance with reasonable to good detection rates of 25%–55% (68,69). Moreover, Gleason score concordance with radical prostatectomy findings may be improved with MR image guidance of transrectal US-guided prostate biopsy (70). Experimental fusion of MR and transrectal US data (71), in which distances between corresponding data points for each technique are rendered as small as possible by means of registration, is used to obtain more accurate MR-guided transrectal US prostate biopsy results (72).

Transrectal MR-guided biopsy improves prostate cancer detection; however, its availability is limited, and examination times are long. MR guidance of prostate biopsy is a very promising method to improve determination of the true pre-treatment Gleason score.

**Clinical questions**

**Detection**

As stated earlier, clinical prostate cancer detection is currently performed by using tools with limited accuracy. Because the specificity of PSA measurement is low, it is often the case that many unnecessary repeat systematic random biopsies are required to establish a diagnosis (9).

Individual multiparametric MR imaging techniques such dynamic contrast-enhanced, DW and MR spectroscopic imaging have been shown (73–75) to be of possible additional value in prostate cancer detection (Fig 9). Because these MR techniques have a relatively high specificity in comparison with PSA measurement,
they could prevent the unnecessary performance of systematic random biopsies and delay in diagnosis and treatment. Furthermore, results of prospective separate functional MR imaging studies for prostate cancer detection are difficult to compare, since criteria for cancer detection, methods of analysis, sample sizes, and mean PSA levels of patient groups differ or are not always presented. It is essential to know if combinations of more than one functional MR technique could improve results even further. In a logistic regression analysis, ADC value was the best performing (area under the receiver operating characteristic curve \( A_z = 0.69 \)) single parameter for prostate cancer detection when compared with T2-weighted imaging findings, \( K^{\text{trans}} \), and extracellular extravascular space volume fraction \( V_e \) (73). In this study (73), a model based on T2-weighted MR imaging findings, ADCs, and \( K^{\text{trans}} \) performed best (\( A_z = 0.706 \)). Although this study had a moderate sample size (\( n = 42 \)) and was retrospective in character, it is one of the few prostate cancer detection studies in which prostatectomy specimens were used as the reference standard. In a recent evaluation of multiparametric MR imaging at 3 T (76), the addition of dynamic contrast-enhanced and/or DW imaging to T2-weighted MR imaging significantly improved prostate cancer detection sensitivity from 63% to 79%–81% in the peripheral zone, while maintaining a stable specificity. In the transition zone, however, multiparametric MR imaging did not improve prostate cancer detection. This study was performed in 57 patients, with prostatectomy specimens as ground truth. The combination of MR spectroscopic imaging with T2-weighted endorectal MR imaging has shown higher sensitivity (72%–89%) and equal specificity (79%–93%) for prostate cancer detection than was shown for anatomic MR imaging alone (sensitivity, 57%–84%; specificity, 50%–94%) (77,78).

Multiparametric MR imaging techniques may also contribute in detection of transition zone prostate cancers. The combined use of DW, dynamic contrast-enhanced, and T2-weighted MR imaging led to increased accuracy in detection of transition zone cancer, from 64% to 79%, in a small (\( n = 23 \)) retrospective study (79). Multiparametric MR imaging may potentially increase prostate cancer detection accuracy compared with the accuracy of T2-weighted MR imaging only. However, future research is needed to confirm initial results.
Figure 9. Added value of combined multiparametric MR imaging for prostate cancer detection in a 63-year-old man with PSA level of 27.5 ng/mL, clinical stage T0, and history of seven previous negative systematic random biopsy sessions (total of 96 cores). T2-weighted and dynamic contrast-enhanced MR imaging findings are indeterminate to suspicious for tumor within the transition zone, whereas ADC maps may help correct localization of this prostate cancer. (a) Axial T2-weighted turbo spin-echo MR image (4260/99; flip angle, 120°) at midprostate shows low-signal-intensity region in midventral prostate (white outline), which is suspicious for prostate cancer. Furthermore, peripheral zone from dorsal aspect to midline in dorsoventral plane has lower signal intensity than the anterior horns (black outline). This area did not show decreased ADC. This may be due to biopsy-related fibrosis. (b) Top: Same image as a with superimposed $K^{\text{trans}}$ map (38/1.35; flip angle, 14°) shows high $K^{\text{trans}}$ in midventral transition zone (outline), in addition to the mediodorsal transition zone. Bottom: Relative gadolinium concentration (y-axis) versus time (x-axis) curve (Dyna1) shows type 3 curve (fast increase and time to peak followed by washout). (c) Axial ADC map (2400/81; $b = 0, 50, 500,$ and $800 \text{ sec/mm}^2$) at same level as a shows restriction (mean ADC = $750 \times 10^{-6} \text{mm}^2/\text{sec}$) in midventral transition zone (T), indicating intermediate to high tumor aggressiveness. MR-guided biopsy revealed a Gleason score 7 (3+4) prostate cancer.
Localization and Local Staging
Prostate cancer localization is the most important clinical indication for multiparametric MR imaging of the prostate. First, accurate definition of prostate cancer location helps improve cancer detection in targeting prostate biopsies with MR imaging guidance. Second, accurate definition of a prostate cancer location also helps improve prostate cancer staging, because better assessment of prostate cancer location(s) near the neurovascular bundle is possible in patients in whom nerve-sparing surgery is planned. Third, improved evaluation of prostate cancer location helps improve and support focused intensity-modulated radiation therapy planning of the dominant prostatic lesion and improves guidance of minimally invasive focal therapies.

In a large retrospective study in 106 patients in which prostatectomy findings were the reference standard (80), MR imaging localization of prostate cancer was significantly more accurate than digital rectal examination and systematic random biopsy results in the whole prostate except for the apex. Sensitivity and especially specificity of endorectal T2-weighted MR imaging prostate cancer localization vary, ranging from 54% to 91% and 27% to 91%, respectively (81–84). Variation of results in these prospective studies, in which prostatectomy findings served as reference standard, might be partially explained by the fact that image analysis was based on different numbers of regions of interest, different cut-off points for a positive result, and inclusion or exclusion of prostate cancer localization in the transition zone. Moreover, results vary as correlation of MR imaging findings with prostatectomy findings is difficult owing to different angles and section intervals of MR sections and prostatectomy slices and to deformation and shrinkage during histopathologic processing of the prostate specimens. Correction for this variability has been attempted by using a shrinkage factor (83,85). In a recent prospective study (84), correlation of MR imaging and prostatectomy findings was performed in an innovative and possibly more accurate way. Aside from dividing the prostate into 30 regions, including peripheral and transition zones, the authors also used an alternative-neighbor analytic approach to correct for prostate shrinkage and deformation. In this approach, tumors visible on MR image and seen in neighboring regions of the positive prostatectomy specimen were also considered to be positive MR results.

Localization merits of multiparametric MR imaging techniques may be used to draw the attention of the radiologist to a suspicious region. This is illustrated in Figures 5, 9, and 10. Localization accuracy with dynamic contrast-enhanced MR imaging
increased to 72%–91%, as compared with 69%–72% for anatomic T2-weighted MR imaging only (85–88). The addition of DW imaging (83) to T2-weighted MR imaging significantly improved sensitivity to 81% (sensitivity for T2-weighted MR imaging alone, 54%), whereas specificity was slightly lower for T2-weighted MR imaging combined with DWI (84%) than for T2-weighted MR imaging alone (91%) in this prospective prostatectomy-referenced study (83). Also, in other prospective studies (89,90), the addition of DW imaging to T2-weighted MR imaging improved prostate cancer localization performance, with Az values of 0.66–0.79. However, in a recent retrospective 3-T study in 51 patients, with prostatectomy specimens as reference standard (91), DW imaging did not add value to T2-weighted MR imaging for prostate cancer localization. Az values were 0.76–0.79 for T2-weighted MR imaging and 0.78–0.79 for T2-weighted MR imaging combined with DW imaging ADC maps. The high percentage of Gleason score 6 (3+3) cancers (36%, of which only 53%–63% were detected) may explain the poor incremental value of DW imaging ADC maps in this study.

MR spectroscopic imaging has shown higher specificity (68%–99%) and lower sensitivity (25%–80%) for prostate cancer localization, when compared with anatomic T2-weighted MR imaging (specificity, 61%–90%; sensitivity, 68%–87%) in prospective studies with prostatectomy specimens as reference standard (82,84,85,92). However, a multicenter trial that included 110 patients, with prostatectomy findings as reference standard (93), did not show any benefit for the addition of 1.5-T MR spectroscopic imaging to T2-weighted MR imaging in prostate cancer localization (Az = 0.60 for T2-weighted MR imaging alone vs 0.58 for combined T2-weighted and MR spectroscopic imaging, P = .09). The omission of a multicenter validation and use of a threshold for increased metabolic ratios as a criterion for malignancy as well as of a clear definition of tumor focus size may have negatively influenced the quality of MR spectroscopic imaging in this trial. In a recent multiparametric 3-T MR imaging study with 57 patients (76), DW and dynamic contrast-enhanced MR imaging increased the accuracy of prostate cancer localization in the peripheral zone but failed to do the same in the transition zone. By using prostatectomy specimens as standard of reference and scoring four quadrants for both peripheral and transition zones, Az values for the peripheral zone increased from 0.81 to 0.91–0.92 by adding DW and/or dynamic contrast-enhanced MR imaging to T2-weighted MR imaging. In the transition zone, however, localization accuracy decreased from Az of 0.84 for T2-weighted MR imaging alone
to 0.70–0.75 when dynamic contrast-enhanced imaging was added. With the addition of DW imaging to T2-weighted imaging, A2 values for cancer localization in the transition zone increased slightly from 0.84 to 0.88. By improving localization multiparametric MR imaging techniques may also contribute to improved local staging accuracy.

For appropriate therapy planning it is important to know if prostate cancer is confined to the gland (stages T1 and T2) or if there is extraprostatic extension (stages T3 and T4) (94). Current clinical staging, generally based on digital rectal examination, PSA and transrectal US findings, results in frequent understaging (59%) and some overstaging (5%) (95).

The main application of T2-weighted MR imaging is in local staging of prostate cancer. The most widely used criteria for extracapsular spread are (asymmetric) low signal intensity in the seminal vesicles, asymmetry of the neurovascular bundle, obliteration of the rectoprostatic angle (Fig 11), irregular bulging of the prostatic contour (Fig 11), low signal intensity indicative of cancer in the rectoprostatic fat, and overt extracapsular cancer. The last three criteria have the highest sensitivity (96) while all criteria have high specificity.
**Figure 10.** Multiparametric MR imaging for prostate cancer localization in a 71-year-old man with stage T1, Gleason score of 7 (3+4) disease in left prostate base who underwent endorectal MR staging: pitfalls in dynamic contrast-enhanced MR imaging localization of prostate cancer. Dynamic contrast-enhanced MR imaging results in enhancement in multiple areas and is therefore indeterminate when performed in addition to T2-weighted MR imaging. DW imaging correctly localizes this cancer and shows its aggressiveness. (a) Axial T2-weighted turbo spin-echo MR image (4260/99; flip angle, 120°) at midprostate shows low-signal-intensity lesion in left peripheral zone (outline) next to region of high signal intensity in peripheral zone, with minimal signs of extracapsular extension (arrow). (b) Axial MR image with a superimposed $K_{trans}$ map (38/1.35; flip angle, 14°) at same level as a shows multiple enhancing areas in both peripheral and transition zones. Tumor area (T) also shows enhancement. Tumor localization is indeterminate. (c) Axial ADC map (2400/81; $b = 0, 50, 500, and 800 \text{ sec/mm}^2$) at same level as a shows restricted diffusion in laterodorsal peripheral zone (T) (mean ADC = $808 \times 10^{-6} \text{ mm}^2/\text{sec}$), which indicates intermediate tumor aggressiveness. (d) Axial whole-mount histopathologic slice at level corresponding to that of a–c shows a Gleason score 7 (3+4), stage T3A prostate cancer in the left laterodorsal peripheral zone (outline), which confirms the T2-weighted and DW imaging data.
## Table 2. Diagnostic Statistics for MR Studies of Prostate Cancer Staging Since 2006

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Field Strength (T)</th>
<th>No. of subjects</th>
<th>PA coil</th>
<th>ER coil</th>
<th>MRI technique</th>
<th>Sensitivity %*</th>
<th>Specificity %*</th>
<th>Accuracy %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. (107), 2010</td>
<td>1.5</td>
<td>91</td>
<td>Yes</td>
<td>Yes</td>
<td>T2-Weighted DW</td>
<td>PA ECE 30 (8/27)</td>
<td>PA ECE90 (18/20)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PA SVI 50 (2/4)</td>
<td>PA SVI 98 (42/43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ERC ECE 32 (7/22)</td>
<td>ERC ECE 96 (21/22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ERC SVI 50 (2/4)</td>
<td>ERC SVI 93 (37/40)</td>
<td></td>
<td></td>
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<tr>
<td>Augustine et al. (100), 2009</td>
<td>3</td>
<td>27</td>
<td>yes</td>
<td>no</td>
<td>T2-Weighted</td>
<td>ECE 67 (4/6)</td>
<td>ECE 100 (21/21)</td>
<td>ECE 85 (23/27)</td>
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<tr>
<td>Porcaro et al. (103), 2009</td>
<td>1.5</td>
<td>154</td>
<td>NR</td>
<td>yes</td>
<td>T2-Weighted</td>
<td>ECE 78 SVI 88</td>
<td>ECE 96 SVI 98</td>
<td>ECE 91 SVI 97</td>
</tr>
<tr>
<td>Torricelli et al. (104), 2008</td>
<td>3</td>
<td>42</td>
<td>yes</td>
<td>no</td>
<td>T2- and T1-Weighted</td>
<td>ECE 69† (11/16)</td>
<td>ECE 92† (24/26)</td>
<td>ECE 83† (35/42)</td>
</tr>
<tr>
<td>Park et al. (109), 2007</td>
<td>3</td>
<td>54</td>
<td>yes</td>
<td>no</td>
<td>T2-Weighted</td>
<td>ECE 81 (17/21) SVI 50 (1/2)</td>
<td>ECE 67 (22/33) SVI 100 (52/52)</td>
<td>ECE 72 (39/54) SVI 98 (53/54)</td>
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<tr>
<td>Park et al. (109), 2007</td>
<td>1.5</td>
<td>54</td>
<td>no</td>
<td>yes</td>
<td>T2-Weighted</td>
<td>ECE 71 (10/14) SVI 75 (3/4)</td>
<td>ECE 73 (29/40) SVI 92 (46/50)</td>
<td>ECE 72 (39/54) SVI 91 (49/54)</td>
</tr>
<tr>
<td>Heijmink et al. (102), 2007</td>
<td>3</td>
<td>46</td>
<td>yes</td>
<td>yes</td>
<td>T2-Weighted</td>
<td>PA 13‡ (2/15) ERC 80‡ (12/15)</td>
<td>PA 100‡ (31/31) ERC 100‡ (31/31)</td>
<td>PA 70‡ (32/46) ERC 93‡ (43/46)</td>
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<tr>
<td>Fütterer et al. (98), 2007</td>
<td>1.5</td>
<td>81</td>
<td>yes</td>
<td>yes</td>
<td>T2-Weighted</td>
<td>64 (23/36)</td>
<td>98 (44/45)</td>
<td>83 (67/82)</td>
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<td>Bloch et al. (106), 2007</td>
<td>1.5</td>
<td>32</td>
<td>yes</td>
<td>yes</td>
<td>dynamic contrast enhanced</td>
<td>ECE 91§ (11/12)</td>
<td>ECE 95§ (21/22)</td>
<td>NR</td>
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<td>1.5</td>
<td>38</td>
<td>yes</td>
<td>yes</td>
<td>T2-Weighted, MR spectroscopic imaging</td>
<td>ECE 69§ SVI 60</td>
<td>ECE 82 SVI 100</td>
<td>ECE 76 SVI 95</td>
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<tr>
<td>Latchamsetty et al. (105), 2007</td>
<td>1.5</td>
<td>80</td>
<td>NR</td>
<td>yes</td>
<td>T2-Weighted</td>
<td>ECE 71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fütterer et al. (96), 2006</td>
<td>3</td>
<td>32</td>
<td>yes</td>
<td>yes</td>
<td>T2-and T1-Weighted</td>
<td>88 (7/8)</td>
<td>96 (23/24)</td>
<td>94 (30/32)</td>
</tr>
</tbody>
</table>

Note.—Reference standard in all studies was prostatectomy specimen. ECE = extracapsular extension, ER = endorectal, NR = not reported, PA = pelvic phased array, SVI = seminal vesicle invasion.*Data in parentheses are numbers from which percentages were calculated. † Obtained by experienced radiologist. ‡ Maximal values for an examination performed independently by four radiologists. § Maximal percentages for assessment of extracapsular extension adjusted to prevalence of disease in the study population at large.|| Highest values from two separate groups of 40 patients.
There has been a longstanding debate on whether or not to use an endorectal coil for prostate cancer staging since its use results in a more labor-intensive and costly examination. In a meta-analysis, Engelbrecht et al (97) reported on 146 studies performed at 1.5 T and found that the use of turbo spin-echo sequences, an endorectal coil and multiplanar acquisitions all significantly increased staging performance. The application of an integrated endorectal-pelvic phased-array coil significantly improved staging performance, particularly sensitivity, compared with that of a pelvic phased-array coil alone: Az increased from 0.57 to 0.74 at 1.5 T and from 0.62 to 0.68 at 3 T \((P<.001)\) (98). Although, in the largest prospective prostate cancer staging study performed at 1.5 T of which we are aware (99), where MR imaging with a body coil only and with an endorectal coil only were compared, body coil imaging performed better (accuracy, 62%) than did endorectal coil imaging (accuracy, 52%).

In the past decade since this trial, technologic developments such as the use as higher field strengths, improved pelvic phased-array coils and multiparametric MR imaging techniques have improved staging accuracy considerably. However, accuracy results vary between different studies. Table 2 provides an overview of recent prostate cancer staging MR imaging studies at both field strengths (100–107). The results of the MR prostate cancer staging studies, as presented in Table 2, seem conflicting. One should be careful, as difficulty remains in comparing and interpreting results of these studies because different field strengths, comparisons of coil types, and endpoints were used for prostate cancer staging.

To our knowledge, only two studies have directly compared 3-T and 1.5-T MR staging of prostate cancer (108,109). This comparison was suboptimal, because use of a pelvic phased-array coil at 3 T was compared with use of a pelvic phased-array coil and/or an endorectal coil at 1.5 T. Conclusions on the effects of higher field strength on MR staging of prostate cancer remain difficult to infer because research on this topic is still immature.

Multiparametric MR imaging may also improve prostate cancer staging. In a large prospective study with 99 patients (110), dynamic contrast-enhanced MR imaging combined with T2-weighted MR imaging significantly improved the accuracy of prostate cancer staging compared with that of T2-weighted MR imaging alone. Az values for less experienced readers were 0.82 for dynamic contrast-enhanced plus T2-weighted MR imaging and 0.66 for T2-weighted imaging alone respectively \((P < .01)\). In a prospective study with 53 patients (111), addition of three-dimensional...
MR spectroscopic imaging results to T2-weighted MR imaging results significantly improved accuracy for predicting extracapsular extension for both experienced and less-experienced readers (Az increase from 0.78 to 0.86 and 0.62 to 0.75, respectively, for T2-weighted imaging only vs combined imaging).

Drawbacks of T2-weighted MR imaging for prostate cancer localization and local staging include differentiation of inflammatory changes from cancer. Furthermore, high inter- and intra-observer variability may lead to under- or overestimation of cancer stage (112). Also, postbiopsy hemorrhage can decrease staging accuracy. Finally, T2-weighted MR imaging cannot be used to detect microscopic capsular invasion. As mentioned earlier, pitfalls of multiparametric MR techniques also affect the ability to facilitate prostate cancer localization and local staging (see Figs 5, 10).

Of all clinical indications for multiparametric MR imaging, localization is the most important. Accurate prostate cancer localization results in more accurate prostate cancer staging and in more accurate MR guidance of prostate biopsy and therapy.

Figure 11. Multiparametric MR imaging in prostate cancer staging in a 70-year-old man with PSA level of 12 ng/mL and well-differentiated prostate carcinoma (C). Axial T2-weighted turbo spin-echo MR image (4260/99; flip angle, 120°) shows low-signal-intensity region (outline) in left peripheral zone. Bulging and obliteration of rectoprostatic angle (open arrows) indicate extracapsular extension. There is invasion of the neurovascular bundle (solid arrow). At MR imaging, stage T3a prostate cancer was reported. Radical prostatectomy revealed a solitary adenocarcinoma with Gleason score 7 (3+4) with extraprostatic extension (stage T3a).
Determination of Prostate Cancer Aggressiveness

Prostate cancer is graded according to the Gleason score, a combination of the two most prevalent Gleason grades (at prostatectomy) or the most prevalent and the highest grade (at prostate biopsy), based on architectural characteristics of prostate cancer tissue (113,114). Sampling error in biopsy specimens obtained at systematic random biopsy occurs in approximately in 64% of procedures (10) and results in a changed Gleason score at histopathologic evaluation of the prostatectomy specimen. This results in incorrect evaluation of prostate cancer aggressiveness, which may cause under- or overtreatment (115). On T2-weighted MR images, signal intensity changes and detection rates for prostate cancer have been associated with its aggressiveness. In a retrospective study with 74 patients, in which prostatectomy specimens were used as standard of reference (14), low-grade cancers were detected at a rate of 43%, while high-grade cancers were detected at a rate of 79%. In another retrospective study, which also used prostatectomy specimens as reference standard (116), higher Gleason scores were associated with lower tumor-to-muscle signal intensity ratios on T2-weighted MR images. In a large retrospective study with 220 patients (117), T2-weighted MR imaging and MR spectroscopic imaging scores based on a three-point scale for clinical prostate cancer aggressiveness were significantly correlated to biologic markers such as androgen receptor levels, which were associated with prostate cancer progression. In that study, the combination of biologic markers with T2-weighted MR imaging and MR spectroscopic imaging results yielded an Az of 0.91 for discrimination of clinically unimportant prostate cancer, which was defined as cancer confined to the organ and 0.5 cm³ or less in volume without poorly differentiated parts at pathologic examination. Moreover, at MR spectroscopic imaging, the choline-plus-creatine-to-citrate ratios have been shown to be associated with Gleason score (118,119). In a retrospective study of 43 patients with biopsy-proved prostate cancer, Kobus et al (120) showed that 3-T MR spectroscopic imaging is an accurate technique for discriminating patients with Gleason grade 2 or 3 cancer from patients with Gleason score 4 or 5 cancer, as determined with prostatectomy specimens. By using a standardized-threshold approach involving both the choline-plus-creatine-to-citrate ratio and the choline-to-citrate ratio, an Az of 0.78 was achieved for discrimination of Gleason score 2–3 from Gleason score 4–5 prostate cancers.
Results for ADC as a possible marker of cancer aggressiveness are very promising: In a retrospective study of 3-T DW imaging ($b= 0, 50, 500,$ and $800$ sec/mm$^2$) Hambrock et al (45) correlated median ADCs with prostatectomy Gleason grades in peripheral zone prostate cancers on a slice-by-slice basis in 51 patients. Cancers with Gleason score 2–3 components were discerned from cancers with Gleason score 4–5 components, with an $A_z$ of 0.90. Furthermore, in a study of 1.5-T DW imaging ($b = 0$ and $600$ sec/mm$^2$) in 110 patients with 197 tumors, Verma and Rajesh (121) found a negative correlation $r = -0.39$) between mean ADC and Gleason score for peripheral zone cancers on prostatectomy specimens. A similar association could not be found for cancers in the transition zone. An $A_z$ of 0.78 was achieved by using both cancer volume and ADC as predictors of tumor aggressiveness (Gleason score $\geq 6$). While preliminary studies in the field of prostate cancer aggressiveness show promising results (45), different parameters from different multiparametric techniques show some overlap among Gleason scores. Because a certain value of an MR parameter, such as ADC, cannot be precisely associated with one Gleason score component, multiparametric MR imaging cannot yet be applied to the determination of prostate cancer aggressiveness in a general clinical environment. However, this technique is very helpful for assessing tumor grade and guiding biopsy to the most aggressive part of the tumor.

**Active Surveillance**

With the observation that low-risk cancers do not progress rapidly when treatment is deferred (122,123), implementation of active surveillance protocols has become more widespread. The aim of this approach is to minimize overtreatment by mean of active observation of low-risk cancers and to intervene with curative therapy when a presumably low-risk cancer shows signs of progression. Low-risk cancer is frequently defined as a cancer with a clinical stage of T2 or lower, a Gleason score of 6 or less without a Gleason 4 or 5 component, a PSA level of 10 ng/mL or less, a PSA density 0.15 ng/mL/mL or less, and systematic random biopsy criteria of two or fewer cores with prostate cancer and 50% volume of cancer or less per core (124).

The cornerstone of active surveillance protocols is the accurate identification of low-risk cancers. A frequent cause for inaccurate estimation of prostate cancer aggressiveness is sampling error at systematic random biopsy with subsequent undergrading of Gleason score. In addition, cancer volume is also often underestimated owing to sampling error in systematic random biopsies, because cancer volume is estimated by measuring the number and volume percentages...
of cancer tissue of cancer-positive biopsy cores (10). In patients in whom risk stratification was incorrectly determined, repeat biopsies may eventually show evidence of high-risk disease, which then triggers a delayed intervention with, perhaps, a missed opportunity for definitive curative therapy (125–127).

Multiparametric MR imaging can potentially aid in adequate risk stratification for patient selection in active surveillance by improving prostate cancer staging and by characterizing cancer aggressiveness (Fig 6). An example of improved staging by using MR imaging in active surveillance is in a prospective study by Berglund et al (128). In that study, 18 (39%) of 66 patients in whom MR imaging findings were suspicious for extracapsular extension were upgraded or upstaged because of progression at histologic examination of the repeat biopsy specimen.

During follow-up in active surveillance, detection of cancer progression within the curative window is essential. MR imaging can also be valuable in this application. Recently, Giles et al (129) showed that ADCs at repeat biopsy were significantly lower in patients with a Gleason score increase than in those with a stable score ($P < .001$). In that study, both tumor volume ($P = .002$) and ADCs calculated from DW imaging (300–800 sec/mm$^2$) ($P = .02$) were significant independent predictors of progression of active surveillance patients. Progression was defined biochemically (PSA increase > 1 ng/mL per year) and/or histopathologically (repeat biopsy Gleason grade ≥4 or cancer presence in more than 50% of biopsy cores).

In another active surveillance study in 86 patients with a mean follow-up of 29 months (130), DW imaging tumor ADC data were significant predictors of a Gleason score 4 component at repeat biopsy ($Az = 0.70, P < .001$) and of the need for initiation of radical treatment during follow-up ($Az = 0.83, P < .001$). Patients were included in this study if they met the following criteria: PSA level of 15 ng/mL or lower, Gleason score of 7 or lower with a primary Gleason score of 3 or less, 50% or fewer of biopsy cores positive at systematic random biopsy, three monthly PSA measurements, repeat systematic random biopsies 12–24 months after inclusion, and performance of DWI imaging before inclusion. Similar results were found in another retrospective study (131), in which an increase to Gleason score 7 or higher at subsequent repeat systematic random biopsy in 114 active surveillance patients was associated with T2-weighted MR imaging results although not with transrectal US or MR spectroscopic imaging results.

These studies may underestimate results because systematic random biopsy specimens, instead of a prostatectomy specimen, were used as the reference standard. On the other hand, in a large retrospective study, Cabrera et al (132)
found that T2-weighted MR imaging and MR spectroscopic imaging performed at baseline were of no additional prognostic value to active surveillance because the presence of cancer on MR images could not be associated with biochemical outcome in multivariate analysis. Biochemical outcome was defined according to serial PSA measurements, which were classified as stable or progressive by using slopes of regression lines. These results conflict with those of previous retrospective studies (130,131). The field strength of 1.5 T used by Cabrera et al and the use of PSA kinetics instead of histologic findings as a measure of prostate cancer progression might partly explain these conflicting results. Despite general promising results, incorporation of multiparametric MR imaging into active surveillance protocols for low-risk prostate cancer is still in an early phase.

Multiparametric MR imaging and MR-guided biopsy may improve initial diagnosis and accurate monitoring of prostate cancer stage and aggressiveness in active surveillance. Future research addressing the use of multiparametric MR imaging in selection and follow-up of patients with low-risk prostate cancer as part of active surveillance protocols is needed.

Conclusion

In this review, we have presented and discussed available data on the additional value of the different functional MR imaging techniques in various clinical diagnostic prostate cancer problems.

To increase MR imaging accuracy for the different clinical prostate cancer indications, one or more functional MR imaging techniques should be combined with T2-weighted MR imaging in a multiparametric MR examination of the prostate. However, within the variety of different acquisition methods, protocols, magnetic field strengths and multiparametric techniques that are used, consensus guidelines on dedicated MR protocols for specific clinical indications are lacking.

Suggested minimal requirements for a multiparametric MR imaging protocol for clinical evaluation of prostate cancer are T1- and T2-weighted MR imaging in combination with DW and dynamic contrast-enhanced MR imaging. T1-and T2-weighted MR imaging should be used for evaluation of anatomy. Dynamic contrast-enhanced MR imaging can be used for high-sensitivity identification of potential
prostate cancer locations. Unfortunately, little standardization in dynamic contrast-enhanced MR acquisition and analysis exists. DW imaging or MR spectroscopic imaging are accurate functional MR techniques, and they may be added to improve specificity for different clinical indications. DW imaging is the most practical and simple accurate functional imaging technique; however, it is prone to motion and susceptibility artifacts. MR spectroscopic imaging is an accurate technique that, like DW imaging, can be used for assessing prostate cancer aggressiveness. Expertise and longer imaging times are prerequisites for MR spectroscopic imaging, which may ultimately decrease its clinical applicability.

Because the reported accuracies of multiparametric MR imaging techniques for different indications are inconsistent, definitive conclusions on the accuracies of (combined) multiparametric MR imaging techniques for a particular clinical prostate cancer problem are difficult to make. In general, the addition of functional MR techniques to T2-weighted MR imaging improves accuracy for both localization and local staging of prostate cancer in comparison to the accuracy of T2-weighted MR imaging alone. Of all clinical indications for multiparametric MR imaging of the prostate, localization is the most important. Accurate determination of prostate cancer location(s) results in more accurate prostate cancer staging and MR guidance of prostate biopsy and therapy.

Currently, multiparametric MR imaging is performed at only a limited number of centers worldwide. Development of expertise in functional MR techniques and increased availability of equipment are needed, so that multiparametric prostate MR imaging can become a more accessible examination. To warrant accurate future multiparametric MR imaging prostate cancer diagnostics, computer programs are needed to support clinicians by allowing simple post-processing and fast evaluation of the data.
References

CHAPTER 2


Transition Zone Prostate Cancer: Detection and Localization with 3-T Multiparametric MR Imaging

Caroline M.A. Hoeks, MD
Thomas Hambrock, MD PhD
Derya Yakar, MD PhD
Christina Hulsbergen-van de Kaa, MD PhD
Ton Feuth, MSc
J. Alfred Witjes, MD PhD
Jurgen J. Fütterer, MD PhD
Jelle. O. Barentsz, MD PhD

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Abstract

Purpose: To retrospectively compare transition zone (TZ) cancer detection and localization accuracy of 3-T T2-weighted magnetic resonance (MR) imaging with that of multiparametric (MP) MR imaging, with radical prostatectomy specimens as the reference standard.

Materials and Methods: The informed consent requirement was waived by the institutional review board. Inclusion criteria were radical prostatectomy specimen TZ cancer larger than 0.5 cm³ and 3-T endorectal presurgery MP MR imaging (T2-weighted imaging, diffusion-weighted [DW] imaging apparent diffusion coefficient [ADC] maps [b, 1000 sec/mm²], and dynamic contrast material–enhanced [DCE] MR imaging).

From 197 patients with radical prostatectomy specimens, 28 patients with TZ cancer were included. Thirty-five patients without TZ cancer were randomly selected as a control group. Four radiologists randomly scored T2-weighted and DW ADC images, T2-weighted and DCE MR images, and T2-weighted, DW ADC, and DCE MR images. TZ cancer suspicion was rated on a five-point scale in six TZ regions of interest (ROIs). A score of 4–5 was considered a positive finding. A score of 4 or higher for any ROI containing TZ cancer was considered a positive detection result at the patient level. Generalized estimating equations were used to analyze detection and localization accuracy by using ROI-receiver operating characteristics (ROC) curve analyses for the latter. Gleason grade (GG) 4–5 and GG 2–3 cancers were analyzed separately.

Results: Detection accuracy did not differ between T2-weighted and MP MR imaging for all TZ cancers (68% vs 66%, P = .85), GG 4–5 TZ cancers (79% vs 72%–75%, P = .13), and GG 2–3 TZ cancers (66% vs 62%–65%, P = .47). MP MR imaging (area under the ROC curve, 0.70–0.77) did not improve T2-weighted imaging localization accuracy (AUC = 0.72) (P > .05).

Conclusion: Use of 3-T MP MR imaging, consisting of T2-weighted imaging, DW imaging ADC maps (b values, 50, 500, and 800 sec/mm²), and DCE MR imaging may not improve TZ cancer detection and localization accuracy compared with T2-weighted imaging.
Introduction

American Cancer Society statistics show prostate cancer accounted for more than a quarter of the cancer incidence in male subjects in the United States, with mortality rates higher than 15%, in 2008 (1). Between 25% and 30% of these cancers were transition zone (TZ) cancers (2). No uniform histopathologic definition of TZ cancer exists, although a cancer volume of 50%–70% or higher within the TZ is commonly used as a histopathologic definition for probable TZ origin (2). TZ prostate cancers have a relatively lower Gleason score (3), local stage (4), and biochemical recurrence rate (5) in comparison with peripheral zone cancers. However, zonal location of high Gleason grade (GG) prostate cancer did not influence biochemical relapse-free survival (5). Furthermore, in a prostatectomy series, a GG 4 or GG 5 component with extracapsular extension and positive resection margins was present in 9% of all TZ cancers (6). Therefore, improvement of TZ cancer detection is an important goal in prostate cancer diagnostics. Anterior TZ cancers in particular are detected less frequently with standard prostate biopsy schemes because they are beyond the reach of general random systematic transrectal ultrasonography (US) guided biopsies in current prostate cancer diagnostic work-up (7).

At T2-weighted magnetic resonance (MR) imaging, TZ prostate cancers are difficult to differentiate from benign prostatic hyperplasia (BPH), as the latter has a heterogeneous signal intensity (SI) with lower SI components, which are similar to the low SI of prostate cancer. Despite this, T2-weighted imaging has been advocated as an accurate technique in the detection of TZ cancer (8,9). Several T2-weighted imaging features, such as homogeneously low SI (sensitivity, 76%–78%; specificity, 78%–87%), ill-defined margins (sensitivity, 76%–78%; specificity, 78%–89%), and lenticular shape (sensitivity, 48%–56%; specificity, 85%–98%), may be applied to accurately predict TZ cancer (8,9). The use of an endorectal coil in T2-weighted imaging tumor localization at 1.5 T resulted in an area under the receiver operating characteristic curve (AUC) of 0.73–0.84 (8,10,11). Reported results for TZ cancer detection and localization accuracy with multiparametric (MP) MR imaging vary. Application of endorectal diffusion-weighted (DW) MR imaging and dynamic contrast material–enhanced (DCE) MR imaging at 1.5 T did not significantly improve TZ cancer detection and localization accuracy compared with T2-weighted imaging alone (10,11). However, at 1.5 T, DW imaging has been shown to increase TZ cancer detection accuracy when high b values (>1000 sec/mm$^2$) are used (12,13). TZ cancer localization accuracy increased from an AUC of 0.69 for T2-weighted imaging alone
to an AUC of 0.84 by adding DW imaging with $b$ values of 2000 sec/mm$^2$ (13). With DCE MR imaging, quantitative parameters, such as the transfer constant (or $K_{\text{trans}}$), can be used to differentiate TZ cancer from glandular BPH but not from stromal BPH (14).

To our knowledge, 3-T endorectal MP MR imaging including DW and DCE MR imaging has not been evaluated in TZ cancer detection and localization. Application of higher field strengths may yield better image quality due to a higher signal-to-noise ratio. Therefore, the purpose of this study was to retrospectively compare TZ cancer detection and localization accuracy of 3-T T2-weighted imaging with those of MP MR imaging by using radical prostatectomy specimens as the reference standard.

**Materials and Methods**

**Patients**

The need for informed consent was waived by the local institutional review board. Inclusion criteria were TZ cancer, with a cancer volume of more than 0.5 cm$^3$ in the radical prostatectomy specimen, and pre-prostatectomy endorectal 3-T MP MR imaging, including T2-weighted imaging, DW MR imaging, and DCE MR imaging. Patients who had undergone prior radiation therapy or transurethral prostate resection were excluded. Twenty-eight patients with TZ cancer met the inclusion criteria. These patients were retrospectively selected from 197 consecutive patients whose histopathologic specimens were obtained at prostatectomy performed within our referral center between January 2007 and August 2011. Subsequently, 35 patients without TZ cancer but with peripheral zone cancer were randomly selected by blindly drawing them from the same group of prostatectomies to serve as a control group, as shown in Figure 1. Four of the 39 selected control subjects were excluded due to postradiotherapy ($n=1$), postbrachytherapy ($n=1$), or posttransurethral ($n=2$) prostate resection status.

**MR imaging acquisition protocol**

MR images were obtained with a 3-T MR imager (Trio Tim; Siemens, Erlangen, Germany) by using a pelvic phased-array coil and an endorectal coil (Medrad, Pittsburgh, Pa) filled with 40 mL of perfluorocarbon (Fomblin; Solvay-Solexis, Milan, Italy). MP MR imaging parameters are presented in Table 1. Axial DW imaging
followed axial T2-weighted imaging of the prostate and seminal vesicles with the same section positions and use of diffusion modules and fat-suppression pulses. Apparent diffusion coefficient (ADC) maps were calculated automatically by using \( b \) values (50, 500, and 800 sec/mm\(^2\), without 0 sec/mm\(^2\) values). DCE MR imaging was performed initially with an axial three-dimensional (3D) proton density–weighted gradient-echo sequence and was followed by an axial 3D T1-weighted spoiled gradient-echo sequence performed during intravenous administration of 0.1 mmol gadopentetate dimeglumine (Dotarem; Guerbet, Paris, France) per kilogram of body weight at a rate of 2.5 mL/sec followed by a 20-mL saline flush. Post-processing of DCE MR imaging data was performed with in-house–developed software (15). Quantitative pharmacokinetic analysis was based on the model by Tofts et al (16), with an automatic per-patient calibration for estimation of the arterial input function (17).

**MR image interpretation**

Four radiologists (D.Y., C.M.A.H., T.H., and J.J.F.; 3, 3, 5, and 10 years of experience, respectively, with prostate MR imaging) independently and randomly scored all cases by using software that was developed in-house (15). Radiologists were informed about the diagnosis of cancer in every patient; however, they were blinded to the zonal location of present prostate cancer. T2-weighted imaging, T2-weighted imaging combined with ADC maps, T2-weighted and DCE MR imaging, and T2-weighted MR imaging combined with DW MR imaging ADC maps and DCE MR imaging were prospectively scored in four separate consecutive sessions with at least 2 weeks between sessions. T1-weighted MR images were available for evaluation of postbiopsy hematoma. The TZ was divided into six regions of interest (ROIs). In the coronal plane, the TZ was divided in three parts: the level of the verumontanum, the level inferior to the verumontanum, and the level superior to the verumontanum. The sagittal plane through the verumontanum was used to divide the TZ into a right and left halves. The following five-point scale was used for every ROI and every reading session: A score of 1 indicated definite absence of TZ cancer; a score of 2, probable absence of TZ cancer; a score of 3, possible presence of TZ cancer; a score of 4, probable presence of TZ cancer; and a score of 5, definite presence of TZ cancer. Radiologists were instructed to score only those cancers with at least 70% of their volume within the TZ (18). For T2-weighted imaging, the presence of homogeneously low SI, irregular boundaries around a low-SI lesion, lenticular shape, interruption of the pseudocapsule, and invasion of the anterior fibromuscular
stroma or lateroventral TZ were considered suspicious for TZ cancer (score, 4–5) (8,9). DW MR imaging ADC maps and DCE MR images were evaluated in conjunction with T2-weighted images. For DW imaging, a homogeneously low ADC value in comparison with the ADC of the surrounding TZ was suspicious for TZ cancer (score, 4–5). For DCE MR imaging (19), quantitative pharmacokinetic modelling according to the model of Tofts et al (16) was used. Parameter maps of the transfer constant and of washout were used as an overlay over T2-weighted images. In addition, qualitative characteristics of the relative gadolinium concentration-time curve were used. When this curve showed a plateau or washout after early enhancement in combination with focal or asymmetric enhancement of an area in the (lateroventral) TZ or of the anterior fibromuscular stroma on the overlaid parametric map, the region was suspicious for prostate cancer (score, 4–5).

Table 1. MR imaging parameters.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Sequence</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Acquisition Time (mins)</th>
<th>Flip angle (degrees)</th>
<th>Slice thickness (mm)</th>
<th>Field of view (mm × mm)</th>
<th>Matrix size</th>
<th>Voxel size (mm × mm × mm)</th>
<th>b-values (s/mm²)</th>
<th>Temporal resolution (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2WI</td>
<td>TSE</td>
<td>4280</td>
<td>99</td>
<td>4.21</td>
<td>120</td>
<td>3</td>
<td>180 × 178</td>
<td>448 × 448</td>
<td>0.4 × 0.4 × 3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>axial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>coronal</td>
<td>3590</td>
<td>98</td>
<td>2.27</td>
<td>120</td>
<td>3</td>
<td>192 × 192</td>
<td>384 × 384</td>
<td>0.5 × 0.5 × 3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sagittal</td>
<td>4290</td>
<td>98</td>
<td>2.39</td>
<td>120</td>
<td>3</td>
<td>192 × 192</td>
<td>384 × 384</td>
<td>0.5 × 0.5 × 3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI</td>
<td>SSEPI</td>
<td>2600</td>
<td>90</td>
<td>4.02</td>
<td>90</td>
<td>3</td>
<td>204 × 204</td>
<td>136 × 136</td>
<td>1.5 × 1.5 × 3.0</td>
<td>0/50/500/800</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>GE</td>
<td>800</td>
<td>1.51</td>
<td>2.13</td>
<td>14</td>
<td>3</td>
<td>192 × 192</td>
<td>128 × 128</td>
<td>1.5 × 1.5 × 3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>spoiled</td>
<td>36</td>
<td>1.4</td>
<td>2.34</td>
<td>14</td>
<td>3</td>
<td>192 × 192</td>
<td>128 × 128</td>
<td>1.5 × 1.5 × 3.0</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

T2WI= T2-weighted MR imaging, DWI= diffusion weighted MR imaging, DCE-MRI= dynamic contrast enhanced MR imaging, TSE= turbo spin echo, SSEPI= single-shot echo-planar imaging, GE= gradient echo, TR= repetition time and TE=echo time, PD= proton density weighted MR imaging.

Histopathologic analysis
Radical prostatectomy specimens served as the reference standard for MP MR Imaging results. Specimens were cut into 4-mm-thick axial step-section slices and were completely processed. A urogenital pathologist with more than 18 years of experience (C.H.) and who was blinded to MP MR imaging results determined
location, stage, and GG components for every individual tumor (2005 International Society of Urological Pathology criteria [20]). Cancer volume was calculated by assuming elliptical tumor shape and multiplying by slice thickness (4 mm) (21). Cancer with a volume of at least 70% within the TZ was defined as TZ cancer in the radical prostatectomy specimen (18).

**Correlation of MR data to the reference standard**
Two radiologists (C.M.A.H., T.H.; 3 and 5 years of experience in prostate MP MR imaging) correlated MR data and radical prostatectomy specimen data in consensus by using landmarks like the verumontanum, urethra, and calcifications. Correlation of prostate MP MR imaging data to histopathology data is known to be difficult (22).

**Statistical Analyses**
Analyses were performed by using PASW Statistics (version 18; SPSS, Hong Kong, China) and SAS (version 9; SAS Institute, Cary, NC) software. A two-sided P value of less than .05 indicated a significant difference. Patient characteristics were compared by using an independent t test for parametric variables, and a Mann-Whitney U test was used for nonparametric variables. Separate subanalyses were performed for GG 4–5 and GG 2–3 TZ cancers. Readers with scores of 4 or higher for any TZ-cancer-containing ROI were considered to have detected TZ cancer in that particular patient. Localization of TZ cancer was defined as finding a cancer (score ≥4) in a cancer-containing ROI. Per patient, all four separate reader evaluations were used for sensitivity, specificity, and accuracy calculations. Differences between diagnostic indexes of the four MP MR imaging readings were evaluated by using generalized estimating equations. When an overall score test indicated a significant difference, we performed Wald tests for pairwise comparisons. TZ cancer sensitivity was corrected for tumor volume.

TZ cancer localization accuracy was analyzed by comparing AUCs of different MP MR imaging readings. For every MP MR reading, average scores over the four readers were calculated per ROI per subject. Generalized estimating equation analysis was applied (binomial distribution, logit link function, and exchangeable correlation structure) to account for within-subject correlation between ROIs. Comparison of the resulting correlated AUCs and calculation of 95% confidence intervals was performed by using the SAS macro roc.sas (http://support.sas.com/kb/25/017.html). Interobserver agreement was evaluated by using the intraclass correlation coefficient based on our random effects model. Levels of interobserver agreement
obtained by using the intraclass correlation coefficient were defined as poor \( (r, 0.0) \), slight \( (r = 0.0 – 0.20) \), fair \( (r = 0.21 – 0.40) \), moderate \( (r = 0.41 – 0.60) \), substantial \( (r = 0.61 – 0.80) \), and almost perfect \( (r = 0.81 – 1.00) \) (23).

Table 2. Patient and prostatectomy characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with TZ cancer (n = 28)*</th>
<th>Control patients without TZ cancer (n=35)</th>
<th>Two-sided P Value for Patients with TZ Cancer versus Control Subjects</th>
<th>Patients with GG 4–5 TZ cancer (n=13)</th>
<th>Patients with GG 2–3 TZ cancer (n=15)*</th>
<th>Two-sided P Value for Patients with GG 4–5 TZ vs Patients with GG 2–3 TZ cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) †</td>
<td>67 (55-73) (63 (45-73)</td>
<td>63 (45-73)</td>
<td>0.18</td>
<td>67 (55-73)</td>
<td>67 (55-71)</td>
<td>0.60</td>
</tr>
<tr>
<td>PSA level (ng/mL) †</td>
<td>9.3 (1.9-44.0)</td>
<td>6.5 (3.2-14.8)</td>
<td>0.15‡</td>
<td>17.4 (3.2-44.0)</td>
<td>5.4 (1.9-16.7)</td>
<td>&lt; 0.01‡§</td>
</tr>
<tr>
<td>Prostate volume (mL) †</td>
<td>37.6 (20.7-103.0)</td>
<td>37.0 (17.0-91.8)</td>
<td>0.75</td>
<td>38.0 (20.7-73.0)</td>
<td>37.0 (23.0-103.0)</td>
<td>0.85</td>
</tr>
<tr>
<td>Cancer volume (cm³) †</td>
<td>4.4 (0.5-22.0)</td>
<td>1.2 (0.5-18.8)</td>
<td>&lt;0.01§</td>
<td>8.5 (1.5-20.9) Mean 8.2</td>
<td>1.5 (0.5-22.0) Mean 4.7</td>
<td>0.03§</td>
</tr>
<tr>
<td>MR imaging to surgery interval, in weeks †</td>
<td>8 (1-28)</td>
<td>7 (1-21)</td>
<td>0.54</td>
<td>8 (1-28)</td>
<td>8 (1-15)</td>
<td>0.75</td>
</tr>
<tr>
<td>Histopathologic stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2a</td>
<td>0</td>
<td>10</td>
<td>N.A.</td>
<td>0</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>pT2c</td>
<td>15</td>
<td>12</td>
<td>N.A.</td>
<td>2</td>
<td>13</td>
<td>N.A.</td>
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<tr>
<td>pT3a</td>
<td>8</td>
<td>12</td>
<td>N.A.</td>
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<td>N.A.</td>
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<tr>
<td>pT3b</td>
<td>3</td>
<td>1</td>
<td>N.A.</td>
<td>3</td>
<td>0</td>
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<tr>
<td>pT4</td>
<td>4</td>
<td>0</td>
<td>N.A.</td>
<td>3</td>
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<tr>
<td>Gleason score</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+2</td>
<td>0</td>
<td>0</td>
<td>N.A.</td>
<td>0</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>2+3</td>
<td>7</td>
<td>0</td>
<td>N.A.</td>
<td>0</td>
<td>7</td>
<td>N.A.</td>
</tr>
<tr>
<td>2+4</td>
<td>1</td>
<td>0</td>
<td>N.A.</td>
<td>1</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>3+2</td>
<td>4</td>
<td>1</td>
<td>N.A.</td>
<td>0</td>
<td>4</td>
<td>N.A.</td>
</tr>
<tr>
<td>3+3</td>
<td>6</td>
<td>12</td>
<td>N.A.</td>
<td>0</td>
<td>6</td>
<td>N.A.</td>
</tr>
<tr>
<td>3+4</td>
<td>2</td>
<td>15</td>
<td>N.A.</td>
<td>2</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>4+2</td>
<td>1</td>
<td>0</td>
<td>N.A.</td>
<td>1</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>4+3</td>
<td>7</td>
<td>7</td>
<td>N.A.</td>
<td>7</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>4+5</td>
<td>2</td>
<td>0</td>
<td>N.A.</td>
<td>2</td>
<td>0</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

Note.—P values were calculated with the Mann-Whitney U test. Mean cancer volume in patients with GG 4–5 TZ cancer and those with GG 2–3 TZ cancer was 8.2 cm³ and 4.7 cm³, respectively. NA = not applicable.
* Two patients had two 2–3 TZ cancers.
† Data are medians, and data in parentheses are the range.
‡ As prostate-specific antigen level was a parametric variable in both patients with GG 2–3 TZ cancer and patients with GG 4–5 TZ cancer, an independent t test was used for this comparison. § Under threshold for significance (two-tailed P value < .05).
Table 3. Diagnostic Accuracy in Detection of All TZ Cancers, of GG 4–5 TZ Cancers, and of GG 2–3 TZ Cancers for All Readers for Different MP-MR Imaging Protocols

<table>
<thead>
<tr>
<th>MR Imaging protocol</th>
<th>All Patients with TZ Cancer vs Control Subjects without TZ Cancer (n = 63)</th>
<th>Patients with GG 4–5 TZ Cancer vs Control Subjects without TZ Cancer (n = 48)</th>
<th>Patients with GG 2–3 TZ Cancer vs Control Subjects without TZ Cancer (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
<td>Accuracy (%)</td>
</tr>
<tr>
<td>T2-weighted imaging</td>
<td>53 (59/112)</td>
<td>80 (112/140)</td>
<td>68 (171/252)</td>
</tr>
<tr>
<td></td>
<td>(44,62)</td>
<td>(73,86)</td>
<td>(62,73)</td>
</tr>
<tr>
<td>T2-weighted imaging and DW imaging</td>
<td>58 (65/112)</td>
<td>72 (101/140)</td>
<td>66 (166/252)</td>
</tr>
<tr>
<td></td>
<td>(49,67)</td>
<td>(64,79)</td>
<td>(58,70)</td>
</tr>
<tr>
<td>T2-weighted imaging and DCE MR imaging</td>
<td>53 (59/112)</td>
<td>76 (107/140)</td>
<td>66 (166/252)</td>
</tr>
<tr>
<td></td>
<td>(44,62)</td>
<td>(60,71)</td>
<td>(60,71)</td>
</tr>
<tr>
<td>T2-weighted imaging and DW imaging ADC maps, and DCE MR imaging</td>
<td>65 (73/112)</td>
<td>67 (94/140)</td>
<td>66 (167/252)</td>
</tr>
<tr>
<td></td>
<td>(56,73)</td>
<td>(59,74)</td>
<td>(60,72)</td>
</tr>
<tr>
<td>Generalized estimating equation analysis overall score test*†</td>
<td>0.004</td>
<td>0.002</td>
<td>0.848</td>
</tr>
<tr>
<td>Wald test†</td>
<td>0.116</td>
<td>0.021</td>
<td>0.021</td>
</tr>
<tr>
<td>T2-weighted imaging vs T2-weighted imaging and DW imaging ADC maps</td>
<td>0.661</td>
<td>0.411</td>
<td>0.411</td>
</tr>
</tbody>
</table>
### MR Imaging Protocol

<table>
<thead>
<tr>
<th>MR Imaging Protocol</th>
<th>All Patients with TZ Cancer vs Control Subjects without TZ Cancer (n = 63)</th>
<th>Patients with GG 4–5 TZ Cancer vs Control Subjects without TZ Cancer (n = 48)</th>
<th>Patients with GG 2–3 TZ Cancer vs Control Subjects without TZ Cancer (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-weighted imaging vs T2-weighted imaging, DW imaging, ADC maps, and DCE MR imaging</td>
<td>Sensitivity (%) = 0.006, Specificity (%) = 0.005, Accuracy (%) = 0.005</td>
<td>Sensitivity (%) = 0.005, Specificity (%) = 0.005, Accuracy (%) = 0.005</td>
<td>Sensitivity (%) = 0.005, Specificity (%) = 0.005, Accuracy (%) = 0.005</td>
</tr>
<tr>
<td>T2-weighted imaging and DW imaging, ADC maps vs T2-weighted imaging, and DCE MR imaging</td>
<td>Sensitivity (%) = 0.092, Specificity (%) = 0.317, Accuracy (%) = 0.327</td>
<td>Sensitivity (%) = 0.092, Specificity (%) = 0.317, Accuracy (%) = 0.327</td>
<td>Sensitivity (%) = 0.092, Specificity (%) = 0.317, Accuracy (%) = 0.327</td>
</tr>
<tr>
<td>T2-weighted imaging and DW imaging, ADC maps vs T2-weighted imaging, DW imaging, ADC maps, and DCE MR imaging</td>
<td>Sensitivity (%) = 0.069, Specificity (%) = 0.296, Accuracy (%) = 0.296</td>
<td>Sensitivity (%) = 0.069, Specificity (%) = 0.296, Accuracy (%) = 0.296</td>
<td>Sensitivity (%) = 0.069, Specificity (%) = 0.296, Accuracy (%) = 0.296</td>
</tr>
<tr>
<td>T2-weighted imaging and DCE MR imaging vs T2-weighted imaging, DW imaging, ADC maps, and DCE MR imaging</td>
<td>Sensitivity (%) &lt; 0.001, Specificity (%) = 0.004, Accuracy (%) = 0.004</td>
<td>Sensitivity (%) &lt; 0.001, Specificity (%) = 0.004, Accuracy (%) = 0.004</td>
<td>Sensitivity (%) &lt; 0.001, Specificity (%) = 0.004, Accuracy (%) = 0.004</td>
</tr>
</tbody>
</table>

Note.—Unless otherwise indicated, data are percentages, data in parentheses are proportions, and data in brackets are 95% confidence intervals. Findings are based on four reader evaluations for every patient (all six ROIs together), resulting in sensitivity denominators of 112 for 28 patients with TZ cancer, 52 for 13 patients with GG 4–5 TZ cancer, and 60 for 15 patients with GG 2–3 TZ cancer. The specificity denominator (i.e., 140) was based on 35 control patients (35x4 = 140). The accuracy denominator was based on the total number of patients with TZ cancer and control subjects per group (n = 63 for all cancer patients, denominator = 252; n = 48 for patients with GG 4–5 TZ cancer, denominator = 192; n = 50 for patients with GG 2–3 TZ cancer, denominator = 200). Readers with a score of 4 or higher for any ROI with TZ cancer were considered to have detected TZ cancer in that particular patient (numerator = 1). * For sensitivities, generalized estimating equation analyses were corrected for tumor volume. † Data are P values.
Results

Radical prostatectomy specimens revealed one TZ cancer location in 26 of 28 patients and two TZ cancer locations in two of 28 patients. Thirteen (46%) of 28 patients with TZ cancer had a GG 4–5 component, and 15 (54%) of 28 patients with TZ cancer had only a GG 2–3 pattern. The mean volume of GG 4–5 TZ tumors (8.2 cm$^3$; range, 1.5–20.9 cm$^3$) did not differ significantly from mean volume of GG 2–3 TZ tumors (4.7 cm$^3$; range, 0.5–22.0 cm$^3$; $P = .12$). Patient characteristics are depicted in Table 2. Examples of patients with endorectal MP MR imaging of GG 4–5 and GG 2–3 TZ cancers are shown in Figures 2 and 3.

The diagnostic accuracy for detection of all TZ cancers, GG 4–5 TZ cancers, and GG 2–3 TZ cancers is presented in Table 3. Findings are based on four reader evaluations for every patient, defining a reader ROI score of 4 or higher for a patient with TZ cancer in that particular ROI as a positive result. Accuracy did not differ significantly between T2-weighted imaging and MP MR imaging for (a) all TZ cancers (68% vs 66%, $P = .85$), (b) GG 4–5 TZ cancers (79% vs 72%–75%, $P = .13$), and (c) GG 2–3 TZ cancers (66% vs 62%–65%, $P = .47$). After stratification by dichotomization for median cancer volume, differences in detection rates of GG 2–3 TZ cancers versus GG 4–5 TZ cancers were not significant (for cancers ≤4 cm$^3$, detection rates were 16%–32% for GG 2–3 cancers vs 25%–50% for GG 4–5 cancers [$P = .37$ to $P = .99$]; for cancers >4 cm$^3$, detection rates were 81%–100% for GG 2–3 cancers vs 77%–91% for GG 4–5 cancers [$P = .18$ to $P = .99$]). These results are presented in Table 4.

Volumes of less frequently detected (≤1 reader) GG 2–3 TZ cancers were lower than volumes of more frequently detected (>1 reader) GG 2–3 TZ cancers. Differences were significant for T2-weighted imaging alone (1.1 vs 12.4 cm$^3$, $P = .04$) and for T2-weighted imaging and DW imaging ADC maps (0.8 vs 12.4 cm$^3$, $P = .01$). No cancer volume differences were present for less versus more frequently detected GG 4–5 TZ cancers. These results are presented in Table E1 (online). In TZ cancer localization, MP MR imaging (AUC range, 0.70–0.77) did not significantly improve T2-weighted imaging accuracy (AUC = 0.72, $P < .05$). T2-weighted imaging and DCE MR imaging (AUC, 0.70) performed significantly worse than other MP MR imaging protocols (AUC range, 0.76–0.77; $P = .0002$–.02). Results of ROI ROC analyses are presented in Table E2 (online) and Figure 4. Interobserver agreement for TZ cancer detection was fair. Intraclass correlation coefficient values for all different multiparametric MR imaging protocols ranged from 0.33 to 0.37.
### Table 4. Comparison of Detection Rate of GG 2–3 TZ Cancer with That of GG 4–5 TZ Cancer

<table>
<thead>
<tr>
<th>MR imaging protocol</th>
<th>Without Stratification for TZ Cancer Volume</th>
<th>With Stratification for Largest TZ Cancer Volume in Every Patient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with GG 2–3 TZ Cancer (n = 15) (%)</td>
<td>Patients with GG 2–3 TZ Cancer ≤4 cm³ (n = 11) (%)</td>
<td>Patients with GG 2–3 TZ Cancer &gt;4 cm³ (n = 4) (%)</td>
</tr>
<tr>
<td></td>
<td>Patients with GG 4–5 TZ Cancer (n = 13) (%)</td>
<td>Patients with GG 4–5 TZ Cancer ≤4 cm³ (n = 2) (%)</td>
<td>Patients with GG 4–5 TZ Cancer &gt;4 cm³ (n = 11) (%)</td>
</tr>
<tr>
<td>T2-weighted imaging</td>
<td>33 (20/60) [23,46]</td>
<td>16 (7/44) [8,30]</td>
<td>81 (13/16) [56,94]</td>
</tr>
<tr>
<td></td>
<td>(39/52) [62,85]</td>
<td>(2/8) [6,60]</td>
<td>(37/44) [70,92]</td>
</tr>
<tr>
<td>T2-weighted imaging</td>
<td>42 (25/60) [30,54]</td>
<td>20 (9/44) [11,35]</td>
<td>100 (16/16) [77,100]</td>
</tr>
<tr>
<td>and DW imaging ADC maps</td>
<td>(40/52) [64,86]</td>
<td>(2/8) [6,60]</td>
<td>(38/44) [73,94]</td>
</tr>
<tr>
<td>T2-weighted imaging</td>
<td>37 (22/60) [26,49]</td>
<td>20 (9/44) [11,35]</td>
<td>81 (13/16) [56,94]</td>
</tr>
<tr>
<td>and DCE imaging</td>
<td>(37/52) [58,82]</td>
<td>(3/8) [13,70]</td>
<td>(34/44) [63,87]</td>
</tr>
</tbody>
</table>

Note.—Unless otherwise indicated, data are detection rates, data in parentheses are proportions, and data in brackets are 95% confidence intervals. Two-sided P values were calculated with the Fisher exact test. Stratification of TZ cancer volume was based on dichotomization around the median cancer volume (4 cm³). For this analysis, the largest TZ cancer volume was chosen per patient.

* Under threshold for significance (two-tailed P value < .05).
Figure 1. Flowchart for patient selection. DWI= DW MR imaging, HIFU= high-intensity focused ultrasound, PZ= peripheral zone, T2WI= T2-weighted MR imaging, TURP= transurethral resection of the prostate.
Figure 2. Images in a 70-year-old patient with a prostate-specific antigen level of 6.1 mg/L and cT1C cancer (Gleason score 3 + 4 = 7) in the right prostate present in 30% of random biopsies. TZ cancer was clearly visible at T2-weighted and MP MR imaging. Radical prostatectomy was performed.

(a) Axial endorectal T2-weighted turbo spin-echo (repetition time msec/echo time msec, 4260/99) image at midprostate level shows low homogeneous SI extending from the anterior fibromuscular stroma into the right TZ, with invasion of the peripheral zone (arrows).

(b) Axial ADC map (2500/81; b value = 0, 50, 500, and 800 sec/mm$^2$) at the same level as a. Low ADC value (mean, 440 x 10$^{-6}$ mm$^2$/sec) is present predominantly in right TZ (white arrows). In the left peripheral zone, there is a slight decrease in ADC value (black arrow).

(c) Axial T2-weighted turbo spin-echo image at same level as a, with superimposed transfer constant parametric map (38/1.35). Asymmetric enhancement of right ventral TZ and right anterior horn of peripheral zone is present (white arrows). Left peripheral zone also shows enhancement (black arrow).

(d) Axial reconstructed whole-mount-section histopathologic sample at the level of a–c shows pT3A (Gleason score 4 + 3 = 7) prostate TZ cancer in right ventral medial TZ (black outline), with cancer-negative or clean resection margins (R0). Minimal ventral extraprostatic extension (2.5 mm) of this tumor was present (arrow). Next to TZ cancer, Gleason 3 + 4 and 3+3 tumors were present in right and left peripheral zones, respectively (black outlines).
Figure 3. Images in a 64-year-old man with a prostate-specific antigen level of 6.0 mg/L and clinical stage T2 prostate cancer (Gleason score, 3 + 3) diagnosed in three of six random biopsy cores in up to 15 volume-percent of every core on the left side; regions suspicious for TZ cancer are depicted less clearly than in Figure 2. (a) Axial endorectal T2-weighted turbo spin-echo image (5200/99) at midprostate level shows a low-SI area in right lateral ventral TZ with irregular growth pattern and a low-SI area in left TZ, which tends to grow anteriorly (white arrows). Furthermore, low-SI area is present in left peripheral zone (black arrow). (b) Axial ADC map (4000/81; b value = 0, 50, 500, and 800 sec/mm²) at same level as a. Areas with low ADC values are present in right (mean ADC, 996 x 10⁻⁶ mm²/sec) and left (mean ADC, 861 x 10⁻⁶ mm²/sec) ventral lateral TZ (black arrows). Left peripheral zone (white arrow) also has decreased ADC value (mean ADC, 674 x 10⁻⁶ mm²/sec). (c) Axial T2-weighted turbo spin-echo MR image at same level as a, with superimposed transfer constant parametric map (38/1.35). Symmetric diffuse enhancement of TZ, not matching areas suspicious for cancer in a and b, is present (black arrows). Left peripheral zone shows asymmetric enhancement (white arrow). (d) Axial reconstructed whole-mount-section histopathologic sample at level of a–c shows multifocal pT2CN0 (Gleason score, 2 + 3 = 5) prostate TZ cancer in right and left ventral lateral TZ (black outline) with cancer-negative resection margins (R0). In left peripheral zone, Gleason 3 + 3 cancer was present next to a small focus of Gleason 3 + 3 cancer in right peripheral zone (black outlines).
CHAPTER 3

Discussion

Our results indicate that 3-T MP MR imaging consisting of T2-weighted imaging, low-\(b\)-value (<1000 sec/mm\(^2\)) DW imaging ADC maps, and DCE MR imaging may not improve TZ cancer detection and localization accuracy compared with those achieved with 3-T T2-weighted imaging alone.

Our results for MP MR imaging are in agreement with those of Delongchamps et al (10), who found no added value of endorectal MP MR imaging compared with T2-weighted imaging for TZ cancer detection and localization at 1.5 T. For TZ cancer detection, MP MR imaging increased the rather low T2-weighted imaging sensitivity; however, it decreased specificity compared with that attained with T2-weighted imaging. Both DCE MR imaging and DW imaging may have false-positive results due to the difficulty of discriminating prostate cancer from BPH. With DCE MR imaging, this difficulty is due to BPH hypervascularity (24). With DW imaging, it is caused by low ADC values of stromal BPH, which may overlap with those of TZ cancer (14). T2-weighted imaging specificity may be higher, as differentiation of TZ cancer from BPH is not based on image (quantitative) SI differences only, but merely on anatomic characteristics of TZ cancer, such as growth pattern, structure, and shape, which are different from those of BPH (8).

The TZ cancer detection accuracy of all TZ cancers for T2-weighted imaging and DW imaging ADC maps (66%) in our study was lower than that reported in prior studies (8,10–12). A potential reason for better combined T2-weighted imaging and DW imaging ADC maps detection accuracy results of some studies (accuracy range, 62%–81%) was the use of higher \(b\) values (≥1000 sec/mm\(^2\)) (12,13). Our results are in agreement with those of studies in which the \(b\) value was less than 1000 sec/mm\(^2\) (10,11). Furthermore, the lack of a fixed ADC window level range may further explain our lower detection accuracy for T2-weighted imaging and ADC compared with the results of Haider et al (11) (accuracy, 81%). For the T2-weighted and DCE MR imaging combination (accuracy, 66% for all TZ cancers), our results are comparable with those of Yoshizako et al (12) at 1.5 T (sensitivity, 69%; specificity, 68%; accuracy, 69%). However, our results differ from those of Delongchamps et al (10). They reported a sensitivity of 47% and a specificity of 77% for TZ cancer detection; their lower sensitivity (56% in our study) may be explained by their lower field strength of 1.5 T. Mean cancer volume of GG 2–3 cancers versus GG 4–5 cancers did not differ significantly. Our patient population may have been too small to enable us to detect a significant difference. Also in TZ cancers of comparable volume, detection
rates of GG 2–3 and GG 4–5 cancers did not differ significantly. This may also have been caused by our small number of patients. However, differences in T2-weighted imaging and MP MR imaging detection rates for GG 2–3 TZ cancers versus GG 4–5 TZ cancers were influenced by cancer volume. Especially for GG 2–3 TZ cancers, the cancers detected by only one reader had significantly smaller or nearly significantly smaller volumes than those that were detected by more readers. These results agree with the findings of Akin et al (8), who also showed that TZ cancer detection was influenced by cancer volume.

For localization of all TZ cancers, GG 2–3 TZ cancers, and GG 4–5 TZ cancers, MP MR imaging did not improve accuracy. Moreover, the addition of DCE MR imaging to T2-weighted imaging significantly decreased localization accuracy in comparison with that of (a) T2-weighted imaging and DW imaging ADC maps and/or (b) T2-weighted imaging, DW imaging ADC maps, and DCE MR imaging. A possible explanation for poor results after addition of DCE MR imaging may be the false-positive enhancement due to similar enhancement of prostate cancer and BPH (23). Our localization accuracy of T2-weighted imaging only (AUC, 0.72) was lower than the localization accuracy of most other studies (AUC, 0.79–0.84) (10,11). A possible explanation is that in those studies, images were read by only highly experienced radiologists. Furthermore, Delongchamps et al (10) used a smaller section thickness (1 mm) than we did (3 mm). Our TZ cancer localization accuracy for combined T2-weighted imaging and DW imaging ADC maps (AUC, 0.76) was comparable to that obtained by Haider et al (AUC, 0.78) (11); however, it was lower than that obtained by Delongchamps et al (AUC, 0.88) (10). Delongchamps et al (10) used quantitative thresholds, which may explain their higher combined T2-weighted imaging and DW imaging ADC maps localization performance. Our results for T2-weighted and DCE MR imaging (AUC, 0.70) and for T2-weighted imaging, DW imaging ADC maps, and DCE MR imaging localization (AUC, 0.77) are comparable with those of Delongchamps et al (10) (AUC = 0.70 for T2-weighted imaging and DCE MR imaging, AUC = 0.75 for MP MR imaging).
Figure 4. Receiver operating characteristic curves of the different MP MR imaging protocols for localization of (a) all TZ cancers, (b) GG 4–5 TZ cancers, and (c) GG 2–3 TZ cancers. MP MR imaging did not significantly increase TZ cancer localization accuracy compared with that attained with T2-weighted imaging (T2WI). T2-weighted and DCE MR imaging performed worse than T2-weighted imaging alone, T2-weighted imaging and DW imaging ADC maps, and T2-weighted imaging, DW imaging ADC maps, and DCE MR imaging. For all TZ cancers (a) and for GG 2–3 TZ cancers (c), differences were significant for T2-weighted imaging and DW imaging ADC maps (AUC = 0.76, \( P = .02 \) for all TZ cancers; AUC = 0.71, \( P = .03 \) for GG 2–3 TZ cancers) and for T2-weighted imaging, DW imaging ADC maps, and DCE MR imaging (AUC = 0.77, \( P < .001 \) for all TZ cancers; AUC = 0.70, \( P = .01 \) for GG 2–3 TZ cancers) versus T2-weighted imaging and DCE MR imaging (AUC = 0.70 for all TZ cancers, AUC = 0.62 for GG 2–3 TZ cancers). For GG 4–5 TZ cancers (b), T2-weighted imaging and DCE MR imaging (AUC = 0.78) only performed significantly worse compared with T2-weighted imaging, DW imaging ADC maps, and DCE MR imaging (AUC = 0.84, \( P = .002 \)). Diagonal black line = reference line of 0.50 AUC. Data below the threshold for significance (two-tailed \( P \) value, .05) (*) are indicated.
Our study had limitations. First, because of the small population, our study may have had insufficient power to enable us to detect a difference between T2-weighted imaging and MP MR imaging in the detection and localization of TZ cancers. Second, we did not use high-b-value DW imaging and ADC threshold values for TZ cancer. Use of quantitative ADC thresholds may have its shortcomings, as ADC values are subject to inter- and intrapatient variation (25). At the time of image reading, we did not calculate high-b-value trace images. Our performance of qualitative image assessment only may have negatively influenced results for interobserver agreement and reliability. Third, to use the optimal reference standard, we selected only those patients who underwent prostatectomy. This may have introduced selection bias into our results, as in many patients with TZ cancer surgery is not performed. Fourth, the median TZ cancer lesion volume of 4.40 mL (range, 0.52–21.99 mL) was larger than that in the study of Akin et al (8) (median 0.77 mL; range, 0.0015–16.2 mL) and that of Yoshizako et al (12) (range, 10–28 mm). Our larger TZ cancer volumes may have positively influenced T2-weighted imaging detection and localization accuracies. Fifth, reproducibility and reliability of our results were limited, as our interobserver agreement was only fair. A possible explanation may be the difference in experience between readers for different MP MR imaging techniques in the prostate TZ.

Our results imply that there is ample room for improvement of MP MR imaging techniques for accurate TZ evaluation. Studies on MP MR imaging (including high-b-value DW imaging) with increased spatial resolution are needed to improve detection and localization of TZ cancers. Furthermore, false-positive MP MR imaging readings may be reduced by training radiologists in recognition of cancer-specific patterns rather than in quantitative evaluation of the TZ. In the future, computer-aided diagnosis may have an important supportive role in pattern recognition in the detection and localization of TZ cancers. In conclusion, 3-T MP MR imaging, which consists of T2-weighted imaging and low-b-value (<1000 sec/mm²) DW MR imaging ADC maps and/or DCE MR imaging, may not improve TZ cancer detection and localization accuracy compared with 3-T T2-weighted imaging alone.
CHAPTER 3

References


Appendix

Table E1. Differences in Mean Cancer Volume for Less versus More Frequently Detected Gleason Grade 2-3 and 45 Transition Zone Cancers

<table>
<thead>
<tr>
<th>Multiparametric MR imaging Protocol</th>
<th>Median Cancer Volume in GG 2-3 TZ Cancers Detected ≤ 1 Reader (mL)</th>
<th>Median Cancer Volume in GG 2-3 TZ Cancers Detected &gt; 1 Reader (mL)</th>
<th>P-value *</th>
<th>Median Cancer Volume in GG 4-5 TZ Cancers Detected ≤ 1 Reader (mL)</th>
<th>Mean Cancer Volume in GG 4-5 TZ Cancers Detected &gt; 1 Reader (mL)</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-weighted MR imaging</td>
<td>1.1 (0.5-2.6)</td>
<td>12.4 (7.8-12.4)</td>
<td>0.04</td>
<td>2.51 (1.6-2.51)</td>
<td>9.2 (8.0-12.2)</td>
<td>0.31†</td>
</tr>
<tr>
<td>T2-weighted MR imaging and DW imaging ADC maps</td>
<td>0.8 (0.5-2.2)</td>
<td>12.4 (4.5-17.3)</td>
<td>0.01</td>
<td>11.3 (1.6-11.3)</td>
<td>8.5 (6.4-11.0)</td>
<td>0.84†</td>
</tr>
<tr>
<td>T2-weighted and DCE MR imaging</td>
<td>1.2 (0.5-2.4)</td>
<td>10.0 (1.0-14.9)</td>
<td>0.05</td>
<td>11.3 (1.6-11.3)</td>
<td>8.5 (6.4-11.0)</td>
<td>0.84†</td>
</tr>
<tr>
<td>T2-weighted MR imaging, DW imaging ADC maps and DCE MR imaging</td>
<td>0.75 (0.5-2.6)</td>
<td>7.9 (1.1-12.6)</td>
<td>0.06</td>
<td>1.60 (NA)†</td>
<td>9.2 (6.9-14.5)</td>
<td>0.11†</td>
</tr>
</tbody>
</table>

Note.—Data in parentheses are the interquartile range. P <.05 indicates a significant difference. ADC = apparent diffusion coefficient, DCE = dynamic contrast material–enhanced, DW = diffusion weighted, GG = Gleason grade, TZ = transition zone. * P values were obtained with the Mann-Whitney U test. In patients with at least one TZ tumor, the tumor with the largest cancer volume was included.† As the number of less frequently (≤1 reader) detected GG 4-5 TZ cancers was small (n = 1-2), results should be interpreted carefully. ‡ There was only one patient. NA = not applicable.
Table E2. Results of Region of Interest Receiver Operating Characteristics Curve Analyses for Localization of All TZ Cancers, GG 4-5 TZ Cancers, and GG 2-3 TZ Cancers.

<table>
<thead>
<tr>
<th>Multiparametric MR imaging Protocol</th>
<th>Localization of all TZ Cancers</th>
<th>Localization of GG 4-5 TZ cancers</th>
<th>Localization of GG 2-3 TZ cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-weighted MR imaging</td>
<td>0.72 (0.66-0.78)</td>
<td>0.81 (0.73-0.89)</td>
<td>0.64 (0.55-0.73)</td>
</tr>
<tr>
<td>T2-weighed MR and DW imaging ADC maps</td>
<td>0.76 (0.70-0.82)</td>
<td>0.81 (0.73-0.90)</td>
<td>0.71 (0.62-0.79)</td>
</tr>
<tr>
<td>T2-weighted and DCE MR imaging</td>
<td>0.70 (0.64-0.77)</td>
<td>0.78 (0.70-0.87)</td>
<td>0.62 (0.52-0.72)</td>
</tr>
<tr>
<td>T2-weighed, DW ADC maps and DCE MR imaging</td>
<td>0.77 (0.71-0.83)</td>
<td>0.84 (0.77-0.92)</td>
<td>0.70 (0.61-0.78)</td>
</tr>
<tr>
<td>Significant differences</td>
<td>X²(3)=17.37, P&lt;.001</td>
<td>X²(3)=10.25, P=0.02</td>
<td>X²(3)=10.67, P=0.01</td>
</tr>
</tbody>
</table>

Note.—Data in parentheses are 95% confidence intervals. Region of interest (ROI) receiver operating characteristics (ROC) curve values were compared by using a generalized estimation equation. Pearson $\chi^2$ tests were used to test for differences in ROI ROC values between MR imaging protocols. All significant differences indicate T2-weighted and DCE MR imaging to have a significantly lower area under the ROC curve compared with other MP MR imaging sessions.
Diffusion Weighted Magnetic Resonance Imaging in the Prostate Transition Zone: Histopathological Validation using Magnetic Resonance-Guided Biopsy Specimens

Caroline M.A. Hoeks, MD
Eline K. Vos, MD
Joyce G.R. Bomers, MSc
C. Hulsbergen-van de Kaa, MD PhD
Jelle O. Barentsz, MD PhD
Tom W.J. Scheenen, MSEE PhD

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Abstract:

Objectives: The objective of this study was to evaluate the apparent diffusion coefficient (ADC) of diffusion-weighted magnetic resonance (MR) imaging for the differentiation of transition zone cancer from non-cancerous transition zone with and without prostatitis and for the differentiation of transition zone cancer Gleason grade (GG) using MR-guided biopsy specimens as a reference standard.

Materials and Methods: From consecutive MR-guided prostate biopsies (2008-2012) in our referral center, we retrospectively included patients from whom diffusion-weighted MR imaging ADC values were acquired during MR-guided biopsy and whose biopsy cores had a (cancer) core length 10 mm or greater and originated from the transition zone. Two radiologists, who were blinded to the ADC data, annotated regions of interest on biopsy sampling locations of MR-guided biopsy confirmation scans in consensus. Median ADC (mADC) of the regions of interest was related to histopathology outcome in MR-guided biopsy core specimens. Mixed model analysis was used to evaluate mADC differences between 7 histopathology categories predefined as MR-guided biopsy core specimens with primary and secondary GG 4Y5 (I), primary GG 4-5 secondary GG 2-3 (II), primary GG 2-3 secondary GG 4-5 (III) and primary and secondary GG 2-3 cancer (IV), and noncancerous tissue without (V) or with degree 1 (VI) or degree 2 prostatitis (VII). Diagnostic accuracy was evaluated using areas under the receiver operating characteristic (AUC) curve.

Results: Fifty-two patients with 87 cancer-containing biopsy cores and 53 patients with 101 non-cancerous biopsy cores were included. Significant mean mADC differences were present between cancers (mean mADC, 0.77-0.86×10⁻³ mm²/s) and noncancerous transition zone without (1.12×10⁻³ mm²/s) and with degree 1 to 2 prostatitis (1.05-1.12×10⁻³ mm²/s; P <0.0001-0.05). Exceptions were mixed primary and secondary GG cancers versus a degree 2 of prostatitis (P = 0.06-0.09). No significant differences were found between subcategories of primary and secondary GG cancers (P = 0.17-0.91) and between a degree 1 and 2 prostatitis and non-cancerous transition zone without prostatitis (P = 0.48-0.94).

The mADC had an AUC of 0.84 to differentiate cancer versus non-cancerous transition zone. AUCs of 0.84 and 0.56 were found for mADC to differentiate prostatitis from cancer and from non-cancerous transition zone. The mADC had an AUC of 0.62 to differentiate a primary GG 4 versus GG 3 cancer.

Conclusions: The mADC values can differentiate transition zone cancer from non-cancerous transition zone and from a degree 1, and from most cases of a degree 2 prostatitis.
prostatitis. However, because of substantial overlap, mADC has a moderate accuracy to differentiate between different primary and secondary GG subcategories and cannot be used to differentiate non-cancerous transition zone from degrees 1 to 2 of prostatitis. Diffusion-weighted imaging ADC may therefore contribute in the detection of transition zone cancers; however, as a single functional MR imaging technique, diffusion-weighted imaging has a moderate diagnostic accuracy in separating higher from lower GG transition zone cancers and in differentiating prostatitis from non-cancerous transition zone.
Introduction

Prostate cancer is the second most frequently diagnosed cancer in men worldwide (1). Based on radical prostatectomy and saturation biopsy specimens, at least 30% to 45% of diagnosed cancers are situated in the prostate transition zone (2,3). In patients with an elevated prostate-specific antigen (PSA) and cancer-negative transrectal ultrasound-guided biopsies, high proportions of transition zone cancer (57%-63%) are detected upon magnetic resonance (MR)-guided biopsy (4,5). The latter finding reflects that many transition zone cancers are missed by transrectal ultrasound-guided biopsy, probably because of undersampling of the ventral prostate transition zone. Performing MR imaging (6) and MR-guided biopsy in patients with an elevated PSA and negative transrectal ultrasound-guided biopsies may therefore improve detection of transition zone prostate cancer. However, upon MR imaging of the prostate transition zone, differentiation of prostate cancer from healthy tissue is difficult because of the overlap of signal intensities and quantitative parameters between prostate cancer and stromal benign prostatic hyperplasia (7,8). Prostate cancer should also be differentiated from prostatitis, which is often present also in the transition zone (9). In prostatitis, inflammatory infiltrates may increase cellular density and may therefore decrease T2-weighted MR imaging signal intensity and diffusion-weighted MR imaging apparent diffusion coefficient (ADC) values. For the peripheral zone, prostatitis can be differentiated from healthy tissue and from low-Gleason grade (GG) cancer; however, for the transition zone, differentiation of prostatitis from a high-GG cancer and from healthy tissue has not been described earlier (10).

Once a transition zone cancer is detected on MR imaging, accurate determination of its Gleason score is important because transition zone cancers are known to have lower Gleason scores and lower biochemical recurrence rates (11). Lower diffusion-weighted imaging ADC values have been related to higher prostate cancer Gleason scores, predominantly for peripheral zone cancers (12,13). Most of these studies have been performed using radical prostatectomy specimens as a reference standard. However, exact alignment of MR imaging slices with prostatectomy specimen sections remains difficult because of differences in angulations of imaging slicing and specimen sectioning and because of prostate shrinkage during histopathology processing. Furthermore, observer bias is almost unavoidable in attributing a certain region of interest (ROI) on MR imaging to a tumor, which is identified in a prostatectomy specimen section (14). Recently, size
and positioning of an ROI were shown to influence tumor ADC measurements and interobserver variability in rectal cancer (15).

Magnetic resonance-guided biopsy specimens may be a reference-standard alternative for radical prostatectomy specimens because the highest GG of an MR-guided biopsy specimen has a high concordance (88%) with the highest GG of the radical prostatectomy specimen (16). This high concordance rate is caused by the ability of multiparametric MR imaging and especially of diffusion-weighted MR imaging to predict and localize the cancer areas with the highest GG (17). When using MR-guided biopsy as a reference standard, T2*-weighted gradient echo images, which confirm needle positioning, are available (5). Locations where prostate cancer biopsy specimens were sampled can be determined from signal voids of the biopsy needle on these MR-guided biopsy confirmation scans. Because annotation of biopsy sampling areas on confirmation scans is unrelated to the ADC map, it may reduce observer bias in relating ADC values to MR-guided biopsy histopathology.

Therefore, our purpose was to evaluate the ADC of diffusion-weighted MR imaging for the differentiation of the transition zone cancer from the non-cancerous transition zone with and without prostatitis and for the differentiation of transition zone cancer GGs using MR-guided biopsy specimens as a reference standard.

Materials and methods

Patients

The need for informed consent for this retrospective study was waived by the institutional review board. From all consecutively performed MR-guided biopsies between March 2008 and February 2012 in our referral center, we included patients using the following inclusion criteria:

- Performed diffusion-weighted imaging and ADC maps as part of the MR-guided biopsy procedure.
- Magnetic resonance-guided biopsy cores with prostate cancer in a cancer core length of 10 mm or greater and a transition zone location on MR-guided biopsy confirmation scans. A cancer core length of 10 mm or greater is 60% of a standard needle notch length of 17 mm and was chosen to limit variation because of mADC measurements in noncancerous tissue. By choosing this limit, at least 60% of the annotated ROI was related to prostate cancer.
• Magnetic resonance-guided biopsy cores without prostate cancer with a core length of 10 mm or greater and a transition zone location of the needle sample on MR-guided biopsy confirmation scans.

The exclusion criteria were an existing diagnosis of prostate cancer before the MR-guided biopsy (n = 50) or unavailable biopsy histopathology specimens from external hospitals (n = 5). Also, needle positions for which MR-guided biopsy core identification was impossible were excluded. The latter was caused by simultaneous unspecified sampling of more cores referred for histopathology analysis as 1 sample unit (n = 22) or caused by a lack of MR-guided biopsy confirmation scans with needle artifacts (n = 1) or caused by impossible accurate registration of the ADC map to the confirmation scans (n = 1). Patient selection is depicted in a flow diagram in Figure 1.
Figure 1. Study flow-diagram. ADC indicates apparent diffusion coefficient in diffusion weighted MR imaging; DWI, diffusion-weighted MR imaging; MRGB, MR guided prostate biopsy; n, number of patients; PSA, prostate specific antigen.

MR imaging and MR guided biopsy acquisition

Two 3-T whole-body systems (MAGNETOM Trio and MAGNETOM Skyra; Siemens Medical Solutions, Erlangen, Germany) were used to perform MR imaging and MR-guided biopsy. An MR compatible manual biopsy device, an endorectal needle
guider, and an 18-gauge biopsy gun (all from Invivo, Gainesville, FL) were used to perform the MR-guided biopsy. To detect prostate cancer, MR-guided biopsies were performed on the basis of the results of a previously performed multiparametric MR imaging examination, consisting of T2-weighted, diffusion-weighted, and dynamic contrast-enhanced MR imaging (5). The multiparametric MR imaging and MR-guided biopsy sequence parameters are depicted in Table 1. Two radiologists with 10 and 19 years of experience in prostate MR imaging (J.J.F. and J.O.B.) evaluated the initial MR images on a clinical software workstation while having access to patient data (18). Cancer suspicious regions were defined as described earlier (19).

The patients received antibiotic prophylaxis of 2 daily doses of 500-mg ciprofloxacin orally for 3 days and the biopsy was performed on the second day. Biopsies were performed by 1 radiologist with 3 years (C.M.A.H.), 1 radiologist with 2 years (J.G.R.B.), and 1 radiologist (E.K.V.) with 1 year of experience in MR-guided biopsy (19). Initially, T2-weighted MR imaging and diffusion-weighted imaging were performed for the re-identification of previously defined cancer suspicious regions. Consequently, sagittal and axial balanced gradient echo sequences were acquired during the repositioning of an endorectally inserted needle guide towards a cancer-suspicious region. When the needle guide was accurately targeted at a cancer-suspicious region, biopsies were taken by insertion of the 18-gauge needle biopsy gun (In vivo, Schwerin, Germany) through the needle guide. Directly after the MR-guided biopsy with the needle situated in the prostate, gradient echo sequences were repeated to confirm the position of the (sampling part of the) needle in a cancer-suspicious region. Acquisition times for the transverse and sagittal confirmation scans for MAGNETOM Trio and Skyra were 8.9 and 9.0 seconds for the axial scans and 7.5 and 7.6 seconds for the sagittal scans, respectively.
Table 1. MR imaging and MR guided biopsy parameters

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Sequence</th>
<th>TA (min:s)</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Flip angle (degrees)</th>
<th>Slice thickness (mm)</th>
<th>Field of view (mm x mm)</th>
<th>Matrix size (mm x mm x mm)</th>
<th>Voxel size (mm x mm x mm)</th>
<th>b-values (s/mm^2)</th>
<th>Temporal resolution (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiparametric MR imaging (Siemens Trio Tim) using the 32-channel spinal and pelvic phased array coils.</td>
<td>T2W MR imaging</td>
<td>3:33</td>
<td>4950</td>
<td>110</td>
<td>120</td>
<td>3.0</td>
<td>180x180</td>
<td>320x320</td>
<td>0.6x0.6x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>axial TSE sagittal</td>
<td>3:22</td>
<td>4480</td>
<td>103</td>
<td>120</td>
<td>3.0</td>
<td>180x180</td>
<td>320x320</td>
<td>0.6x0.6x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>coronal</td>
<td>1:55</td>
<td>4250</td>
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<tr>
<td></td>
<td>DWI EPI</td>
<td>3:08</td>
<td>2500</td>
<td>64</td>
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<td>4.0</td>
<td>256x256</td>
<td>128x128</td>
<td>2.0x2.0x4.0</td>
<td>50/500/800</td>
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</tr>
<tr>
<td>DCE-MRI</td>
<td>3D Ultrafast GE</td>
<td>2:43</td>
<td>32*</td>
<td>147</td>
<td>10</td>
<td>4.0</td>
<td>230230</td>
<td>128x128</td>
<td>1.8x1.8x4.0</td>
<td>n.a.</td>
<td>4.7</td>
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<tr>
<td></td>
<td>Axial</td>
<td>2.43</td>
<td>32*</td>
<td>147</td>
<td>10</td>
<td>4.0</td>
<td>230230</td>
<td>128x128</td>
<td>1.8x1.8x4.0</td>
<td>n.a.</td>
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<tr>
<td>Multiparametric MR imaging (Siemens Magnetom Skyra)</td>
<td>T2W MR imaging</td>
<td>2.53</td>
<td>3510</td>
<td>101</td>
<td>160</td>
<td>3.0</td>
<td>180x180</td>
<td>320x320</td>
<td>0.6x0.6x3.0</td>
<td>n.a.</td>
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</tr>
<tr>
<td></td>
<td>axial TSE sagittal</td>
<td>2.45</td>
<td>5400</td>
<td>104</td>
<td>160</td>
<td>3.0</td>
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<td>384x384</td>
<td>0.5x0.5x3.0</td>
<td>n.a.</td>
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<tr>
<td></td>
<td>coronal</td>
<td>1:57</td>
<td>4320</td>
<td>101</td>
<td>160</td>
<td>3.0</td>
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<td>0.6x0.6x3.0</td>
<td>n.a.</td>
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<tr>
<td></td>
<td>DWI EPI</td>
<td>3:29</td>
<td>2700</td>
<td>63</td>
<td>128</td>
<td>3.0</td>
<td>256x256</td>
<td>128x128</td>
<td>2.0x2.0x3.0</td>
<td>50/500/800</td>
<td>n.a.</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>3D Ultrafast GE</td>
<td>2:34</td>
<td>36*</td>
<td>141</td>
<td>14</td>
<td>3.0</td>
<td>192x192</td>
<td>128x128</td>
<td>1.5x1.5x3.0</td>
<td>n.a.</td>
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<tr>
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<td>2.34</td>
<td>36*</td>
<td>141</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>4.7</td>
</tr>
<tr>
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<td>T2w MR imaging</td>
<td>3.35</td>
<td>4570</td>
<td>101</td>
<td>120</td>
<td>3.0</td>
<td>256x256</td>
<td>320x320</td>
<td>1.1x0.8x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
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<tr>
<td></td>
<td>Axial</td>
<td>3.35</td>
<td>4570</td>
<td>101</td>
<td>120</td>
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<td>256x256</td>
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<tr>
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<td>DWI EPI</td>
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<td>4.0</td>
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<td>50/500/800</td>
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<tr>
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<td>448</td>
<td>22.4</td>
<td>70</td>
<td>3.0</td>
<td>256x256</td>
<td>320x320</td>
<td>1.1x1.1x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
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<tr>
<td></td>
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<td>0:08</td>
<td>44.8</td>
<td>22.4</td>
<td>70</td>
<td>3.0</td>
<td>256x256</td>
<td>320x320</td>
<td>1.1x1.1x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>MRGB (Siemens Magnetom Skyra)</td>
<td>T2w MR imaging</td>
<td>3.32</td>
<td>4510</td>
<td>101</td>
<td>120</td>
<td>3.0</td>
<td>256x256</td>
<td>320x320</td>
<td>0.8x0.8x3.0</td>
<td>n.a.</td>
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<tr>
<td></td>
<td>Axial</td>
<td>3.32</td>
<td>4510</td>
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<td>120</td>
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<td>256x256</td>
<td>320x320</td>
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<td>n.a.</td>
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<td></td>
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<td>50/500/800</td>
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<td></td>
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<td>22.8</td>
<td>70</td>
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<td>320x320</td>
<td>1.1x1.1x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
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<tr>
<td></td>
<td>Sagittal GE</td>
<td>0.09</td>
<td>45.6</td>
<td>22.8</td>
<td>70</td>
<td>3.0</td>
<td>256x256</td>
<td>320x320</td>
<td>1.1x1.1x3.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

*All partitions.

2D indicates 2-dimensional; 3D, 3-dimensional; DWI, diffusion-weighted magnetic resonance imaging; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; EPI, echo-planar imaging; GE, gradient echo; MR, magnetic resonance; SSEPI, steady-state echo planar imaging; SSFP, steady state free procession; T2w MR imaging, T2-weighted magnetic resonance imaging; TA, acquisition time; TE, echo time; TR, repetition time; TSE, turbo spin echo.
Histopathology

Biopsy core specimens were directly fixated in formalin. The cores were fixated and analyzed separately. All cores were histopathologically re-evaluated by 1 experienced urogenital pathologist with 20 years of experience (C.A.H.), who was blinded to the MR imaging results. Gleason grade was evaluated using the 2005 International Society of Urological Pathology-modified Gleason grading criteria (20). Prostatitis was defined as the presence of inflammatory infiltrates in the prostate (21). A degree 1 (mild), 2 (moderate), and 3 (severe) prostatitis were respectively defined as follows: an MR-guided prostate biopsy specimen core tissue area involvement of 1 lower than 10% by inflammatory cell infiltrates consisting of individual cells, separated by distinct intervening spaces (<100 cells/mm²), 2 10% to 50% consisting of confluent sheets of inflammatory cells with no tissue destruction or lymphoid nodule or follicle formation (100-500 cells/mm²), 3 greater than 50% consisting of confluent sheets of inflammatory cells with tissue destruction or nodule/follicle formation (>500 cells/mm²) (21). Differentiation was made between chronic, chronic active, and granulomatous prostatitis (21).

Annotation of MR guided biopsy confirmation scans

Magnetic resonance-guided biopsy confirmation scans were analyzed with an in-house-developed software (18). Two radiologists (one with 3 years [C.M.A.H.] and one with 1 year [E.K.V.] of experience in prostate MR imaging) annotated ROIs in consensus while they were blinded for histopathology results. In case of prostate displacement during the MR-guided biopsy procedure, the ADC maps were manually registered with the post-biopsy confirmation scans to correct for this displacement. Slices that most optimally represented the middle of the needle artifact were identified on both the sagittal and the transversal post-biopsy T2-weighted balanced gradient echo images. Subsequently, the presumed in vivo needle track of 22 mm was measured from the visible needle tip inside the signal void, taking into account a signal void of the needle artifact (2-3 mm) in front of the needle trajectory. The last 17 mm of this 22 mm represented the needle notch, where the tissue core was obtained. This last 17 mm area was annotated on the transverse T2-weighted balanced-gradient echo image. The notch length of 17 mm was annotated with overlapping ROIs (4.0×4.0×4.0 mm) matching the visible needle within the artifact signal void. An example of our annotation method is depicted in Figure 2. The radiologists annotated all cores over the entire core length (17 mm) in all patients. In patients in whom the core sample involved extraprostatic tissue, only the core parts situated in the prostate
were annotated. All ROIs of 1 notch length represented 1 core and were analyzed as a unit. For every annotated core, the mean, the SD, and the median ADC (mADC) were calculated by the software using the ADC values from all annotated ROIs in the core.

Statistics
The analyses were performed using Predictive Analytics SoftWare (PASW) Statistics version 18 (SPSS, Inc, Quarry Bay, Hong Kong). The threshold for significance was defined as P < 0.05. Differences in patient characteristics were evaluated using independent t tests for parametric continuous variables and the Mann-Whitney test for non-parametric continuous variables.

The ROI ADC was related to the histopathology outcome in MR-guided biopsy specimens, which served as a reference standard. Linear multilevel mixed model analysis was used to evaluate mADC differences for 7 histopathology categories, defined as MR-guided biopsy core specimens with a primary and secondary GG 4-5 (I), primary GG 4-5 secondary GG 2-3 (II), a primary GG 2-3 secondary GG 4-5 (III) and primary and secondary GG 2-3 cancer (IV) cancer, and noncancerous transition zone tissue without (V) or with degree 1 prostatitis (VI) or degree 2 prostatitis (VII).

To correct for possible correlations between different cores coming from 1 patient, patients were used as a random factor in this model. Because non-cancerous parts in cancer-containing cores may have caused mADC variation, we compared mADC for cancer core lengths of respectively 10 to 12, 13 to 15, and greater than 15 mm.

Receiver operating characteristic (ROC) analyses were performed to evaluate diagnostic accuracy for mADC to differentiate between predefined histopathological categories.

Results
We included 87 MR-guided biopsy cores containing transition zone cancer in 52 patients and 101 non-cancerous transition zone cores in another 53 patients. Patient characteristics are depicted in Table 2. For every patient, MR-guided biopsy cores were taken from 1 cancer-suspicious region. A patient example is depicted in Figure 3. Of the 87 cancer-containing cores, 27 cores had a primary and secondary GG 4-5, 12 cores had a primary GG 4-5 and a secondary GG 2-3, 24 cores had a primary GG 2-3 and a secondary GG 4-5, and another 24 cores had both primary and secondary GG 2-3. Of the 101 non-cancerous transition zone cores, 46 cores
existed out of healthy transition zone tissue without prostatitis, 50 cores contained a degree 1 prostatitis (of which 88% [44/50] were of a chronic type and 12% [6/50] were of a chronic active type), and 5 cores involved prostatitis up to a degree of 2 (2 of the chronic and 3 of the chronic active type). Because the subtotals of cores with a chronic (active) type of prostatitis were very small, no further analyses were performed to differentiate between the chronic and chronic active types of prostatitis. For patients with transition zone cancer, MR-guided biopsy core lengths ranged from 12.0 to 16.0 mm (interquartile range) and were invaded by cancer (cancer core length) in a length of (interquartile range) 11.0 to 14.0 mm. Core length of the non-cancerous MR-guided biopsy specimens ranged from 10.3 to 15.0 mm. Upon linear mixed model analysis, significant mADC differences were present between transition zone cancers (mean mADC, \(0.77-0.86 \times 10^{-3}\) mm\(^2\)/s) and non-cancerous transition zone without \((1.12 \times 10^{-3}\) mm\(^2\)/s) and with degrees 1 to 2 prostatitis \((1.05-1.12 \times 10^{-3}\) mm\(^2\)/s; \(P<0.0001-0.05\)). The exceptions were transition zone cancers with a primary GG 4-5 and a secondary GG 2-3 or a primary GG 2-3 and a secondary GG 4-5 versus a degree 2 of prostatitis \((P = 0.06-0.09)\). No significant differences were found between subcategories of transition zone cancer primary and secondary GG \((P = 0.17-0.91)\) and between healthy transition zone without prostatitis versus both degree 1 and 2 prostatitis \((P = 0.48-0.94)\). In Figure 4, boxplots of mADC values for MR guided biopsy specimen histopathological categories are presented. Comparing the cores with a Gleason score 3+3 \((n = 14)\) versus a Gleason score 4+4 \((n = 6)\) only, the mean ADC values were \(0.85 \times 10^{-3}\) mm\(^2\)/s (95% confidence interval[CI], 0.70-0.99\( \times 10^{-3}\) mm\(^2\)/s) and \(0.79 \times 10^{-3}\) mm\(^2\)/s (CI, 0.57-1.01\( \times 10^{-3}\) mm\(^2\)/s), respectively \((P = 0.66)\). Because only 1 core had a single GG 5 pattern, this core was left out of the analysis. For cancer-containing cores, a scatterplot depicting mADC values for different Gleason scores is shown in Figure 5. Taking into account the MR-guided biopsy cancer core length, no significant mADC differences were present for cancer core lengths of, respectively, 10-≤12, >12-≤15 and greater than 15 mm for patients with primary GG 3 \((P = 0.22-0.87)\), 4 \((P = 0.05-0.84)\), and 5 cancers \((P = 0.70-0.91)\). Receiver operating characteristic analysis for mADC to differentiate transition zone cancer cores \((n = 87)\) from non-cancerous transition zone cores \((n = 46)\) resulted in an AUC of 0.84 (95% CI, 0.77-0.91). For the differentiation between the cancerous \((n = 87)\) and non-cancerous cores with prostatitis \((n = 55)\), the AUC also was 0.84 (0.77-0.90). The AUC for differentiating the non-cancerous cores with any degree of prostatitis \((n = 55)\) versus the non-cancerous cores without \((n = 46)\) prostatitis was 0.56 (0.44-0.67). The mADC had an AUC of 0.62 (0.49-0.74) for the differentiation of primary GG 4-5 \((n = 39)\) from GG 2-3 \((n = 48)\) cancers.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with cores containing TZ cancer (n=52)</th>
<th>Patients with cores containing non-cancerous TZ (n=53)</th>
<th>p-value†</th>
</tr>
</thead>
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<tr>
<td>Age (yrs)</td>
<td>67 (63-71)</td>
<td>66 (61-68)</td>
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<tr>
<td>PSA (ng/mL)</td>
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<td>14.0 (9.5-20.6)</td>
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<tr>
<td>Prostate volume (mL)</td>
<td>43.0 (35.0-62.0)</td>
<td>57.3 (55.1-107.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA density (ng/mL/mL)</td>
<td>0.42 (0.28-0.70)</td>
<td>0.19 (0.09-0.32)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Previous TRUS biopsy sessions</td>
<td>3 (2-4)</td>
<td>2 (1-3)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Included MRGB cores per patient</td>
<td>2 (1-2)</td>
<td>2 (2-3)</td>
<td>n.a.</td>
</tr>
<tr>
<td>MRGB cancer core length (mm)</td>
<td>12.0 (11.0-14.0)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>MRGB total core length (mm)</td>
<td>15.0 (12.0-16.0)</td>
<td>13.0 (10.3-15.0)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Gleason score‡

| 2+4 | 1 | n.a. | n.a. |
| 3+2 | 10 | n.a. | n.a. |
| 3+3 | 14 | n.a. | n.a. |
| 3+4 | 18 | n.a. | n.a. |
| 3+5 | 5  | n.a. | n.a. |
| 4+3 | 9  | n.a. | n.a. |
| 4+4 | 6  | n.a. | n.a. |
| 4+5 | 13 | n.a. | n.a. |
| 5+3 | 3  | n.a. | n.a. |
| 5+4 | 7  | n.a. | n.a. |
| 5+5 | 1  | n.a. | n.a. |

Gleason score is given on a core basis because some patients had different Gleason scores in different magnetic resonance-guided prostate biopsy cores. Continuous parametric variables were compared with independent t tests. A significance level of P < 0.05 was used.

*The Mann-Whitney test was used to evaluate the differences between continuous non-parametric variables. †P values between the patients with magnetic resonance-guided prostate biopsy specimens containing transition zone cancer versus the patients with magnetic resonance-guided prostate biopsy specimens containing non-cancerous transition zone. ‡Numbers of MR guided biopsy core specimens. IQR indicates interquartile range; MRGB, magnetic resonance-guided prostate biopsy; n.a., not applicable; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.
Figure 2. Illustration of the annotation of an MR guided biopsy core on a T2-weighted balanced gradient echo confirmation scan. Note the appearance of the inserted needle as a large signal void, strongly exaggerating the true size of the needle (diameter 1.27 mm). (a) Measurement of the needle pathway of 22 mm in the needle artifact on a transversal T2-weighted balanced gradient echo confirmation scan (TR 4.48 ms, TE 2.24 ms). (b) Annotation of the core length (the last 17 mm of the 22 mm as depicted in (a)) with regions of interest on a transversal T2-weighted balanced gradient echo confirmation scan (TR 4.48 ms, TE 2.24 ms). This anatomical scan was used to reconfirm correct positioning of the whole needle sampling part within the prostate transition zone. (c) Completed annotation of an MR guided biopsy core. Regions of interest are appended in one unit for analysis. The location of the annotated core (IV) can be seen in the baseline diffusion weighted image (TR 3300 ms, TE 60 ms) (I), baseline T2-weighted image (TR 3620 ms, TE 103 ms) (II) and the corresponding sagittal T2-weighted balanced gradient echo confirmation scan (TR 4.48 ms, TE 2.24 ms) (III).
Figure 3. Projection of annotated cores on the MR-guided biopsy ADC maps. A 63-year-old man with a PSA of 20 ng/mL and 1 previous negative transrectal ultrasound biopsy session. During the MR-guided biopsy, a GG 3+5 prostate cancer was detected in 100% volume percent of the depicted core. A, The annotated MR-guided biopsy core on a transversal T2-weighted balanced gradient echo confirmation scan (TR, 4.48 milliseconds; TE, 2.24 milliseconds). B, Gradient echo image (A) fused with the diffusion-weighted imaging ADC map in color. The diffusion-weighted imaging ADC values within the annotated MR-guided biopsy core (black demarcations) are visible. In the middle of the core, the ADC was 0.4×10^{-3} mm^2/s, whereas, at both core ends, the ADC was 0.7-0.9×10^{-3} mm^2/s. The color scale of the ADC map on image B and C was as follows: red-pink, 0.135×10^{-3} mm^2/s or less; dark blue, 0.852×10^{-3} mm^2/s or less; light blue, 1.330×10^{-3} mm^2/s or less; and green-yellow 1.750×10^{-3} mm^2/s or less. C, The same annotated MR-guided biopsy core (black demarcations) over a sagittal projection of the diffusion-weighted imaging ADC map. D, Hematoxylin and eosin-stained tissue section of the prostate biopsy core with indications of GG at scanning magnification of ×10. This core is corresponding to the core in A to C. I to III, Higher magnifications of the different areas indicated by the boxes (×20). The lower ADC value in the middle of the core agrees with a primary GG 5 situated in between lower GGS.
Discussion

Our results show that mADC values can differentiate the transition zone cancer from the non-cancerous transition zone (AUC 0.84) and from any degree of prostatitis (AUC 0.84). However, because of substantial overlap, mADC has a poor accuracy to distinguish primary GG 4-5 from GG 2-3 transition zone cancers (AUC 0.62) and cannot be used to differentiate between noncancerous transition zone with and without prostatitis (AUC 0.56).

Our significant mADC differences for transition zone cancer versus non-cancerous transition zone confirm findings in other studies (8,13,22,23). The ADC for transition zone cancer in these studies varied between $0.61-1.13 \times 10^{-3}$ mm$^2$/s versus the ADC values for noncancerous transition zone of $1.08-1.73 \times 10^{-3}$ mm$^2$/s. In so far as the ADC values can be compared for diffusion-weighted MR imaging sequences with different b-values, our mean mADC values for both cancer ($0.77-0.86 \times 10^{-3}$ mm$^2$/s) and for non-cancerous transition zone tissue ($1.12 \times 10^{-3}$ mm$^2$/s) were in the lower range of these reported values. As we targeted cancer-suspicious regions using MR-guided biopsy specimens as a reference standard, our ADC values may have been in the lower ranges of the former radical prostatectomy-referenced studies. To our knowledge, one other study also used MR-guided biopsy specimens as a reference standard for diffusion-weighted imaging ADC (10). Our significant mADC differences between degrees and 1 and 2 of prostatitis and most transition zone cancers confirmed the results of the latter study, in which a significant ADC difference between prostatitis and low-GG transition zone cancer was found ($P < 0.001$) (10).

Inflammatory infiltrates in prostatitis lead to an increased cellular density and may therefore decrease ADC (21). In a healthy transition zone, a large ADC variation may be present because of higher variability of the different tissue components with different cellular densities. Stromal benign prostatic hyperplasia has a more compact and more homogeneous cell density and is known to have lower ADC values ($1.27 \times 10^{-3}$ mm$^2$/s) compared with glandular benign prostatic hyperplasia ($1.73 \times 10^{-3}$ mm$^2$/s) (8). Therefore, a relative local ADC decrease due to focal chronic prostatitis may not be discerned in the transition zone. The higher the degree of the prostatitis is, the lower the mADC is, as is depicted in Figure 4. Despite only including 5 cores with a degree 2 of prostatitis, we showed that, because of a lower ADC in a higher degree of prostatitis, a significant mADC difference between the magnetic resonance-guided prostate biopsy (MRGB) specimen cores with degree
2 prostatitis (mADC, \(1.12 \times 10^{-3} \text{ mm}^2/\text{s}\)) versus the primary GG 4-5 and secondary GG 2-3 transition zone cancers and vice versa (histopathological categories II and III) did not exist (\(P = 0.06-0.09\)). This significant mADC difference did exist for cores with a degree 1 prostatitis (mADC, \(1.05 \times 10^{-3} \text{ mm}^2/\text{s}\)), which had a higher ADC compared with any transition zone cancer (\(P < 0.0001\)). Our mean mADCs for primary GG 2-3 and 4-5 cancer-containing cores (mean [SD], \(0.84-0.85 \times 10^{-3} \text{ mm}^2/\text{s}\) and \(0.77-0.86 \times 10^{-3} \text{ mm}^2/\text{s}\), respectively) differ from the ADC values reported for primary GG 2-3 versus 4-5 cancers upon radical prostatectomy by Kobus et al (13) (respectively, minimum 25th percentiles of \(0.51-0.95 \times 10^{-3} \text{ mm}^2/\text{s}\) and \(0.61 \times 10^{-3} \text{ mm}^2/\text{s}\)) and by Kitajima et al (22) (respectively, mean ADC of \(1.12-1.21 \times 10^{-3} \text{ mm}^2/\text{s}\) and \(0.64-1.01 \times 10^{-3} \text{ mm}^2/\text{s}\)). Kobus et al (13) reported minimum 25th percentiles, which are lower compared with our mean 50th percentiles, whereas Kitajima et al (22) reported mean ADC values, which may be higher compared with our median values. Next to differences in image to histopathology correlation between studies, these ADC differences may have been caused by the application of b-values of 0 and 1000 s/mm\(^2\) by Kitajima et al (22) versus the applied b-values of 50, 500, and 800 s/mm\(^2\) in our study (22).

Our AUC value of 0.84 for discriminating transition zone cancer from non-cancerous transition zone tissue agrees with the results reported by Kitajima et al (22) (0.87-0.89) and by Oto et al (8) (0.78-0.99). To our knowledge, our study is the first to report AUC values for mADC differentiation of prostatitis from the transition zone cancer (0.84) and from the noncancerous transition zone (0.56).

Our moderate AUC value for differentiation of a primary GG 4-5 versus a GG 2-3 in MR-guided biopsy cores acquired in the transition zone (0.62) is comparable with AUC values of 0.61 to 0.62 found by Verma et al (12) for differentiation of a radical prostatectomy specimen Gleason score higher than 6 versus 6 or lower in the transition zone using both mean ADC and tumor volume. Our moderate accuracy in differentiating primary GG 4 from GG 3 cancer cores was caused by mADC overlap between the GGs, which, itself, may have been the result of mADC variations. mADC variations may have been caused by the inclusion of a secondary GG core tissue and by inter-patient and intra-patient mADC variations (24). Variation of the amount of noncancerous tissue in the cancer-containing cores did not cause significant mADC differences when we analyzed mADC for the primary GG 3 and 4 transition zone cancer cores with a cancer core length of 10-\(<12\), \(>12-\leq15\), and \(>15\) mm (\(P = 0.22-0.87\)).
This study has limitations. First, our results are subject to selection bias. Because we used a cancer core length of 10 mm and greater, we excluded smaller cancers from our retrospective analysis. However, because MR-guided biopsy is performed in a larger patient group compared with patients undergoing surgery, still, less patient selection bias is present compared with radical prostatectomy specimens. Second, as mentioned, including secondary GG tissue that was different from the primary GG may have reduced accuracy of our differentiation of primary GG 4 from primary GG 3 cancers. Although present in a smaller volume compared with the primary GG, the presence of a different secondary GG causes variation and overlap in ADCs for primary GG. As mentioned earlier, our results clearly showed a larger ADC difference and less overlap for a secondary GG, which was identical to the primary GG compared with a secondary GG, which was different from the primary GG. Furthermore, inaccuracies in our measurements may have been caused by possible needle, prostate, or patient movement in the short time gap between the actual biopsy and the acquisition of confirmation scans (25). Despite our manual registration of confirmation scans to the diffusion-weighted imaging ADC maps, some variation in measurements due to patient movement throughout the whole MR-guided biopsy procedure may still have occurred. Third, we took into account a larger apparent size of the needle tip artifact on the MR images compared with the actual needle size. However, we did not adjust this measure for the angle of needle insertion with the static field (B0) of the MR scanner, which may influence the apparent needle size (26). Fourth, because our reference standard MR-guided biopsy was based on targeting MR imaging cancer-suspicious regions, selection bias may have occurred. Cancer-suspicious regions may have a relatively higher cell density, resulting in lower ADC values compared with the whole transition zone.
**Figure 4.** Box plot of median ADC values in annotated ROIs on MRGB needle artifacts versus MRGB core specimen histopathology categories. Values in between 1.5 to 3 box lengths above the upper box margin are presented as outliers with a circle. GG indicates Gleason grade; mADC, median apparent diffusion coefficient values; MRGB, MR guided biopsy; TZ, prostate transition zone.

**Figure 5.** Scatterplot of median ADC values in annotated ROIs on MRGB needle artifacts versus MRGB core specimen Gleason scores. ADC indicates apparent diffusion coefficient; MRGB, MR guided biopsy; ROI, region of interest.

To clinically apply our detected mADC differences for different histopathology entities in the transition zone, variation of ADC values should be reduced. In a recent study, correction for interpatient variation of healthy peripheral zone ADC significantly improved ($P = 0.04$; AUC, 0.91-0.96) differentiation of GG 4 and/or 5 versus GG 2 and/or 3 cancers (27). This principle may also be applied for cancers located in the transition zone.
In conclusion, mADC values can differentiate the transition zone cancer from the non-cancerous transition zone and from degree 1 and, sometimes, from degree 2 prostatitis. However, because of mADC overlap between the histopathology categories, mADC had a poor accuracy to distinguish between different subcategories of transition zone cancer primary and secondary GG and cannot be used for differentiation between non-cancerous transition zone with and without prostatitis. Diffusion-weighted MR imaging ADC may therefore contribute in the detection of transition zone cancers, but as a single functional MR imaging technique, diffusion-weighted MR imaging has a moderate diagnostic accuracy in separating higher versus lower GG components in transition zone cancers and in differentiating prostatitis from non-cancerous transition zone.
References


Three-Tesla Magnetic Resonance–Guided Prostate Biopsy in Men With Increased Prostate-Specific Antigen and Repeated, Negative, Random, Systematic, Transrectal Ultrasound Biopsies: Detection of Clinically Significant Prostate Cancers.

Caroline M.A. Hoeks, MD
Martijn G. Schouten, MSc
Joyce G.R. Bomers, MSc
Stefan P. Hoogendoorn, medical student
Christina A. Hulsbergen-van de Kaa, MD PhD
Thomas Hambrock, MD PhD
Henk Vergunst, MD PhD
J.P. Michiel Sedelaar, MD PhD
Jurgen J. Fütterer, MD PhD
Jelle O. Barentsz, MD PhD

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Abstract:

Background: Patients with elevated prostate-specific antigen (PSA) and one or more previous negative transrectal ultrasound (TRUS) biopsy sessions are subject to diagnostic uncertainty due to TRUS-biopsy undersampling. Magnetic resonance (MR)–guided biopsy (MRGB) has shown high prostate cancer (PCa)–detection rates in studies with limited patient numbers. Objective: Determine the detection rate of (clinically significant) PCa for MRGB of cancer suspicious regions (CSRs) on 3-T multiparametric MR imaging (MP-MRI) in patients with elevated PSA and one or more negative TRUS-biopsy session(s). Design, setting, and participants: Of 844 patients who underwent 3-T MP-MRI in our referral centre between March 2008 and February 2011, 438 consecutive patients with a PSA >4.0 ng/ml and one negative TRUS-biopsy session or more were included. MRGB was performed in 265 patients. Exclusion criteria were existent PCa, endorectal coil use, and MP-MRI for indications other than cancer detection. Intervention: Patients underwent MRGB of MP-MRI CSRs. Measurements: (clinically significant) MRGB cancer-detection rates were determined. Clinically significant cancer was defined based on PSA, Gleason score, stage, and tumour volume. Follow-up PSA and histopathology were collected. Sensitivity analysis was performed for patients with MP-MRI CSRs without MRGB. Results and limitations: In a total of 117 patients, cancer was detected with MRGB (n = 108) or after negative MRGB (n = 9). PCa was detected in 108 of 438 patients (25%) and in 41% (108 of 265) of MRGB patients. The majority of detected cancers (87%) were clinically significant. Clinically significant cancers were detected in seven of nine (78%) negative MRGB patients in whom PCa was detected during follow-up. Sensitivity analysis resulted in increased cancer detection (47–56%). Complications occurred in 2.0% of patients (5 of 265). Conclusions: In patients with elevated PSA and one or more negative TRUS-biopsy session(s), MRGB of MP-MRI CSRs had a PCa-detection rate of 41%. The majority of detected cancers were clinically significant (87%).
Introduction:

Prostate cancer (PCa) is a major health care problem with 899,000 new cases and 258,000 deaths per year in Europe (1). In patients with elevated prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE), random systematic transrectal ultrasound (TRUS) biopsy is the most commonly used technique to further evaluate PCa diagnosis. However, like PSA, which is an unspecific marker (specificity: 36%), and DRE, which is a rather insensitive examination (sensitivity: 37%) for PCa detection, TRUS biopsy also has its shortcomings (2,3). Due to sampling error, >20% of cancers are not detected in the first TRUS biopsy session (4). With repeat TRUS biopsies, PCa detection rates decreased from 22% to 4% in four subsequent TRUS-biopsy sessions (4). As a result of the mentioned issues, a large number of patients with a persistently elevated or increasing PSA and one or more negative TRUS-biopsy sessions are subject to diagnostic uncertainty.

Magnetic resonance (MR)–guided prostate biopsy (MRGB) of a detected cancer-suspicious region (CSR) on MR imaging (MRI) is a feasible diagnostic technique: PCa detection rates with this method range from 37% to 59% (5–10). Moreover, the implementation of MRGB has resulted in detection of predominantly (93%) clinically significant PCa (8). Functional MRI techniques increased PCa-localization accuracy (area under the curve (AUC): 0.84–0.91) when added to anatomic T2-weighted MRI (T2WI; AUC: 0.69–0.81) in a multiparametric MRI (MP-MRI) exam (11,12). Using its localization strength, MP-MRI of the prostate has increased opportunities for image-guided techniques like MRGB. However, most MRGB studies were performed with a low number of patients at a lower field strength of 1.5 T. Therefore, we aimed to determine the detection rate of (clinically significant) PCa for MRGB of CSRs detected on 3-T MP-MRI in patients with an elevated PSA and at least one previous negative TRUS-biopsy session in a large population.

Material and Methods

Patients

The need for informed consent for this retrospective study was waived by our institutional review board. Between March 2008 and February 2011, 844 consecutive patients underwent MP-MRI in our referral centre. Of these, 438 patients with PSA >4 ng/ml and at least one previous negative TRUS-biopsy session and who had
undergone MP-MRI and/or MRGB were included. Exclusion criteria were existent PCa, use of an endorectal coil, and MP-MRI for other indications than cancer detection. Patient selection is shown in a flow diagram in Figure 1.

Magnetic resonance imaging
MP-MRI and MRGB were performed on two comparable 3-T MR scanners (MAGNETOM Trio and MAGNETOM Skyra; Siemens Medical Solutions, Erlangen, Germany) using a combined spinal and pelvic-phased array coil. MRI parameters are presented in Table 1.

Magnetic resonance imaging interpretation
Two radiologists with 9 yr and 18 yr of experience in prostate MRI, respectively, evaluated the MP-MRI examinations using in-house-developed software (13). CSRs were defined on T2WI in combination with diffusion-weighted MRI (DWI) and dynamic contrast-enhanced MRI as described earlier (14). In addition to apparent diffusion coefficient (ADC) maps, DWI-calculated b1400 images were used to determine CSRs. A lesion was defined as a CSR on DWI in cases of focal restriction on the ADC map combined with an iso- to hyper-signal intensity on the calculated b1400 image. Clinical data of all patients were available at MRI reading.

Magnetic resonance-guided prostate biopsy
MRGB was performed in a separate session and every CSR was targeted. Two radiologists with 2 yr and two radiologists with 1 yr of MRGB experience performed transrectal prostate MRGB as described earlier (14). Axial T2WI and DWI were acquired as baseline images for targeting.

Histopathology
Biopsy specimens were immediately fixed in formalin and subsequently underwent routine histopathologic evaluation by a urogenital histopathologist who had 18 yr of experience.

Prostate cancer: clinical significance
When prostatectomy was not performed, clinical significance of MRGB-detected PCa was defined by: (1) a PSA >10 ng/ml and a PSA density >0.15 ng/ml per ml; (2) clinical stage ≥T2b; (3) a Gleason grade (GG) 4 or 5 within the biopsy specimen; or (4) a total cancer-core length (TCCL) ≥10 mm, where TCCL is the total cancer length
in all MRGB cores from one CSR (15–18). This definition was based on i.a. Epstein and D'Amico criteria (15,18). In case of performed prostatectomy, PCA was considered clinically significant when PCA volume was ≥0.5 ml or a stage ≥pT3 or a GG 4 or 5 (19,20) was present.

Follow-up
Post-MRGB PSA measurements and histopathology results were collected until July 22, 2011, for all MRGB patients.

Statistical analysis
Parametric continuous variables were reported as mean plus or minus the standard deviation; nonparametric continuous variables were reported as median and the interquartile range (IQR). The Pearson chi-square test was used to test for differences in proportions. In a multivariable logistic regression analysis, PSA, PSA density, and prostate volume were assessed as predictors for MRGB PCA detection. We used sensitivity analyses in which we assumed that, in all patients with visible MRI lesions, PCA would have been detected if MRGB would have been performed. A significance level of <0.05 was used for all analyses.
Figure 1. Study flow diagram. MP-MRI = multiparametric magnetic resonance imaging; TRUS = transrectal ultrasound; PSA = prostate-specific antigen; MRGB = magnetic resonance guided prostate biopsy.

**Table 1.** Multiparametric (MP) magnetic resonance imaging (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</th>
<th>Matrix size, mmm×mmm</th>
<th>Voxel size, mmm×mmm×mmm</th>
<th>b-values, s/mm²</th>
<th>Temporal resolution, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP-MRI of the prostate (MAGNETOM Trio)</td>
<td>T2WI axial (TSE) and coronal sagittal</td>
<td>4480 103 120</td>
<td>3.0</td>
<td>180×180</td>
<td>320×320</td>
<td>0.6×0.6×3.0</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI SSEPI axial</td>
<td>4950 110 120</td>
<td>3.0</td>
<td>180×180</td>
<td>320×320</td>
<td>0.6×0.6×3.0</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCE-MRI GE Axial 3D</td>
<td>500 1.47 8</td>
<td>4.0</td>
<td>230×230</td>
<td>180×180</td>
<td>1.8×1.8×4.0</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP-MRI of the prostate (MAGNETOM Skyra)</td>
<td>T2WI axial coronal sagittal</td>
<td>5180 101 160</td>
<td>3.0</td>
<td>192×192</td>
<td>320×320</td>
<td>0.6×0.6×3</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI SSEPI axial</td>
<td>4320 101 160</td>
<td>3.0</td>
<td>192×192</td>
<td>320×320</td>
<td>0.6×0.6×3</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCE-MRI GE Axial 3D</td>
<td>4000 101 160</td>
<td>3.0</td>
<td>180×180</td>
<td>320×320</td>
<td>0.6×0.6×3</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCE-MRI GE Axial 3D</td>
<td>3000 64 NA</td>
<td>4.0</td>
<td>256×256</td>
<td>128×128</td>
<td>2×2×4</td>
<td>0/50/100/1200</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRGB (MAGNETOM Trio)</td>
<td>T2WI TSE axial</td>
<td>3620 103 120</td>
<td>4.0</td>
<td>256×256</td>
<td>320×320</td>
<td>0.8×0.8×4.0</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI EPI axial</td>
<td>3300 60 NA</td>
<td>3.6</td>
<td>260×211</td>
<td>160×120</td>
<td>2.2×1.6×3.6</td>
<td>0/100/400/800</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balanced SSFP GE Axial and Sagittal</td>
<td>4.48 2.24 70</td>
<td>3.0</td>
<td>280×280</td>
<td>256×256</td>
<td>1.1×1.1×3.0</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRGB (MAGNETOM Skyra)</td>
<td>T2WI TSE Axial</td>
<td>3560 104 120</td>
<td>120</td>
<td>256×256</td>
<td>320×320</td>
<td>0.8×0.8×4</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI EPI Axial</td>
<td>3000 64 NA</td>
<td>4.0</td>
<td>256×212</td>
<td>128×128</td>
<td>2.0×2.0×4.0</td>
<td>50/100/1600</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balanced SSFP GE Axial and Sagittal</td>
<td>4.56 2.28 70</td>
<td>3.0</td>
<td>280×280</td>
<td>256×256</td>
<td>1.1×1.1×3.0</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

T2WI = T2-weighted magnetic resonance imaging; DWI = diffusion weighted magnetic resonance imaging; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; SSFP = steady-state free procession; TR = repetition time; TE = echo time; TSE = turbo spin echo; SSEPI = steady-state echo planar imaging; GE = gradient echo; EPI = echo-planar imaging; NA = not applicable.
Results

Inclusion criteria were met in 438 of 844 consecutive men. MRGB was performed in 265 of these 438 men (Fig. 1). MRGB was not performed due to lack of visible lesions (n = 80); advice for follow-up MP-MRI in lesions suspicious for prostatitis, benign prostatic hyperplasia, or low-grade cancer (n = 64); or despite MRGB advice (n = 29). Patient characteristics are presented in Table 2. The last TRUS biopsy had a median of nine cores (IQR: 9–10, available in 123 of 265 MRGB patients) with transition zone (TZ) sampling in protocols of eight or more cores. The median MRGB duration was 44 min (IQR: 35–51 min).

In a total of 117 patients, PCa was detected with MRGB (n = 108) or during follow-up after negative MRGB (n = 9). PCa-detection rates were 25% (108 of 438; 95% confidence interval (CI), 21–29%) in included patients and 41% (108 of 265; CI, 35–47%) in patients who underwent both MP-MRI and MRGB. The majority of detected cancers were clinically significant: a total of 87% (94 of 108) met the clinical criteria and 93% (26 of 28) met radical prostatectomy-specimen criteria.

A total of 368 CSRs were indicated in the 265 MRGB patients. With a median of two cores per CSR, PCa was detected in 33% of CSRs (123 of 368; CI, 29–38%). The majority of CSRs (63% (78 of 123); CI, 55–71%) were detected in the TZ. Thirty-three percent (40 of 123; CI, 25–41%) of detected CSRs were located in the peripheral zone (PZ). The remaining 4% (5 of 123; CI, 2–9%) were situated on the TZ-PZ border or in the seminal vesicles. Other predominant CSR diagnoses are shown in Table 3.

Significantly more PCa was detected in patients with a prostate volume ≤50 ml (60%) versus >50 ml (36%; p < 0.0001) and in patients with PSA density >0.15 ng/ml per ml (52%) versus ≤0.15 ng/ml per ml (24%; p < 0.0001). With multivariable logistic regression. PSA was not a predictor of MRGB PCa detection. After correction for PSA, only prostate volume ≤50 ml (p = 0.008) and PSA density >0.15 ng/ml per ml (p < 0.0001) were predictors of MRGB PCa detection in a final multivariable logistic regression model. These results are presented in Table 4.

In sensitivity analysis, PCa-detection rates would have increased to 47% (137 of 294; CI, 41–52%) if MRGB would have been performed and PCa would have been detected in patients with a MP-MRI CSR who were advised to undergo MRGB (n = 29). Detection rates would have increased even further to 56% (201 of 358; CI, 51–56%) if MRGB would have been performed and PCa would also have been detected in patients with an MP-MRI suspicious for prostatitis, benign prostatic

hyperplasia, or low-grade cancer, and in whom repeat MP-MRI was advised (n = 64). A patient example of MP-MRI and MRGB is shown in Figure 2.

Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=438)</th>
<th>Patients with detected prostate cancer on MRGB (n=108)</th>
<th>Patients without detected prostate cancer on MRGB (n=156)</th>
<th>p-value* for patients with vs. without detected prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, median (IQR)</td>
<td>66 (61-69)</td>
<td>65 (62-70)</td>
<td>64 (61-69)</td>
<td>0.29</td>
</tr>
<tr>
<td>PSA level, ng/mL, median (IQR)</td>
<td>11.4 (8.6-18.3)</td>
<td>18.0 (10.0-27.9)</td>
<td>12.0 (9.1-17.1)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Prostate volume, ml, median (IQR)</td>
<td>67 (50-93)</td>
<td>53 (36-68)</td>
<td>70 (51-89)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Previous negative TRUS biopsy sessions, median (IQR)</td>
<td>2 (2-3)</td>
<td>3 (2-3)</td>
<td>2 (2-3)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Interval last TRUS – MRGB, mo, median (IQR)</td>
<td>12 (5-20)</td>
<td>13 (6-21)</td>
<td>11 (5-20)</td>
<td>0.16</td>
</tr>
<tr>
<td>Interval MRI–MRGB, mo, median (IQR)</td>
<td>2 (1-2)</td>
<td>1 (1-2)</td>
<td>2 (1-2)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Biopsied CSR, median (IQR)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>2 (1-2)</td>
<td>n.a.</td>
</tr>
<tr>
<td>MRGB cores for one CSR, median (IQR)</td>
<td>2 (2-3)</td>
<td>2 (2-3)</td>
<td>2 (2-3)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

MRI= Magnetic Resonance Imaging, IQR = interquartile range; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; MRGB = magnetic resonance–guided biopsy; CSR = cancer-suspicious region; NA = not applicable. * P values were calculated using an independent t test and a Mann-Whitney U test for nonparametric variables. ‡ Mann-Whitney U test. † p < 0.05 was considered statistically significant.
A 76-yr-old patient with a prostate-specific antigen level of 32 ng/ml and density of 0.46 ng/ml per ml, clinical stage T1C, and one previous negative transrectal ultrasound–guided biopsy session underwent multiparametric magnetic resonance imaging (MRI) for a clinical indication of prostate cancer detection. (A) A ventral transition-zone cancer is visible (demarcated regions). A focal lenticular-shaped homogeneous low-signal intensity (blue demarcation) in the ventral prostate is visible on (iii) sagittal and (v) axial T2-weighted MRI (T2WI). A focal (ii) low apparent diffusion-coefficient value (blue demarcation) and (iv) high signal intensity (blue demarcation) on the calculated b1600 image are visible in the same area on diffusion-weighted

MRI. (i) The $K_{\text{trans}}$ overlay on T2WI can be appreciated. Dynamic contrast-enhanced MRI shows symmetric increased enhancement (black demarcation) matching the other functional images and T2WI. Benign prostate hyperplasia nodules are also enhanced (white arrows). (B) Sagittal and (C) transverse balanced gradient echo images were made to confirm the needle positions. Needle artefacts (white lines) and needle guiders (blue lines with white-dotted top) are visible. In this magnetic resonance–guided biopsy specimen, a Gleason score 4 + 5 prostate cancer was found in the ventral transition zone.

Table 3. Magnetic resonance–guided biopsy histopathology results for cancer-suspicious regions on multiparametric magnetic resonance imaging

<table>
<thead>
<tr>
<th>Histology in MRGB cores of CSRs</th>
<th>Percentage of CSRs*, % (no./total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>33 (123/368)</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>30 (109/368)</td>
</tr>
<tr>
<td>Healthy intra-prostatic tissue</td>
<td>23 (85/368)</td>
</tr>
<tr>
<td>Atrophia</td>
<td>8 (31/368)</td>
</tr>
<tr>
<td>Material not representative for prostate tissue</td>
<td>5 (18/368)</td>
</tr>
<tr>
<td>HGPIN</td>
<td>4 (16/368)</td>
</tr>
<tr>
<td>Reactive atypia</td>
<td>2 (9/368)</td>
</tr>
<tr>
<td>AAH</td>
<td>2 (8/368)</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0.003 (1/368)</td>
</tr>
<tr>
<td>Total number of CSRs</td>
<td>100 (368/368)</td>
</tr>
</tbody>
</table>

CSRs = cancer-suspicious regions; MRGB = magnetic resonance–guided biopsy; HGPIN = high-grade intraprostatic neoplasia; AAH = atypical adenomatous hyperplasia. * Because some CSRs had more than one diagnosis, the sum of percentages is higher than 100%.

In sensitivity analysis, PCa-detection rates would have increased to 47% (137 of 294; CI, 41–52%) if MRGB would have been performed and PCa would have been detected in patients with a MP-MRI CSR who were advised to undergo MRGB ($n = 29$). Detection rates would have increased even further to 56% (201 of 358; CI, 51–56%) if MRGB would have been performed and PCa would also have been detected in patients with an MP-MRI suspicious for prostatitis, benign prostatic hyperplasia, or low-grade cancer, and in whom repeat MP-MRI was advised ($n = 64$). A patient example of MP-MRI and MRGB is shown in Figure 2.

Follow-up

Reported MRGB complications were sepsis with hospitalization in one patient and a vasovagal reaction in four other patients.

Only in 51 of 156 negative-MRGB patients was a follow-up of 5 mo, including two PSA measurements or histopathology, available. In 6% (9 of 156; CI, 3–6%) of negative-MRGB patients, PCa was detected during this mean follow-up of 5 mo.
Detected cancers were clinically significant in 78% (seven of nine patients) based on clinical criteria and in 100% (four of four) based on radical prostatectomy-specimen criteria. Follow-up results of patients who underwent MP-MRI for suspicion of PCa are presented in Figure 3.

### Table 4. Univariable and multivariable analysis of dichotomized prostate-specific antigen, prostate volume, and PSA density related to magnetic resonance–guided biopsy (MRGB) prostate cancer detection in patients with initial positive MRGB and initial negative MRGB results*

<table>
<thead>
<tr>
<th>Percentage of patients with prostate cancer, % (no./total)</th>
<th>Patients with prostate cancer upon MRGB, % (no./total) [95% CI]#</th>
<th>Univariable analysis X² test</th>
<th>Multivariable logistic regression analysis, Initial model OR [95% CI] (p value)</th>
<th>Multivariable logistic regression analysis, Final model OR [95% CI] (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRGB+ MRGB-</td>
<td>100 (108/108) 6 (9/156)</td>
<td>96-100 3-11</td>
<td>44 (116/263), [38-50]</td>
<td>NA</td>
</tr>
<tr>
<td>PSA ≤ 10 ng/mL MRGB+ MRGB-</td>
<td>100 (28/28) 4 (2/57)</td>
<td>86-100 0-13</td>
<td>36 (30/84), [26-46]</td>
<td>0.06</td>
</tr>
<tr>
<td>PSA &gt; 10 ng/mL MRGB+ MRGB-</td>
<td>100 (80/80) 6 (6/99)</td>
<td>95-100 3-13</td>
<td>48 (86/179), [41-55]</td>
<td>NA</td>
</tr>
<tr>
<td>Prostate volume ≤50 cc MRGB+ MRGB-</td>
<td>100 (47/47) 13 (5/40)</td>
<td>96-100 5-27</td>
<td>60 (52/86), [50-70]</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Prostate volume &gt;50 cc MRGB+ MRGB-</td>
<td>100 (61/61) 3 (3/116)</td>
<td>93-100 1-8</td>
<td>36 (64/177), [29-43]</td>
<td>2.28 (prostate volume ≤50/ &gt;50 cc) [1.23-4.21] (0.009†)</td>
</tr>
<tr>
<td>PSA density ≤0.15 ng/mL/mL MRGB+ MRGB-</td>
<td>100 (15/15) 4 (2/57)</td>
<td>76-100 0-13</td>
<td>24 (17/71), [15-35]</td>
<td>2.21 (prostate volume ≤50/ &gt;50 cc) [1.23-3.97] (0.008†)</td>
</tr>
<tr>
<td>PSA density &gt;0.15 ng/mL/mL MRGB+ MRGB-</td>
<td>100 (93/93) 6 (6/99)</td>
<td>95-100 3-13</td>
<td>52 (99/192), [45-59]</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

CI = confidence interval; PSA = prostate-specific antigen; MRGB+ = patients with prostate cancer on initial MRGB; MRGB_ = patients without prostate cancer on initial MRGB; CI = confidence interval; DR = detection rate; OR = odds ratio; X² = Pearson chi-squared test; NA = not applicable.

* The final multivariable logistic regression model consisted of two independent variables (PSA density and prostate volume [as dichotomized categorical covariates]) and one dependent variable (prostate cancer detection on MRGB). † Statistically significant difference at a threshold of p < 0.05.

# One patient with initial negative MRGB had prostate cancer detected upon TRUS biopsy. This patient is not added to the totals in the fourth column.

Figure 3. Follow-up histopathology results in patients with multiparametric magnetic resonance imaging (MP-MRI): (A) excluded patients with MP-MRI, (B) patients without magnetic resonance–guided biopsy (MRGB), (C) patients with MP-MRI and MRGB. GG = Gleason grade; TRUS = transrectal ultrasound; PCa = prostate cancer; RP = radical prostatectomy specimen; PSA = prostate-specific antigen.

(A)

Excluded patients with MP-MRI without endorectal coil on indication of a clinical suspicion for prostate cancer (n=123)

n= 82
no previous negative TRUS biopsy

n= 30
PSA ≤ 4 ng/ml

n= 11
missing PSA and/or number of negative TRUS biopsies

n= 17 MRGB
n= 12 PCa MRGB
n= 9 TRUS biopsy (no MRGB)

n= 8 MRGB
n= 4 PCa MRGB
n= 1 TRUS biopsy (no MRGB)

n= 1 PCa TRUS biopsy

n= 8 MRGB
n= 2 PCa MRGB
n= 4 TRUS biopsy (no MRGB)

n= 2 PCa TRUS biopsy

(B)

Patients without MRGB n=173
Mean follow-up 7 months, range (0-33)

n= 29 MRGB advised by radiologist, however not performed

n= 64 visible lesion suspect for prostatitis, benign prostatic hyperplasia or GG 1-3 prostate cancer. Advice: Follow-up MR imaging in 6 months

n= 80 no visible lesions on MR imaging

n= 9 TRUS biopsy
n= 6 PCa
n= 4 clinically significant PCa

n= 1 repeat MRGB
n= 0 PCa

n= 5 TRUS biopsy
n= 1 PCa
n= 1 clinically significant PCa

n= 1 repeat MRGB
n= 0 PCa

n= 1 repeat MRGB
n= 1 PCa
n= 1 clinically significant PCa based on clinical criteria

(C)

Patients in whom prostate cancer was not detected upon MRGB
n=156
Mean follow-up 5 months, range (0-38)

n= 4 TRUS biopsy
n= 1 PCa

n= 10 repeat MRGB
n= 8 PCa
n= 7 clinically significant PCa based on clinical criteria

Patients with detected prostate cancer upon MRGB
n=108

n= 28 RP
n= 26 RP criteria clinically significant PCa

n= 94 clinically significant PCa based on clinical criteria
Discussion

In patients with one or no negative TRUS-biopsy sessions, MRGB of 3-T MP-MRI–detected CSRs resulted in a PCa detection rate of 41%. In our study, MRGB detected more cancers than repeated TRUS biopsy (≤18%) (21,22). Furthermore, our number of detected clinically significant cancers (87%) is high compared to an estimated 56% of clinically significant cancers for repeat TRUS biopsy in screening (23). We detected more clinically significant cancers because our referred patient population probably contained cancers of higher Gleason score than a screening population. Another reason for detecting many clinically significant cancers may be higher MRI detection rates for higher Gleason score cancers (24). Furthermore, MRGB has higher GG concordance with prostatectomy specimens compared to systematic TRUS biopsy and, therefore, less undergrading may have occurred (25). Our detection rate of 41% is in agreement with some MRGB publications (37–39%) (6,10). However, our detection rate is lower compared to other MRGB studies (52–59%) (5,8,9). This may be explained by the fact that in our study, as opposed to these last studies, not all patients underwent MRGB. Finally, for clinically significant cancers, our detection rate (87%) approaches that of Hambrock et al. (93%). The detection rate of clinically significant cancers of Roethke et al. was lower than ours (81%) (5). This may be explained by the fact they did not add MP-MRI to T2WI in the first 52 of their 100 patients.

Our relatively high detection rates of PCa in the TZ (63%) agree with results of Hambrock et al. (57% in TZ) (8). However, in other reports, TZ cancer-detection rates (47% and 35%, respectively) were lower than PZ cancer-detection rates (respectively, 53% and 64%) (5,6). Heterogeneity of patient populations due to differences in the number of previous TRUS-biopsy sessions, the TRUS-biopsy protocol, and in the number of cores in TRUS biopsies makes it difficult to compare results of reported predominant PCa locations.

Clinical alternatives to MRGB are limited to saturation biopsy protocols (including transperineal template biopsies). Saturation biopsies have the disadvantages of possibly requiring anaesthesia and a high number of cores. Detection rates of protocols including 20–38 cores ranged from 14% to 41% without significantly increasing the likelihood of detecting clinically significant cancers (26). In MRGB, only a limited number of cores (median two cores per CSR) are needed to detect a high percentage (86%) of clinically significant cancers. Furthermore, in MRGB, no general anaesthesia is required. Clinical use of MRGB is currently restricted by its
limited availability and its rather long procedure times (median: 44 min). However, application of MR-ultrasound fusion techniques (using registration), needle-guide tracking sequences, and implementation of robotics may improve these drawbacks in the near future (27–29). When these issues are solved, MP-MRI and MRGB could be applied on a larger scale for PCa detection in patients with an elevated PSA and one or more negative TRUS-biopsy sessions. However, PCa-detection rates for random systematic TRUS biopsy versus targeted MRGB should be prospectively compared in patients stratified for previously performed similar TRUS-guided biopsy protocols. Our study has several limitations. First, our follow-up is limited to two or fewer PSA measurements within 1 yr without histopathology examinations in most patients. Inferring conclusions from false-negative MRGB results remains difficult based on this limited follow-up. However, regardless of follow-up duration, differentiation of a patient with small-volume cancer missed by MRGB from a patient without PCa remains problematic without availability of radical prostatectomy specimens directly after MRGB. Second, as our work was performed in a referral centre, inter-patient variation in the number and the protocols of previous negative TRUS-biopsy sessions is present. Furthermore, intra-patient variation exists due to time differences between protocols of different TRUS-biopsy sessions in a single patient. Furthermore, in some patients, bias may have been caused by the relatively low number of TRUS-biopsy cores for the sampled prostate-cancer volume. Third, MRGB was performed by four radiologists who did not perform consensus image reading. Possible differences in image interpretation between reading radiologists and MRGB radiologists may have biased our results. Finally, a TCCL ≥10 mm, recently defined to predict a radical prostatectomy specimen tumour volume ≥0.5 ml using TRUS (5-mm grid) template biopsy simulations (17), was used as a criterion for targeted precisely to a lesion and is not taken every 5 mm according to a grid, our TCCL criterion may have overestimated MRGB results for clinically significant cancers. However, as no results on MRGB TCCL for prediction of tumour volume exist currently, we incorporated this ultrasound criterion for estimation of tumour volume based on MRGB specimens.

Conclusions

In conclusion, in patients with an elevated PSA level and one or more previous negative TRUS-guided prostate biopsy session(s), MRGB of 3-T MP-MRI-detected CSRs has a detection rate of 41% for predominantly clinically significant PCa (87%).
References


Prospective Assessment of Prostate Cancer Aggressiveness Using 3-T Diffusion-Weighted Magnetic Resonance Imaging–Guided Biopsies Versus a Systematic 10-Core Transrectal Ultrasound Prostate Biopsy Cohort.

Thomas Hambrock, MD
Caroline Hoeks, MD
Christina Hulsbergen-van de Kaa, MD PhD
Tom Scheenen, PhD
Jurgen Fütterer, MD PhD
Stefan Bouwense, medical student
Inge van Oort, MD PhD
Fritz Schröder, MD PhD
Henkjan Huisman, MD PhD
Jelle Barentsz, MD PhD

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Abstract

Background: Accurate pre-treatment assessment of prostate cancer (PCa) aggressiveness is important in decision making. Gleason grade is a critical predictor of the aggressiveness of PCa. Transrectal ultrasound–guided biopsies (TRUSBxs) show substantial undergrading of Gleason grades found after radical prostatectomy (RP). Diffusion-weighted magnetic resonance imaging (MRI) has been shown to be a biomarker of tumour aggressiveness.

Objective: To improve pre-treatment assessment of PCa aggressiveness, this study prospectively evaluated MRI-guided prostate biopsies (MR-GBs) of abnormalities determined on diffusion-weighted imaging (DWI) apparent diffusion coefficient (ADC) maps. The results were compared with a 10-core TRUSBx cohort. RP findings served as the gold standard.

Design, setting, and participants: A 10-core TRUSBx (n = 64) or MR-GB (n = 34) was used for PCa diagnosis before RP in 98 patients.

Measurements: Using multiparametric 3-T MRI: T2-weighted, dynamic contrast enhanced imaging, and DWI were performed to identify tumour-suspicious regions in patients with a negative TRUSBx. The regions with the highest restriction on ADC maps within the suspicions regions were used to direct MR-GB. A 10-core TRUSBx was used in a matched cohort. Following RP, the highest Gleason grades (HGGs) in biopsies and RP specimens were identified. Biopsy and RP Gleason grade results were evaluated using chi-square analysis.

Results and limitations: No significant differences on RP were observed for proportions of patients having a HGG of 3 (35% vs 28%; p = 0.50), 4 (32% vs 41%; p =0.51), and 5 (32% vs 31%; p = 0.61) for the MR-GB and TRUSBx cohort, respectively. MR-GB showed an exact performance with RP for overall HGG: 88% (30 of 34); for TRUS-GB it was 55% (35 of 64; p = 0.001). In the MR-GB cohort, an exact performance with HGG 3 was 100% (12 of 12); for HGG 4, 91% (10 of 11); and for HGG 5, 73% (8 of 11). The corresponding performance rates for TRUSBx were 94% (17 of 18; p = 0.41), 46% (12 of 26; p = 0.02), and 30% (6 of 20; p = 0.01), respectively.

Conclusions: This study shows prospectively that DWI-directed MR-GBs significantly improve pre-treatment risk stratification by obtaining biopsies that are representative of true Gleason grade.
Introduction

The Gleason grading system is the key method to describe the pathologic characteristics of prostate cancer (PCa). Of all the clinically determinable parameters, the Gleason score (GS) has proven to be the most important in measuring aggressiveness, disease outcome, and the risk of mortality from PCa (1). Transrectal ultrasound–guided biopsy (TRUSBx) is currently the most accepted method for establishing a definite diagnosis of PCa in patients with a clinical suspicion based on prostate-specific antigen (PSA) values or digital rectal examination (DRE). The most frequently used schemes include sampling 10–12 cores with emphasis on the lateral peripheral zone and transition zone (2,3). The tumour biopsy cores are scored according to the Gleason grading scheme to determine aggressiveness. PCa can be multifocal and heterogeneous in composition, often presenting with well-, moderately, and poorly differentiated components in the same tumour. TRUSBx determined GS has been shown (4–6) to be substantially discordant (undergrading in 34–38%) with the GS determined in radical prostatectomy (RP) specimens. Because risk stratification affects individualised treatment decisions and prognosis, the accurate pre-treatment prediction of GS remains essential. Multiparametric MR imaging (MP-MRI), including T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced MR imaging (DCE-MRI), have all been shown (especially in combination) to localise PCa accurately (7,8). Improved localisation of suspicious regions on MP-MRI have also been biopsy targeted under MR guidance and shown to increase tumour detection rates substantially (9,10). DWI has been shown to provide information about tumour aggressiveness (11,12). The aim of this study was to determine prospectively whether DWI-guided prostate biopsies could improve the pre-treatment assessment of PCa aggressiveness. These results were compared with a standard clinical cohort of patients who underwent 10-core TRUSBxs. In both cohorts the performance of Gleason grades in biopsy and RP (the gold standard) was determined.
CHAPTER 6

Materials and methods

Patients
Between August 2006 and April 2009, 123 consecutive patients underwent RP at the Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, and were retrospectively included after a PCa diagnosis was made with 10-core TRUSBx or MR-GB. Patients with prior hormonal/radiotherapy were excluded.

Transrectal ultrasound–guided biopsy sampling
Extended systematic 10-core TRUSBx (6 lateral and 4 transition zone) were obtained using a Pro Focus B-K ultrasound device (B-K Medical, Herlen, Denmark) and 18G needles with a 17-mm sampling length. Indications for biopsies were based on clinical parameters: elevated PSA ≥4 ng/ml and/or abnormal DRE. TRUSBx represented the first biopsy session in these patients.

Magnetic resonance imaging
MP-MRI at 3-T (Trio Tim, Siemens, Erlangen, Germany) that included T2-weighted, DWI, and DCE-MRI was performed in patients with at least one prior negative 10-core TRUSBx but persistent clinical suspicion for PCa defined by elevating or persistently elevated PSA >4 ng/ml. Table 1 lists the MRI parameters. Apparent diffusion coefficient (ADC) maps were calculated from the DWI by the scanner. Two radiologists determined up to three tumour-suspicious regions (TSRs) per patient in consensus using the combined information of the features suspicious for malignancy on the different MP-MRI modalities. PSA values were available to radiologists. Each of the imaging modalities was scored on a tumour probability scale of 1–5 with a maximum cumulative score of 15. Per modality, the scale is defined as follows: 1, definitely no tumour; 2, probably no tumour; 3, possibly tumour; 4, probably tumour; and 5, definitely tumour. A score ≥8 of 15 was an indication for biopsy of a TSR.
Table 1. Magnetic resonance imaging sequence parameters

<table>
<thead>
<tr>
<th>Sequence type</th>
<th>Slice thickness mm</th>
<th>No. of slices</th>
<th>In-plane resolution mm</th>
<th>TR ms</th>
<th>TE ms</th>
<th>Averages GRAPPA b-values mm/s²</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-w axial</td>
<td>4</td>
<td>15-19</td>
<td>0.6x0.6</td>
<td>3540</td>
<td>104</td>
<td>2</td>
</tr>
<tr>
<td>T2-w coronal</td>
<td>4</td>
<td>15-19</td>
<td>0.6x0.6</td>
<td>3350</td>
<td>105</td>
<td>2</td>
</tr>
<tr>
<td>T2-w sagittal</td>
<td>4</td>
<td>15-19</td>
<td>0.6x0.6</td>
<td>3810</td>
<td>105</td>
<td>2</td>
</tr>
<tr>
<td>DWI</td>
<td>SE-EPI</td>
<td>4</td>
<td>15-19</td>
<td>2800</td>
<td>81</td>
<td>10</td>
</tr>
<tr>
<td>T1-w DCE</td>
<td>GRE (FLASH 3D)</td>
<td>4</td>
<td>14</td>
<td>37</td>
<td>1.47</td>
<td>1</td>
</tr>
</tbody>
</table>

TR = repetition time; TE = echo time; GRAPPA = parallel imaging factor; T2-w = T2-weighted; TSE = turbo spin echo; DWI = diffusion-weighted imaging; SE-EPI = spin echo-echo planar imaging; T1-w = T1-weighted; DCE = dynamic contrast enhanced imaging; GRE = gradient echo imaging; FLASH = fast low-angle shot imaging.

Magnetic resonance imaging–guided biopsy
An average of 4 wk (range: 2–6 wk) following tumour detection by MP-MRI, an MR-GB (using MR-compatible 18G needles with a sampling length of 17 mm) of the previously determined TSRs was performed using a commercially available transrectal MR biopsy device (Invivo, Schwerin, Germany). The translation of initial MR imaging findings to the subsequent MR-GB was previously described in detail (13). The lowest signal areas on the ADC maps within the TSR were used to target biopsies.

Histopathologic analysis of biopsy specimens
Biopsy tissue cores were fixed in 10% neutral-buffered formalin stained with haematoxylin-eosin, and a 5-mm tissue section was prepared before evaluation by one urogenital pathologist (CAHK) with 17 yr of experience in prostate pathology. All clinical features were available to the histopathologist. For cores containing cancer, a GS was determined using the 2005 International Society of Urogenital Pathology (ISUP) criteria. The primary, secondary, and tertiary Gleason grades were determined, and the highest Gleason grade (HGG) was identified.

Reconstructed whole-mount step-section preparation
Following RP, specimens were processed and cut into 4-mm-thick slices, perpendicular to the dorsal-rectal surface and parallel to the transverse T2-weighted imaging plane. All slices were completely evaluated on 5-mm sections stained with haematoxylin-eosin. The presence and extent of PCa was outlined by the same
pathologist (who also evaluated all biopsies). Each tumour was graded according to the 2005 ISUP modified Gleason grading system (14). As with the assessment of biopsies, the primary to tertiary Gleason grades and the HGG identified within the prostate was noted.

**Statistical analysis**

Cross-tabulation analysis of the biopsy and RP findings was done. For both MR-GB and TRUSBx cohorts, performance rates (percentage) with RP were determined for the HGG. Then, for RP HGG 5, undergrading was further defined as “substantial” if the corresponding biopsy was HGG 3. Finally, performance rates between biopsy and RP HGG groups were determined separately for patients with PSA ≤10 ng/ml and those with PSA >10 ng/ml. Chi-square analyses with Fisher exact tests were performed to evaluate the significance of differences between MR-GB and TRUSBx performance rates. The t test was performed to determine the differences in mean PSA, prostate volume, and dominant tumour volume. Significance was considered when p < 0.05. Statistical analyses were performed with SPSS software v.16.0.01 (IBM Corp, Somers, NY, USA) (Figs. 1–3).

**Results**

Ninety-eight patients fulfilled the inclusion criteria. In 34 of 98 patients a tumour diagnosis was made using MR-GB (median: 3 cores, range: 1–5; median number of biopsies/TSR: 2, range: 1–3), and in 64 of 98 patients a diagnosis was made using 10-core TRUSBx. The median duration of the procedure for MR-GB was 29 min (range: 15–75 min). The median duration between MR-GB and RP was 6 wk (range: 3–11 wk) and between TRUSBx and RP was 5 wk (range: 2–9 wk). Table 2 summarises the patients’ demographic and clinical parameters.

No significant differences between MR-GB and TRUSBx cohorts were observed for percentage stage pT3 (35% vs 38%; p = 0.83), mean dominant aggressive tumour volume (4.85 cm$^3$ vs 4.52 cm$^3$; p = 0.69), or mean prostate volume (41 cm$^3$ vs 36 cm$^3$; p = 0.61). No significant differences were observed for the overall proportions of patients on RP having HGG 3 (35% vs 28%; p = 0.50), 4 (32% vs 41%; p = 0.51), and 5 (32% vs 31%; p = 1.00) for the MR-GB and TRUSBx cohort, respectively. The RP presence of HGG 4 was associated with extracapsular extension in 39–46% and the presence of HGG 5, in 64–70%. Table 3 and 4 present a summary of biopsy and RP findings.
Categorisation of HGG on biopsy and RP revealed an overall performance for MR-GB of 88% (30 of 34) versus 55% (35 of 64) for TRUSBx. In the MR-GB cohort, an exact performance with RP HGG 3 was 100% (12 of 12); for HGG 4, 91% (10 of 11); and for HGG 5, 73% (8 of 11). The corresponding performance rates for TRUSBx were 94% (17 of 18; p = 0.41), 46% (12 of 26; p = 0.01), and 30% (6 of 20; p = 0.02), respectively (Fig. 1). For biopsies determined as low grade (HGG 3), the positive predictive value (PPV) for MR-GB to represent true low grade was 92% (12 of 13); for TRUSBx the PPV was 45% (17 of 38; p = 0.001). Overall, undergrading of tumours with RP HGG 4/5 was 46% (25 of 46) for TRUSBx and 5% (1 of 22) for MR-GB. No overgrading was observed for MR-GB, although this was evident in one TRUSBx patient (false HGG 4 instead of 3). Undergrading for RP HGG 5 was 27% (3 of 11) in MR-GB compared with 70% (14 of 20) for TRUSBx. TRUSBx showed substantial undergrading (RP HGG 5) in 57% (8 of 14), whereas no substantial undergrading occurred with MR-GB.

**Table 2.** Patient and pathology characteristics

<table>
<thead>
<tr>
<th></th>
<th>MR-GB</th>
<th>10-core biopsy</th>
<th>Significance, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>34</td>
<td>64</td>
<td>NA</td>
</tr>
<tr>
<td>Age, yr (range)</td>
<td>66 (51-74)</td>
<td>66 (41-74)</td>
<td>0.22</td>
</tr>
<tr>
<td>No. of biopsies (range)</td>
<td>3 (1-5)</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>Stage (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>22/34 (65)</td>
<td>40/64 (62)</td>
<td>0.83</td>
</tr>
<tr>
<td>pT3</td>
<td>12/34 (35)</td>
<td>24/64 (38)</td>
<td></td>
</tr>
<tr>
<td>Prostate volume Median, cm³ (range)</td>
<td>41 (12-79)</td>
<td>36 (17-126)</td>
<td>0.61</td>
</tr>
<tr>
<td>PSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, ng/ml (range)</td>
<td>12 (3-40)</td>
<td>8 (2-47)</td>
<td>0.02*</td>
</tr>
<tr>
<td>DA tumour volume Median, cm³ (range)</td>
<td>4.85 (0.1-33)</td>
<td>4.52 (0.1-33.5)</td>
<td>0.69</td>
</tr>
<tr>
<td>Prevalence of tumours in RP HGG category, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HGG 3</td>
<td>35 (12/34)</td>
<td>28 (18/64)</td>
<td>0.50</td>
</tr>
<tr>
<td>•Stage pT3</td>
<td>0 (0/12)</td>
<td>0 (0/18)</td>
<td>NA</td>
</tr>
<tr>
<td>HGG 4</td>
<td>32 (11/34)</td>
<td>41 (26/64)</td>
<td>0.51</td>
</tr>
<tr>
<td>•Stage pT3</td>
<td>45 (5/11)</td>
<td>38 (10/26)</td>
<td>0.73</td>
</tr>
<tr>
<td>HGG 5</td>
<td>32 (11/34)</td>
<td>31 (20/64)</td>
<td>1.00</td>
</tr>
<tr>
<td>•Stage pT3</td>
<td>64 (7/11)</td>
<td>80 (16/20)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

MR-GB = magnetic resonance imaging guided prostate biopsies; NA = not applicable; PSA = prostate-specific antigen; DA = dominant aggressive; RP = radical prostatectomy; HGG = highest Gleason grades.
PSA values for the MR-GB cohort (median PSA: 12 ng/ml) and TRUSBx cohort (median PSA: 8 ng/ml) showed a significant difference (p = 0.02). Subgroup analysis was performed for patients with PSA >10 ng/ml versus PSA ≤10 ng/ml. For patients with PSA ≤10 ng/ml, 0% (0 of 12) undergrading was seen for MR-GB, whereas for TRUSBx, undergrading occurred in 41% (18 of 44; p = 0.01). For patients with PSA > 10 ng/ml, MR-GB revealed an 18% (4 of 22) undergrading and TRUSBx a 55% (11 of 20; p = 0.01) undergrading. Table 3 summarises the performance rates. Figs. 2 and 3 show imaging findings in a TRUSBx and MR-GB patient.

Discussion

In this prospective study, 3-T DWI targeted MR-GB sampling improved the pre-treatment assessment of PCa aggressiveness. The Gleason grades as determined with MR-GB showed a high performance rate (88%) with prostatectomy. This is in sharp contrast to 10-core TRUSBx, which showed a 55% performance rate. In this study the most abnormal ADC regions following MP-MRI localisation of tumour were used to target biopsies. To our knowledge, this is the first prospective report on the use of DWI to obtain PCa biopsies that are more representative for true RP Gleason grade. These results confirm prior retrospective studies on the ability of DWI to visualise tumour aggressiveness and serve as a platform for improved pre-treatment prediction of true Gleason grades (15,16).

Table 3. Cross-tabulations for cohorts based on highest Gleason grade grouping

<table>
<thead>
<tr>
<th></th>
<th>Prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HGG 3</td>
</tr>
<tr>
<td>TRUSBx</td>
<td></td>
</tr>
<tr>
<td>HGG 3</td>
<td>17</td>
</tr>
<tr>
<td>HGG 4</td>
<td>1</td>
</tr>
<tr>
<td>HGG 5</td>
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</tr>
<tr>
<td></td>
<td>94% (17/18)</td>
</tr>
<tr>
<td>MR-GB</td>
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</tr>
<tr>
<td>HGG 3</td>
<td>12</td>
</tr>
<tr>
<td>HGG 4</td>
<td>0</td>
</tr>
<tr>
<td>HGG 5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>100% (12/12)</td>
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HGG = highest Gleason grade; TRUSBx = transrectal ultrasound-guided biopsy; MR-GB = magnetic resonance imaging guided biopsy.
Prospective Assessment of Prostate Cancer Aggressiveness Using 3-T Diffusion-Weighted Magnetic Resonance Imaging–Guided Biopsies Versus a Systematic 10-Core Transrectal Ultrasound Prostate Biopsy Cohort.

**Figure 1.** Performance rates according to highest Gleason grade (HGG) categorization: 10-core transrectal ultrasound-guided biopsy (TRUSBx) versus magnetic resonance imaging–guided biopsy (MR-GB).

<table>
<thead>
<tr>
<th>Table 4. Performance analysis between biopsy and radical prostatectomy cohorts</th>
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<td>Performance rates MR-GB, %</td>
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<td>Overall Bx concord. with RP HGG</td>
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<td>Bx concord. With RP HGG 3</td>
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<td>Bx concord. With RP HGG 4</td>
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<td>Bx concord. With RP HGG 5</td>
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<td>Bx concord. With RP HGG 4/5</td>
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<td>PPV for Bx and RP HGG 3</td>
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<td>PSA ≤10 ng/ml (percentage of patients)</td>
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<td>Overall HGG performance</td>
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<tr>
<td>PSA &gt;10 ng/ml (percentage of patients)</td>
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<td>Overall HGG performance</td>
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</table>

MR-GB = magnetic resonance imaging guided biopsy; TRUSBx = transrectal ultrasound-guided biopsy; RP = radical prostatectomy; Bx = biopsy; concord. = concordance; PPV = positive predictive value; PSA = prostate-specific antigen. * Denotes significance.
Figure 2. Patient with prostate-specific antigen of 11 ng/ml. Transrectal ultrasound–guided biopsy revealed a Gleason 3 plus 4 score. (a) T-2 weighted image shows a large tumour region in the entire dorsal peripheral zone (arrows). (b) On the apparent diffusion coefficient (ADC) maps, restriction is clearly visible for the same lesion. (c) On dynamic contrast-enhanced imaging, the $K_{trans}$ map shows irregular enhancement of the tumour. (d) Within the restricted regions, however, two regions with higher restriction are visible (yellow asterisks). (e) On the corresponding pathology step section, the tumour is delineated in light blue, corresponding to the findings on magnetic resonance imaging. Regions with focal Gleason grade 5, delineated with a dotted line, correspond exactly to the ADC “hot spots” findings. Final pathology showed a Gleason 3 + 4 + 5, pT3 tumour.
Figure 3. Patient with prostate-specific antigen of 12 ng/ml and a four times prior negative transrectal ultrasound–guided biopsy. (a) T2-weighted image with focal lesion visible in right peripheral zone. (b) On the dynamic contrast-enhanced imaging $K^{trans}$ map, diffuse enhancement of the peripheral zone is seen. (c) Apparent diffusion coefficient (ADC) derived from diffusion-weighted imaging shows a focal small lesion with clear restriction (yellow asterisk). (d) True fast imaging with steady-state precession image during biopsy with the needle guider directed towards the most suspicious region before taking a magnetic resonance imaging–guided biopsy (MR-GB). The MR-GB revealed a Gleason 4 component. (e) Prostatectomy step section showed a pT2c tumor in the right peripheral zone (light blue = Gleason 3 component; red = Gleason 4). (f) The volume of the Gleason 3 component is underestimated by the MRI; however, volume of the focal “hot spot” on the ADC images exactly matches with the final pathology: Gleason 4. The red lines indicate the lateral areas where TRUSBx usually sample the prostate and why this can miss the hotspot of aggressive tumour.
The importance of correct pre-treatment assessment of PCa aggressiveness is widely accepted. A shift from radical therapy to individualised tailored therapy has been advocated (17). A cornerstone of this individual-based risk stratification is the correct pre-treatment identification of true Gleason grades. Patients without grade 4/5 components are potential candidates for less invasive treatment, such as active surveillance or local therapy (18). Patients harbouring high-grade components definitely need further evaluation for possible extracapsular extension and skeletal or nodal metastasis. High-grade PCa managed with non-curative intent substantially reduces life expectancy (19). A European Organisation for Research and Treatment of Cancer trial showed that high-risk patients definitely benefit from adjuvant hormone therapy. Correctly stratifying patients into low or high risk, therefore, is of utmost importance (20).

Numerous studies have addressed the correlation between GS in biopsy and corresponding RP. These show that increasing the number of biopsies increases the performance. In earlier studies using sextant biopsies, undergrading was reported in 44–60% (21,22), whereas recent studies with extended biopsy schemes reported lower values of 32–38% (4,5,21,23). When comparing overall performance rates between studies, the most important factor that needs diligent consideration is the prevalence of low-grade tumours. Using extended 12 cores, San Francisco et al. (24) showed an exact GS performance rate of 76%. However, the prevalence of low-grade tumours in their RP was 72%. This artificially increases the overall performance rates. When only evaluating their high-grade tumours (HGG 4/5), a 32% undergrading was still evident. A large cohort from John Hopkins (25) revealed an overall GS agreement of 76%. The prevalence of low-grade tumours in RP was high at 67%. When only the high-grade tumours on RP were chosen, an undergrading of 42% was noted. Our TRUSBx revealed a 46% undergrading of tumours identified as HGG 4/5 on RP. This is in agreement with these two studies. Yet, for MR-GB, only a 5% undergrading of high-grade tumours was seen. Our TRUSBx revealed substantial undergrading in 57% of RP HGG 5 tumours (i.e., showing a biopsy HGG of 3). In all cases of HGG 5 undergrading, MR biopsies revealed a HGG of 4, thus showing a more acceptable underestimate. The prevalence of HGG 3, 4, and 5 groups in our two cohorts did not show statistically significant differences. We therefore believe our results with MR-GB show a substantial improvement of performance rates compared with current practice and literature. In addition, with MR-GB, only a median of 3 cores per patient were taken, instead of 10 with TRUSBx.
Clinically important factors may be associated with prostate biopsy undergrading. Isariyawongse et al. (26) showed that both age and PSA values are important in this respect. Biopsies in patients with PSA values 10–20 ng/ml and PSA >20 ng/ml had odds ratios of 2.11 and 3.64, respectively, compared with PSA <10 ng/ml for representing undergrading of true GS in prostatectomy. Our overall baseline PSA values for the two cohorts did indeed show a significant difference, however, to the detriment of MR-GB where higher PSA values were found. Usually a PSA cut-off value of 10 ng/ml is used as an integral part of decision making regarding further diagnostic tests and treatment (i.e., opting for active surveillance) (27). We therefore performed a subgroup analysis for patients with PSA ≤10 ng/ml and those with PSA >10 ng/ml. For both subgroups, MR-GBs were superior in performance rates. The PSA value evidently did not influence the performance rates of biopsies with RP findings in our study. Stackhouse et al. (28) evaluated additional factors that may predict undergrading. Of relevance to our study would also be their identified factors: patient age and prostate weight (and thus prostate volume). Increasing age has been shown to have increasing odds ratios for undergrading. In our cohort, both groups had the same median ages of 66 yr (p = 0.22). No significant differences in prostate volumes (p = 0.61) or dominant tumour volume (p = 0.69) were seen in our cohorts.

In addition, we evaluated two further factors that in our opinion may also represent biases in cohorts and possibly having an influence on the degree of undergrading: dominant aggressive tumour volume and tumour stage at RP. In a paper by Resnick et al. (29) with a large cohort of 2411 patients, biopsy and prostatectomy features of patients at first, second, and third TRUSBx sessions were evaluated. With each increase in the number of biopsy sessions, the undergrading of GS ≥7 increased from 18% at the first biopsy session, to 55% at the second, to 58% at the third, despite the increasing overall prevalence of GS 6 tumours with every subsequent session. These findings would suggest an increased likelihood of undergrading for our repeat biopsies. On the contrary, however, despite representing a re-biopsy session, our MR-GB still outperformed a first-session 10-core TRUSBx. We therefore believe that despite these minor differences between our cohorts, no important clinical or pathologic factor could be determined that might bias our MR-GB cohort to a more favourable group regarding the likelihood of undergrading.

DWI is rapidly gaining importance as a valuable non-invasive biomarker for determining tumour response to therapy in a large variety of tumours (30). In addition, DWI is also increasingly being used to determine tumour aggressiveness
noninvasively. Its role for the assessment of aggressiveness and cellularity in breast tumours (31), soft tissue sarcomas (32), renal tumours (33), and hepatocellular tumours (34) has been reported. For PCa, recent data have shown that ADC values derived from DWI have a high discriminatory performance in separating low-grade versus combined intermediate- and high-grade cancers (15).

A number of limitations exist. A randomised trial between MR-GB versus TRUSBx or performing both TRUS- and Mr-guided biopsies in the same patient would represent the ideal scenario. Our approach, however, was to determine the performance in a routine clinical setup as performed in our hospital. A second limitation was the relatively low number of patients. Nonetheless, differences were statistically significant, even with this small number of patients. Although a multiparametric approach has been proven to be the most useful for the evaluation of PCa on MR imaging, it still requires a high level of expertise, and observer variability may be an issue (35). Our results represent findings of an expert centre that uses in-house developed analytical software and whose clinicians have numerous years of experience, so they might be an overoptimistic prediction of performance attainable in smaller non-expert institutions. A final limitation is the potential differences of the two cohorts as discussed previously.

Conclusions

Biopsies targeted towards the most abnormal regions on 3-T DWI MR imaging represent a substantially improved method for the assessment of true tumour aggressiveness and can therefore represent an indispensable tool in the diagnosis and management of patients with PCa. This will probably also hold true for other malignancies. Thus its use is strongly advocated.
References


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

Submitted to Radiology
Abstract

Purpose: To evaluate 3T multiparametric magnetic resonance (MR) imaging (MP-MRI) and MR guided biopsy (MRGB) for early risk re-stratification of patients on active surveillance in the Prostate cancer Research International: Active Surveillance (PRIAS) trial.

Materials and Methods: Within 4 hospitals participating in PRIAS, a side-study was initiated in 66 of 82 consecutively and prospectively included patients (2009-2012). Informed consent was obtained and institutional review boards approved our study. Pelvic MR imaging, prostate MP-MRI and MRGB were performed at 3 and at 12 months after prostate cancer diagnosis. Cancer suspicious regions (CSR)s were defined on MP-MRI using PI-RADS scores.

Risk re-stratification criteria for active surveillance discontinuance were 1) based on MR imaging: histopathologically proven MR imaging suspicion of node/bone metastases and/or 2) based on MRGB specimen histopathology: Gleason grade (GG) 4 and/or 5 and/or a stage ≥ pT3 (cancer invading peri-prostatic fat or seminal vesicles) and/or cancer multifocality (≥ 3 foci).

Results: Based on MP-MRI and MRGB an additional 24% (15/64) and 10% (3/30) of patients were risk re-stratified at 3 and 12 months of follow-up. An overall CSR PI-RADS ≤ 2 had a negative predictive value (NPV) of 84% (38/45) and 100% (45/45) for detection of cancer and GG 4-5 cancer upon MRGB. A CSR PI-RADS ≥ 4 had a sensitivity of 92% (11/12) for detection of GG 4-5 cancer upon MRGB.

Conclusion: Application of MP-MRI and MRGB in active surveillance may contribute in early identification of patients with GG 4-5 prostate cancers, while improving the selection of active surveillance suitable patients.
Introduction

Prevalence of low-risk prostate cancer (PCa) has increased due to the application of prostate-specific antigen (PSA) testing (1). Low-risk PCa patients are prone to overtreatment and its complications, which can undermine a patient’s quality of life (1, 2). To avoid overtreatment, active surveillance is an accepted treatment alternative for low-risk PCa patients (3).

Active surveillance is mostly performed within trials, such as the Prostate cancer Research International: Active Surveillance (PRIAS) trial (4). Selected patients with presumed low-risk PCa are followed by regular PSA measurements, digital rectal examinations and annual repeat systematic transrectal ultrasound-guided biopsy (TRUS-Bx). PSA kinetics, Gleason grade (GG) upgrading (GG 4 or 5) and volume progression are generally used as criteria for disease progression (5). However, rather due to TRUS-Bx undersampling upon inclusion than due to true cancer progression, 20-30% of active surveillance patients actually harbor intermediate-to high-risk cancers at inclusion (5, 6, 7). Early identification of these patients, who were incorrectly deemed suitable for active surveillance, may be essential to maintain the opportunity for appropriate curative treatment within their window of curability. The detection of a GG 4-5 component or of a larger cancer volume or of multifocality of a GG ≤3 cancer (5), results in re-stratification of these PCa patients into a higher risk category. Risk re-stratification implies that a patient cannot continue active surveillance and needs radical treatment.

Magnetic resonance (MR) guided biopsy (MRGB) has shown to improve identification of patients with GG 4-5 cancers due to a better highest GG concordance (88%) with prostatectomy specimens compared to TRUS-Bx (55%, p=0.001). This higher GG concordance of MRGB specimens with radical prostatectomy specimens is possible due to better detection and targeting of the most aggressive area of a cancer suspicious region (CSR) on MR imaging (8). Only a few studies have related MR imaging results to active surveillance outcome (9-13).

To our knowledge, MRGB has not previously been evaluated at active surveillance inclusion. Our hypothesis is that combined multiparametric MR imaging (MP-MRI) and MRGB will improve current TRUS-Bx-based selection of patients for active surveillance by early detection of patients harboring intermediate- to high-risk cancers. Therefore, our purpose is to evaluate the value of 3T MP-MRI and MRGB for early risk re-stratification of patients on active surveillance in the Prostate cancer Research International: Active Surveillance (PRIAS) trial.
Total of included PRIAS patients from August 12th 2009 – March 2nd 2012, n=1487

Included PRIAS patients in participating referral centers, n=82

Included patients in MR-PRIAS side-study, n=66 (4% (66/1487) of total and 80% (66/82) of inclusion in participating centers)

MR imaging pelvic and lower lumbar lymph nodes and bones and MP-MRI of the prostate, n=66 (part of index test)

PRIAS patients not in side study due to contra-indications for MRI or Gadolinium or due to patient-related issues (e.g. burden MRI and/or MR-Bx), n=16

Exclusion based on patient request, n=2

No CSRs on MP-MRI, no performance of MR-Bx, n=1

Exclusion due to MR imaging detected bone metastasis of malignancy of unknown origin in third lumbar vertebra, n=1

Initial risk re-stratified patients, who were no longer eligible for active surveillance, n=15, 24% (15/63)

MR-Bx, n=63 (part of index test)

Patients who were active surveillance suitable, n=47 (75%)

Patients remaining in MR-PRIAS after MR-MRI and MR-Bx, n=48, 75% (48/64)

At 31-7-2012: Repeat MP-MRI, repeat MR-Bx and repeat TRUS-Bx, N=37

Exclusion n=7, based on:
- impossible repeat examinations due to: shoulder injury (n=1), pain after MR-Bx (n=1) or complications of chemotherapy for lymphoma (n=2)
- patient request, n=3

Patients remaining in MR-PRIAS after MR-MRI and MR-Bx, n=16, 53% (16/30)

Repeat risk re-stratified patients, who were no longer eligible for active surveillance, n=14, 47% (14/30)

**Figure 1.** Study Flow-diagram showing patient selection. CSR= cancer suspicious region, MRI= magnetic resonance imaging, MP-MRI= multiparametric MR imaging, MRGB= MR guided prostate biopsy, MR= magnetic resonance, PRIAS= Prostate Cancer Research International Active Surveillance study, MR-PRIAS= MR-PRIAS= MR imaging sub-study of the Prostate Cancer Research International Active Surveillance study, CSR= cancer suspicious region on magnetic resonance imaging, TRUS-Bx= systematic transrectal ultrasound biopsy.
Materials and methods
Within 4 reference centers participating in the PRIAS trial (NTR1718 http://www.trialregister.nl), a prospective side-study (MR-PRIAS: NTR2006) was initiated in consecutively and prospectively included 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 active surveillance underwent MP-MRI in the second and MRGB in the third month of follow-up after initial cancer diagnosis upon systematic TRUS-Bx (time-point zero). Initial systematic TRUS-Bx existed out of 9-10 cores sampling both the transition and the peripheral zone. Part of our patient population has been reported earlier (14). The earlier paper described the value of apparent diffusion coefficient values of MRGB DWI scans for PCa differentiation in prostate cancer patients on active surveillance. The current study reports on overall outcome of incorporating MP-MRI and MRGB in active surveillance 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, diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCE-MRI) (40 min protocol). Imaging was performed on a 3T MR system (Trio Tim, Siemens, Erlangen, Germany) using a pelvic phased-array and an endorectal coil (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 Table 1.
Appendix 1. Inclusion and Exclusion criteria used in the PRIAS study with an additional exclusion criterion used in the MR-PRIAS sub-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
- 1 or 2 biopsy cores invaded with 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

### Additional exclusion criterion MR-PRIAS sub-study
- Contra-indications to MRI or to gadolinium based contrast agents


### Table 1. MP-MRI and MRGB 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)</th>
<th>Matrix size (mm×mm×mm)</th>
<th>Voxel size (mm×mm×mm)</th>
<th>b-values (s/mm²)</th>
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3D= three-dimensional, T2WI= T2-weighted MR imaging, DWI= diffusion-weighted MR imaging, DCE-MRI= dynamic contrast-enhanced MR imaging, TSE= turbo-spin echo, GE= gradient echo, SSEPI= single-shot echo-planar imaging, SSFP= steady state free precession, TR= repetition time, TE= echo time, MR= magnetic resonance.
**MR imaging interpretation**

An experienced radiologist (x.x) with 18 years of experience in prostate MR imaging evaluated the MP-MRI examinations on in-house developed software, while disposing of clinical patient data (15). On the software, T2-weighted MR imaging, DWI and DCE-MRI were interpreted simultaneously (16). The PI-RADS system was used to define CSRs (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 (17). 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 (18). When MP-MRI lacked CSRs, active surveillance was continued without performing MRGB.

**MR guided prostate biopsy**

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

**Risk re-stratification**

Risk re-stratification, i.e. stratification into a higher PCa risk category, was based on 1) histopathologically proven MR imaging suspicion of node/bone metastases of PCa (4) and/or 2) MRGB histopathology specimens (of CSRs) containing a) a GG 4 and/or 5 component (4) and/or b) stage ≥ pT3 cancer (cancer invading peri-prostatic fat or seminal vesicles) (19) and/or c) multifocality of ≥ 3 foci Gleason score ≤3+3 cancer (including the foci in the initial TRUS-Bx). The latter criterion of cancer multifocality was applied to evaluate the number of additionally detected cancer foci by MRGB and to compare it to the PRIAS risk re-stratification criterion of >2 cores with PCa in TRUS-Bx (4). An MRGB focus located contra-lateral to the initial TRUS-Bx 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 were referred to undergo radical treatment.

In order to evaluate cancer volume using MRGB and TRUS-Bx specimens, we retrospectively measured maximal cancer core length (MCCL): the longest biopsy core specimen cancer core length taken from one CSR. A MCCL ≥ 6 mm is related to a cancer volume ≥ 0.5 mL in RP specimens using schematic mapping biopsy (20).
Follow-up
After 11-12 months of follow-up, repeat MP-MRI of the local prostate, with identical imaging parameters to the initial MR imaging exam, was performed. Based on repeat MP-MRI, an additional repeat MRGB, similar in procedure to the initial MRGB, was performed in a second separate imaging session. After repeat MRGB, a repeat TRUS-Bx session was performed later on the same day by a nurse practitioner of our Urology Department, who was blinded for MR imaging results. Repeat TRUS-Bx existed out of 10 cores from the peripheral zone and transition zone. TRUS-Bx risk re-stratification criteria consisted of PCa presence in >2 cores or a Gleason score ≥7 (7). Risk re-stratification criteria for repeat MP-MRI and repeat MRGB were according to initial criteria.

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

Statistical analysis
Patient risk re-stratification rates were determined for initial and repeat MRGB and for repeat TRUS-Bx. 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 (IQR). 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. Receiver operating characteristic 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 (Figure 1). Two patients requested to be excluded from the protocol before MRGB. Patient

Characteristics of the remaining 64 active surveillance patients are shown in Table 2. 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 2.

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 3. Sixty percent (9/15) of risk re-stratified patients had an MCCL ≥ 6.0 mm. The remaining 48 patients continued active surveillance. 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 4. 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-Bx. 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 2. Patient Characteristics of 64 MP-MRI patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All included patients # (n=64)</th>
<th>Patients remaining on active surveillance (n=48) ^</th>
<th>Patients with risk re-stratification (n=15) ¶</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Median (IQR)</td>
<td>65.7 (62.1-70.1)</td>
<td>66.9 (62.0-70.5)</td>
<td>65.2 (61.8-68.2)</td>
<td>n.a.</td>
</tr>
<tr>
<td>PSA (ng/mL), Mean (CI)</td>
<td>6.5 (5.99-6.93)</td>
<td>6.5 (5.87-7.03)</td>
<td>6.6 (5.8-7.4)</td>
<td>0.90</td>
</tr>
<tr>
<td>PSA density (ng/mL/mL), Mean (CI)</td>
<td>0.1 (0.12-0.14)</td>
<td>0.1 (0.11-0.14)</td>
<td>0.2 (0.14-0.19)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Prostate volume (mL), Median (IQR)</td>
<td>45.8 (38.0-66.1)</td>
<td>48.2 (40.0-69.4)</td>
<td>38.0 (30.0-55.0)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Number previous negative TRUS-Bx sessions Median (Range)</td>
<td>0 (0-7)</td>
<td>0 (0-7)</td>
<td>0 (0-0)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Total number of TRUS-Bx cores at diagnosis, Median (IQR)</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
<td>9 (9-10)</td>
<td>n.a.</td>
</tr>
<tr>
<td>TRUS-Bx to MRI interval in months, Median (IQR)</td>
<td>2.1 (1.6-2.7)</td>
<td>2.3 (1.6-2.8)</td>
<td>1.8 (1.5-2.3)</td>
<td>n.a.</td>
</tr>
<tr>
<td>TRUS-Bx to MR-Bx Interval months, median (IQR)</td>
<td>2.7 (2.0-3.3)</td>
<td>2.7 (2.1-3.4)</td>
<td>2.4 (2.0-2.7)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Clinical stage, T1c</td>
<td>76.6 (49/64), [64.8-85.4]</td>
<td>77.1 (37/48), [63.3-86.9]</td>
<td>73.3 (11/15), [47.6-89.5]</td>
<td>1.00</td>
</tr>
<tr>
<td>Clinical stage, T2a</td>
<td>18.8 (12/64), [10.9-30.1]</td>
<td>18.8 (9/48), [10.0-32.2]</td>
<td>20.0 (3/15), [6.2-46.0]</td>
<td>1.00</td>
</tr>
<tr>
<td>Clinical stage, T2b</td>
<td>3.1 (2/64), [0.2-11.3]</td>
<td>2.1 (1/48), [0.0-11.9]</td>
<td>6.7 (1/15), [0-31.8]</td>
<td>0.42</td>
</tr>
<tr>
<td>Clinical stage, T2c</td>
<td>1.6 (1/64), [0.0-9.1]</td>
<td>2.1 (1/48), [0.0-11.9]</td>
<td>0.0 (0/15), [0-23.9]</td>
<td>1.00</td>
</tr>
<tr>
<td>Positive TRUS-Bx cores at diagnosis, 1</td>
<td>67.2 (43/64), [55.0-77.5]</td>
<td>68.8 (33/48), [54.6-80.1]</td>
<td>60.0 (9/15), [35.7-80.3]</td>
<td>0.76</td>
</tr>
<tr>
<td>Positive TRUS-Bx cores at diagnosis, 2</td>
<td>32.8 (21/64), [22.5-45.0]</td>
<td>31.3 (15/48), [19.9-45.4]</td>
<td>40.0 (6/15), [19.8-64.3]</td>
<td>0.78</td>
</tr>
<tr>
<td>Gleason score at diagnosis, 3+3=6</td>
<td>93.8 (60/64), [84.6-98.0]</td>
<td>91.7 (44/48), [79.9-97.2]</td>
<td>100.0 (15/15), [76.1-100.0]</td>
<td>0.56</td>
</tr>
<tr>
<td>Gleason score at diagnosis, lower</td>
<td>6.3 (4/64), [2.0-15.4]</td>
<td>8.3 (4/48), [2.8-20.1]</td>
<td>0.0 (0/15), [0-23.9]</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Prostate volume 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 MR-Bx patients + 1 patient without MR-Bx 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= random systematic tranrectal ultrasound biopsy, AS= active surveillance, PSA= prostate specific antigen, MRI = magnetic resonance imaging, CI= 95% confidence interval, MR-Bx= MR guided prostate biopsy.
Table 3. Reasons for initial patient risk re-stratification and deferred treatment at 3 of follow-up.

<table>
<thead>
<tr>
<th>MRGB results: MR-PRIAS unsuitable patients with risk re-stratification</th>
<th>Number (%)</th>
<th>MRGB 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 extracapsular extension#</td>
<td>2 (13)</td>
<td>8.5 (6.5-10.5) ≥6 mm: n=1</td>
</tr>
<tr>
<td>Total (% MR-Bx)</td>
<td>15 (24)</td>
<td>6.9 (4.3-9.5) ≥6 mm: n=9</td>
</tr>
</tbody>
</table>

# not conform predefined risk re-stratification criteria, MRGB= MR guided prostate biopsy, MR-PRIAS= MR imaging sub-study of the Prostate Cancer Research International Active Surveillance study, 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. A stage T3 was defined as cancer invading the (peri-prostatic) fat in the MR guided biopsy specimen core.

**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 peripheral zone, 15% (23/155) were located in the transition zone or at the border of the peripheral and transition zone 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). Az values for PCa and GG 4-5 PCa detection using overall PI-RADS scores were 0.73 (0.65-0.82) and 0.81 (0.70-0.92) respectively.

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 to DWI (in 32% (33/107), p=0.07).

An overall CSR PI-RADS ≤2 had a NPV of 84% (38/45) for detection of cancer and a NPV of 100% (45/45) for detection of a GG 4-5 cancer upon MRGB. A CSR PI-RADS ≥4 had a sensitivity of 75% (36/48) and f 92% (11/12) for detection of cancer and of GG 4-5 cancer upon subsequent MRGB respectively. Sixty-four percent (69/107) of cancer-negative CSRs had an overall PI-RADS ≥3.
Table 4. Reasons for patient risk re-stratification and deferred treatment at repeat examinations at 12 months of follow-up.

<table>
<thead>
<tr>
<th>Repeat MRGB results: MR-PRIAS unsuitable patients with risk re-stratification at 12 months of follow-up</th>
<th>Number ( % subtotal risk re-stratification patients)</th>
<th>MR-Bx maximal cancer core length in mm (mean, 95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both MRGB and TRUS-Bx GG 4 and/or 5</td>
<td>4 (31)</td>
<td>5.3 (3.8-6.8)</td>
</tr>
<tr>
<td>MRGB GG 4 and/or 5 and TRUS-Bx GS ≤3+3 cancer in &gt;2 cores</td>
<td>1 (8)</td>
<td>4.4 (n.a.)</td>
</tr>
<tr>
<td>Only TRUS-Bx GG 4 and/or 5</td>
<td>1 (8)</td>
<td>2.7 (n.a.)</td>
</tr>
<tr>
<td>TRUS-Bx GS ≤3+3 cancer in &gt;2 cores and MRGB multifocality</td>
<td>2 (14)</td>
<td>6.5 (5.5-7.5)</td>
</tr>
<tr>
<td>Only MRGB multifocality, 2 foci, n=1#</td>
<td>3 (21)</td>
<td>4.2 (1.3-7.0)</td>
</tr>
<tr>
<td>Only TRUS-Bx GS ≤3+3 cancer in &gt;2 cores</td>
<td>3 (23)</td>
<td>5.7 (2.8-8.6)</td>
</tr>
<tr>
<td>Total ( % MR-Bx)</td>
<td>14 (47)</td>
<td>5.0 (3.0-6.0)</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= systematic transrectal ultrasound biopsy, MR-PRIAS= MR imaging sub-study of the Prostate Cancer Research International Active Surveillance study, GG= Gleason grade, GS= Gleason score, MP-MRI= multiparametric MR imaging.

Discussion

Our initial results show that the application of multiparametric MR imaging and MR guided biopsy in an active surveillance protocol may contribute in early identification of patients with GG 4-5 cancers, while also improving the selection of active surveillance 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 repeat TRUS-Bx within 3 months after initial diagnosis (10, 22). At 12 months of follow-up, combined MP-MRI and MRGB added little to repeat systematic TRUS-Bx, 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-Bx. Due to TRUS-Bx systematic sampling of GG 2 and/or 3 cancers (23) or of small(er) volume GG 4 and/or 5 cancers, which may have been missed on initial and/or repeat MR imaging, repeat TRUS-Bx 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 GG and/or a small volume GG 4-5 components (23). In general, detected cancers at 12 months of follow-up had a lower mean cancer volume (5.0 mm MCCL) compared with cancers detected at 3 months of follow-up (6.9 mm MCCL).

MP-MRI had a sensitivity of 92% for detection of GG 4-5 cancer in case of higher PI-RADS scores (≥4) and a NPV of 100% for detection of GG 4-5 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 cancer presence (13). 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 prostate cancer detection accuracy using MP-MRI and MRGB in patients on active surveillance are difficult to compare to literature. Other studies on MRI implementation in active surveillance did not use MP-MRI and/or MRGB (9,11-13,24,25). Our accuracies of 73% and 81% for detection of PCa and GG 4-5 PCa were quite reasonable considering the expected prevalence of predominantly lower GG (2-3) cancers in this selected active surveillance patient population. Lower GG cancers are known to have lower detection rates compared to higher GG cancers (23).

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 (26).

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 (low 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 active surveillance patients, false-positive results may be reduced. However, within the current explorative phase of MRI implementation in active surveillance, an important clinical implication of our study is that in active surveillance 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 (9, 12, 24, 25).

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 cancer in both MRGB and TRUS-Bx also were risk re-stratified. Therefore, our risk re-stratification rates may be inaccurate. Fourthly, as MP-MRI results were read by an experienced radiologist, the general applicability of our results may be limited.

Incorporation of MR-MRI and MRGB in patients on active surveillance may be useful as it results in early additional risk re-stratification and radical treatment of patients with intermediate to high-risk cancers, who were undersampled by initial TRUS-Bx. Standardized MP-MRI interpretation using PI-RADS reveals that MP-MRI is a promising technique for differentiation between active surveillance suitable patients and patients with GG 4-5 cancers, the latter needing radical treatment. However, smaller (< 4.4 mm MCCL) 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 active surveillance may contribute in early identification of patients with GG 4-5 cancers, while also selecting active surveillance suitable patients.
Figure 2. Sixty-one year-old male on active surveillance with a PSA level of 7.1 ng/mL, a PSA density of 0.19 ng/mL/mL and a clinical stage T1C. This patient was diagnosed with Gleason score 6 (3+3) prostate cancer in 5 volume-percent in 1 out of 12 cores in the peripheral zone right base. Multiparametric MR imaging and MR guided biopsy, existing out of 4 cores only,
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/mm$^2$) at the level of the mid-prostate. A low ADC value of ADC $0.50 \times 10^{-3}$ mm$^2$/s, suspicious for prostate cancer, was present in the right side of the ventral transition zone (dotted line). (c) Axial overlay of $K^{max}$ 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). (e) 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.

References

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Evaluation of Diffusion-Weighted MR Imaging at Inclusion in an Active Surveillance Protocol for Low-Risk Prostate Cancer

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

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Abstract:

Purpose: We aimed to determine whether diffusion-weighted magnetic resonance imaging, by means of the apparent diffusion coefficient (ADC), is able to guide magnetic resonance guided biopsy 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 magnetic resonance imaging (MP-MRI) at inclusion for AS. Cancer-suspicious regions (CSRs) upon 3-T MP-MRI were identified in all patients, and magnetic resonance guided biopsy 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 was performed to detect differences between the groups. We used the area under the receiver operating characteristic curve 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} mm^2/s (SD, 0.29), whereas the CSRs with no PCa displayed a mean mADC of 1.26×10^{-3} mm^2/s (SD, 0.25; P < 0.001). Cancer-suspicious regions with a high-grade Gleason component displayed a mean mADC of 0.84×10^{-3} mm^2/s (SD, 0.35) vs a mean mADC for the low-grade CSRs of 1.09×10^{-3} mm^2/s (SD, 0.25; P < 0.05). A diagnostic accuracy of mADC for predicting the presence of PCa in a CSR with an area under the receiver operating characteristic curve of 0.73 was established (95% confidence interval, 0.61-0.84).

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

With the increasing incidence of low-risk prostate cancer (PCa) due to prostate-specific antigen (PSA) testing (1), active surveillance (AS) for PCa has become an appealing strategy in an increasing number of patients (2). 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 (3-7), 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 magnetic resonance (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 (8). 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 less than 0.2 ng/mL/mL, TRUS-guided biopsy Gleason score of 3 + 3 = 6 or lesser, and 2 positive TRUS-guided biopsy cores or lesser. Initial TRUS-guided biopsies were obtained according to local protocols with 9 to 13 cores taken. All consecutive patients included in PRIAS in 4 participating referral centers without contraindications for magnetic resonance imaging (MRI) were asked to sign informed consent for inclusion in a separate arm of PRIAS incorporating MP-MRI and MRGB (MRPRIAS, Dutch Trial Register NTR2006), which was approved by the local institutional review board.

**Multiparametric MRI and MRGB**

All patients underwent MP-MRI including anatomical T2-weighted and DWI sequences within 12 weeks from the inclusion in our protocol. Two radiologists (J.J.F., J.O.B.), with 9 and 18 years of experience in prostate MRI, evaluated the MP-MRI studies while being informed on the clinical data of the patients during the reading. Multiparametric magnetic resonance imaging was obtained on a 3-T MR system (Trio Tim; Siemens, Erlangen, Germany) using a pelvic phased-array coil and an endorectal coil (Medrad, Pittsburgh, PA) filled with 40 mL of perfluorocarbon. Dynamic contrast-enhanced MR imaging was performed using fast intravenous injection (2.5 mL/s) of 0.1 mmol of gadopentetate dimeglumine per kilogram of body weight. The used MP-MRI parameters are shown in Table 1. Every CSR was defined on anatomical T2-weighted MRI using DWI and dynamic contrast-enhanced MRI as described earlier (9). In short, all obtained MP-MRI imaging modalities were separately analyzed for CSRs according to the established criteria (10), and in case of an equivocal suspicion of PCa on any of the imaging modalities, the region was defined as a CSR delivering a high sensitivity reading. Importantly, DWI-derived b800 images (s/mm$^2$) were used to delineate CSRs. A lesion was defined as a CSR on DWI in case of focal restriction on the conventional ADC map in combination with an isointense to hyperintense signal intensity on the b800 image. From every CSR, at least 1 real-time MRGB was obtained on a 3-T scanner (MAGNETOM Skyra; Siemens, Erlangen, Germany) in a separate session by a single radiologist (C.M.H.) with 3 years of experience in prostate MRGB according to local protocol; MP-MRI data obtained at the MRGB procedure was not used for determination of additional CSRs. All patients received antibiotic prophylaxis with ciprofloxacin (500 mg) twice a day for 3 days, which started on the day before the biopsy. Two radiologists (C.M.H., T.H.), with 3 and 6 years of experience in MRGB, determined CSR sampling accuracy in a blinded consensus reading of MRGB confirmation scans.
Determination of ADC Characteristics
In a consensus reading by 2 observers (D.M.S., C.M.H.) who were blinded to patient and biopsy characteristics, regions of interest (ROIs), 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 (C.A.H.) using the International Society of Urological Pathology modified Gleason score classification (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, 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.
Table 1. Multiparametric MRI and MRGB characteristics.

<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</th>
<th>Voxel size, mm × mm × mm</th>
<th>b-values, s/mm²</th>
<th>Temporal resolution, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endorectal MP-MRI of the prostate</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</td>
<td>axial (TSE)</td>
<td>4280</td>
<td>99</td>
<td>120</td>
<td>3.0</td>
<td>180 × 178</td>
<td>448 × 448</td>
<td>0.4 × 0.4 × 3.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>coronal sagittal</td>
<td>3590</td>
<td>98</td>
<td>120</td>
<td>3.0</td>
<td>192 × 134</td>
<td>384 × 384</td>
<td>0.5 × 0.5 × 3.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>DWI</td>
<td>SSEPI Axial</td>
<td>2600</td>
<td>90</td>
<td>n.a.</td>
<td>3.0</td>
<td>204 × 204</td>
<td>136 × 136</td>
<td>1.5 × 1.5 × 3.0</td>
<td>0/50/500/800</td>
<td>n.a.</td>
</tr>
<tr>
<td>DCE-MRI GE Axial 3D</td>
<td></td>
<td>800</td>
<td>1.51</td>
<td>14</td>
<td>3.0</td>
<td>192 × 192</td>
<td>128 × 128</td>
<td>1.5 × 1.5 × 3.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>DCE-MRI Spoiled GE Axial 3D</td>
<td></td>
<td>36</td>
<td>1.4</td>
<td>10</td>
<td>3.0</td>
<td>192 × 192</td>
<td>128 × 128</td>
<td>1.5 × 1.5 × 3.0</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>T2WI</td>
<td>TSE Axial</td>
<td>3620</td>
<td>103</td>
<td>120</td>
<td>4.0</td>
<td>256 × 256</td>
<td>320 × 320</td>
<td>0.8 × 0.8 × 4.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>DWI</td>
<td>EPI Axial</td>
<td>3300</td>
<td>60</td>
<td>n.a.</td>
<td>3.6</td>
<td>260 × 211</td>
<td>160 × 120</td>
<td>2.2 × 1.6 × 3.6</td>
<td>0/100/400/800</td>
<td>n.a.</td>
</tr>
<tr>
<td>Balanced SSFP GE Axial and Sagittal</td>
<td></td>
<td>4.48</td>
<td>2.24</td>
<td>70</td>
<td>3.0</td>
<td>280 × 280</td>
<td>256 × 256</td>
<td>1.1 × 1.1 × 3.0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

DCE indicates dynamic contrast-enhanced; EPI, echo-planar imaging; GE: gradient echo; NA, not applicable; SSEPI, single-shot echo-planar imaging; SSFP, steady-state free precession; TE, time-to-echo; TR, time-to-repetition; TSE, turbo-spin echo; T2WI, T2-weighted imaging; and 3D, 3-dimensional.

Table 2. 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</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>
</tr>
<tr>
<td>Mean PSA-density</td>
<td>0.13 (0.02-0.28)</td>
<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</td>
<td>1.4 (1-2)</td>
<td>1.3 (1-2)</td>
<td>.5 (1-2)</td>
</tr>
<tr>
<td>Mean number of CSRs identified at MP-MRI</td>
<td>2.1 (0-4)</td>
<td>2.1 (0-4)</td>
<td>1.7 (1-2)</td>
</tr>
<tr>
<td>Mean number of PCA-positive CSRs on MRGB</td>
<td>0.6 (0-2)</td>
<td>0.5 (0-1)</td>
<td>1.2 (1-2)</td>
</tr>
<tr>
<td>Mean number of MRGB cores taken</td>
<td>3.9 (0-6)</td>
<td>3.8 (0-6)</td>
<td>4.0 (3-5)</td>
</tr>
</tbody>
</table>

All values are expressed as mean (range).
Figure 1. Case presentation. Images taken from a 62-year old patient with an initial PSA of 7.2 ng/mL and a PSA-density of 0.11 ng/mL/mL. Digital rectal examination revealed no abnormalities (cT1c), with a Gleason 3+3=6 PCa in 2 out of 9 random TRUS-guided biopsies. Multiparametric 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 hypo-intense lesion in the left peripheral zone upon T2-weighted imaging, corresponding to an area of hyperperfusion on dynamic contrast-enhanced imaging and hypo-intensity on the ADC-map, defined as CSR. Conventional ADC map at MRGB (D) showing a hypo-intense lesion in the left peripheral zone corresponding to CSR on the pre-MRGB multiparametric MRI (dotted outline). MRGB of CSR as identified on multiparametric MRI (E). Apparent diffusion coefficient calculation of this specific CSR 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 ROI. 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 density 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.

Magnetic resonance-guided biopsy confirmed PCa in 29 of the 53 patients (54.7%) and 32 of 104 CSRs (30.8%), thus leaving 24 of the 53 patients (45.3%) 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 density, or number of positive TRUS-guided biopsy cores were recorded for the patients with Gleason upgrading vs those without Gleason upgrading upon MRGB (Table 2).

The mean mADC for all CSRs was 1.19×10^{-3} mm^2/s (SD, 0.28) compared with a mean mADC of 1.43×10^{-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 1.04×10^{-3} mm^2/s (SD, 0.29), whereas the CSRs with no PCa upon MRGB displayed a mean mADC of 1.26×10^{-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 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 0.84×10^{-3} mm^2/s (SD, 0.35) vs a mean mADC for the low-grade CSRs of 1.09×10^{-3} mm^2/s (SD, 0.25; P < 0.05; Fig. 3).
Figure 2. ROC-curve of mADC for discrimination between CSRs harbouring no PCa versus any PCa upon MRGB.

Figure 3. Box-plots of mADC for CSRs harbouring no, low-grade or high grade PCa.
Discussion

In our presented series, we found mADC, as acquired from DWI, to significantly predict the presence of PCa when sampled by targeted MRGB in the lesions qualified as CSR upon MP-MRI. We therefore think that obtaining DWI within an MP-MRI setting might be able to efficiently guide targeted biopsies in participants who are supposed to be fit for AS. In our cohort, MRGB was able to establish high-grade (Gleason 4 and/or 5 component) PCa not sampled by TRUS-guided biopsy in 6 of the 54 patients (11.1%), with CSRs harboring high-grade PCa displaying a significantly lower mADC compared with the low-grade CSRs. Because the progression rate in AS is likely to be dependent on the inclusion criteria used, we can only refer to the published short-term results of the PRIAS project, with 22% Gleason and/or volume upgrade at repeat biopsy (5). Interestingly, 10% of the patients in this series were subject to Gleason upgrade, which is more or less comparable with the 11.1% percentage we found in our current series. However, direct comparison between the 2 series is difficult because the progression rates within PRIAS are 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 our presented cohort.

Stringent inclusion criteria 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 (6,12). 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 (13,14). 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 (15-17). An interesting approach by Eggener et al (18) 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 (19,20).

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. Multiparametric magnetic resonance imaging 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 PCs (21), whereas T2-weighted MRI combined with DWI in a radical prostatectomy correlated series has been shown to have good sensitivity and specificity for detecting clinical significant PCs, defined as a Gleason score of 6 or greater and a tumor diameter greater than 4 mm (22). 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 (23). Apparent diffusion coefficient values have been established to correlate well with Gleason score in TRUS-guided biopsies (24,25) and, more importantly, radical prostatectomy specimens (26-28).

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 (29) and did outperform TRUS-guided biopsy Gleason grade as a predictor of low-risk Gleason grade vs intermediate/high-risk Gleason grade upon radical prostatectomy (30), 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 PCs is likely to be high, which might lead to a high false-negative ratio of MP-MRI for predicting the presence of PCs upon MRGB. This was confirmed by the inability of MP-MRI and MRGB to detect PCs in 45.3% of patients in our series, thus failing to diagnose PCs 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 PCs 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 (8,31). 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. Magnetic resonance guided biopsy has been established to more accurately sample prostate cancer Gleason grade compared to TRUS-guided biopsies (32) and therefore seems to be a more appropriate method to determine histopathological Gleason grade in AS candidates who are not undergoing radical prostatectomy. 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 MRPRIAS 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 (33). 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


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CHAPTER 8


General Discussion
Key Findings

Multiparametric MR imaging and MR guided biopsy in prostate cancer diagnosis

The first aim of this thesis was to evaluate 3T multiparametric MR imaging and MR guided biopsy for prostate cancer diagnosis. One of the studies, which was performed to investigate this purpose, was a retrospective multi-reader study for detection and localization of transition zone prostate cancer (Chapter 3). In this study multiparametric MR imaging did not improve detection and localization accuracy for transition zone cancers compared to T2-weighted MR imaging alone. Multiparametric MR imaging generally increased sensitivity, while decreasing specificity for transition zone cancer diagnosis compared with T2-weighted MR imaging. A decrease in specificity, i.e. an increase in false positive results may have been caused by varying quantitative parameters due to varying cellular densities in benign prostatic hyperplasia on diffusion weighted MR imaging and due to hypervascularity in benign prostatic hyperplasia on dynamic contrast-enhanced MR imaging (1,2). T2-weighted MR imaging alone may have been subject to less false-positive results, as differentiation of transition zone cancer from benign prostatic hyperplasia is not based on quantitative parametric differences only, but merely on general anatomical characteristics and patterns of transition zone cancer which differ from those of benign prostatic hyperplasia. T2-weighted MR imaging findings should therefore outweigh other functional techniques for evaluation of the prostate transition zone.

In a retrospective analysis, we aimed to evaluate the diffusion weighted MR imaging apparent diffusion coefficient for differentiation of transition zone cancer from non-cancerous transition zone and from prostatitis and for differentiation of transition zone cancer Gleason grades (Chapter 4). MR guided biopsy specimens were used as a reference standard in this study. We found that, despite overlap, apparent diffusion coefficient values can differentiate transition zone cancer from non-cancerous transition zone and from a degree 1, and most cases of a degree 2 prostatitis. However, due to substantial overlap, the apparent diffusion coefficient has a moderate accuracy (AUC 0.62) to distinguish between different primary and secondary Gleason grade cancer subcategories and cannot be used to differentiate between non-cancerous transition zone and degrees 1 to 2 of prostatitis.

In a prospective study, MR guided biopsy prostate cancer detection rates were investigated in patients with an elevated prostate specific antigen and one or more
cancer-negative previous TRUS biopsy sessions (Chapter 5). MR guided biopsy had a detection rate of 41%, mainly for clinically significant cancers (87%), based on i.a. prostate cancer Gleason score. Accurate multiparametric MR imaging localization accuracy (72-91%) (3-5) explains these high prostate cancer detection rates compared with systematic TRUS biopsies (≤18%) (6,7). Furthermore, MR guided biopsy detection rates for clinically significant cancer may be higher compared to detection rates for cancers with Gleason grade 4-5 components (0-29.8%) in the second to fourth repeat TRUS biopsy session (8). The high proportion of clinically significant cancers may have been attained by MR guided biopsy targeting areas with the lowest apparent diffusion coefficient of a presumed cancer suspicious region, which may harbour the highest local Gleason grade component (9,10).

Conclusions:

• 3T multiparametric MR imaging, consisting of T2-weighted imaging, diffusion-weighted imaging ADC maps (b-values, 50, 500, and 800 sec/mm²), and dynamic contrast-enhanced MR imaging may not improve TZ cancer detection and localization accuracy compared with T2-weighted imaging alone (Chapter 3).

• Despite overlap, median apparent diffusion coefficient values can differentiate transition zone cancer from non-cancerous transition zone and from a degree 1 and most cases of a degree 2 prostatitis. However, due to substantial overlap, apparent diffusion coefficient values had a moderate accuracy to distinguish between different primary and secondary Gleason grade cancer subcategories and cannot be used to differentiate between non-cancerous transition zone and degrees 1 to 2 of prostatitis (Chapter 4).

• In patients with elevated prostate specific antigen and one or more negative random systematic TRUS biopsy sessions, MR guided biopsy had a prostate cancer detection rate of 41% for predominantly clinically significant cancers (87%) (Chapter 5).

### Multiparametric MR imaging and MR guided biopsy in risk-stratification of prostate cancer patients

An accurate prostate cancer diagnosis implies more than accurate cancer detection only. The established Gleason score, stage, multifocality and volume are of prognostic importance for patient risk stratification (11-14). Therefore, a second aim in this thesis was to investigate combined 3T multiparametric MR imaging and MR guided biopsy for risk-stratification in prostate cancer patients. To this end, a study was performed in
which concordance with radical prostatectomy specimen highest Gleason grade was evaluated for MR guided biopsy specimens highest Gleason grade in comparison to random systematic TRUS biopsy specimen highest Gleason grade (Chapter 6). For radical prostatectomy specimens containing cancers with a highest Gleason grade 4 and/or 5, concordance for MR guided biopsy specimens was 95% (21/22) versus 54% for TRUS biopsy specimens ((25/46), p=0.001). These results reflect that the established prostate cancer diagnosis and its corresponding risk stratification is significantly more accurate for MR guided biopsies compared with TRUS biopsies. In order to clinically apply the MR guided biopsy advantages of increased prostate cancer detection rates (Chapter 4) and accurate prediction of highest prostate cancer Gleason grade (Chapter 6), a prospective multicentre sub-study was started in the existing PRIAS (Prostate Cancer Research International: Active Surveillance) trial (Chapter 7) (15). Our purpose was to evaluate 3T multiparametric MR imaging and MR guided biopsy for early risk re-stratification of prostate cancer patients on active surveillance. Multiparametric MR imaging and MR guided biopsy risk re-stratified an additional 24% at 3 and 10% of patients at 12 months of follow-up. Multiparametric MR imaging cancer suspicious region (CSR) PI-RADS scores ≤2 had a high negative predictive value (84% and 100%), while PI-RADS scores ≥4 had a high sensitivity (75% and 92%) for detection of prostate cancer and Gleason grade (GG) 4-5 prostate cancer at subsequent MR guided biopsy in patients on active surveillance. Therefore, multiparametric MR imaging and MR guided biopsy may contribute in early identification of active surveillance patients with Gleason grade 4-5 cancers, while also selecting active surveillance suitable patients based on cancer-negative MR guided biopsy specimens. An important finding in the latter study is the high number (48%) of cancer-negative MR guided biopsies, mainly caused by false-positive MR imaging results due to prostatitis. These false positives, however, may be partly caused by the low threshold we applied for biopsy in this study. False-positive results underline the importance of histopathology confirmation in multiparametric MR imaging cancer suspicious regions in active surveillance patients. Lack of targeted biopsies of MR imaging cancer suspicious regions may explain the poor results for MR-imaging as a predictive tool in other active surveillance studies (16-19).

A possible limitation of this study was that it was not designed as a randomized clinical trial to compare random systematic TRUS biopsies and MR guided biopsies in two separate arms. However, this comparison is rather difficult as both imaging techniques are fairly different and need a different approach. TRUS biopsies are
performed randomly, as over 40% of prostate cancers are iso-echogenic (20). The performance of random systematic TRUS biopsy has led to studies, which estimated the odds of diagnosing (clinically significant) cancer using both clinical criteria and random systematic TRUS biopsy outcome (13,21). On the other hand, MR guided biopsies, which are targeted to the most aggressive area of a presumed cancer suspicious region, can predict cancer presence and Gleason score (22) and Chapter 6 this thesis. Therefore, comparing both diagnostic tools for prostate cancer risk re-stratification is possible to the extent of the detected Gleason score, however not for tumour volume or multifocality criteria.

The design of the latter study (Chapter 7) was used to determine whether diffusion-weighted MR imaging apparent diffusion coefficient values can be used to differentiate (high Gleason grade 4-5) prostate cancer in patients on active surveillance for presumed low-risk prostate cancer (Chapter 8). Diffusion weighted MR imaging apparent diffusion coefficient maps were used to evaluate biopsied cancer suspicious regions, which were pre-defined on multiparametric MR imaging. Mean median apparent diffusion coefficient values differed significantly for cancer suspicious regions with \(1.04 \times 10^{-3} \text{ mm}^2/\text{s} \) (SD\(\pm0.29\)) versus cancer suspicious regions without prostate cancer \(1.26 \times 10^{-3} \text{ mm}^2/\text{s} \) (SD\(\pm0.25\); \(p<0.001\)) and for cancer suspicious regions with \(0.84 \times 10^{-3} \text{ mm}^2/\text{s} \) (SD\(\pm0.35\)) versus without a cancer with a Gleason grade 4-5 component \(1.09 \times 10^{-3} \text{ mm}^2/\text{s} \) (SD\(\pm0.25\); \(p<0.05\)). An area under the receiver operating characteristic curve (AUC) of 0.73 was established (95% CI: 0.61-0.84) for predicting the presence of prostate cancer in a cancer suspicious region by the median apparent diffusion coefficient. This moderate accuracy may be caused by variation of the apparent diffusion coefficient due to low prostate cancer volume percentages in biopsy core specimens and therefore due to inclusion of non-cancerous tissue in cancer-containing cancer suspicious regions.

**Conclusions:**

- Diffusion weighted MR imaging guided biopsies significantly improve pre-treatment patient risk stratification, as MR guided biopsy specimen highest Gleason grade shows high concordance with radical prostatectomy specimen highest Gleason grade (Chapter 6).
- Multiparametric MR imaging and MR guided biopsy may contribute in early identification of active surveillance patients with cancers containing a Gleason grade 4 and/or 5, while also selecting active surveillance suitable patients (Chapter 7).
• As part of a multiparametric MR imaging exam, diffusion weighted MR imaging apparent diffusion coefficient values may contribute in predicting prostate cancer presence in cancer suspicious regions identified by multiparametric MR imaging in patients deemed eligible for active surveillance (Chapter 8).

Clinical implications

Recommendation
This thesis have shown that combined multiparametric MR imaging and MR guided biopsy, in addition to improved prostate cancer detection, also include an accurate patient risk stratification (Chapters 4 and 6). Therefore, in men with an elevated prostate specific antigen, application of multiparametric MR imaging and MR guided biopsy should be recommended at least after one cancer-negative TRUS biopsy session. Men with diagnosed prostate cancer can also benefit from improved risk stratification by multiparametric MR imaging and MR guided biopsy. Examples are prostate cancer patients with a clinical suspicion of TRUS biopsy undersampling and patients with presumed low-risk prostate cancer.

Volume and Gleason grade
The concept that a high Gleason grade, regardless of the existence of multifocality or the volume of tumour, is most likely to determine clinical prognosis, is important for the clinical application of prostate multiparametric MR imaging and MR guided prostate biopsy (23). This concept is supported by studies that disagreed with the idea of the index lesion (based on largest tumour volume) Gleason score as the most important predictive parameter (24,25). High Gleason grades, which also can be situated in lower volume tumours present in addition to the index lesion, may determine patient outcome in multifocal prostate cancer.

If a high prostate cancer Gleason grade would be the most important prognostic factor, the implementation of multiparametric prostate MR imaging and MR guided biopsy would be supported, as this combination may accurately predict the highest Gleason grade compared to radical prostatectomy specimens (Chapter 6). Conversely, cancers with a lower Gleason grade, sparse growth patterns and small volumes are less frequently detected by MR imaging (26,27). The latter could be advantageous in preventing overdiagnosis in prostate cancer screening.
Improving the application of MR guided biopsies

Obstacles for the widespread clinical application of MR guided biopsy are availability of the procedure, expertise and equipment as well as a relatively long procedure time if more than one lesion needs to be targeted. Current research focuses on improving these issues: developments of needle guide tracking sequences shorten examination time by reducing the time needed for manual adaptation of the sequence settings after needle guider re-positioning (28). Furthermore, investigation of robots, which enable remote control of movements of the needle guider, will further reduce examination time by cancelling the time for the examiner to walk into the scanner room in order to manually re-position the needle guider (29).

The availability of MR guided prostate biopsy will be enhanced by MR imaging-ultrasound fusion, in which MR images are registered to the ultrasound data (30,31). Subsequently, ultrasound biopsy can be guided to lesions, which are accurately localized on multiparametric MR imaging. Fusion techniques aim to combine the accuracy of the MR imaging examination with the practicality, availability and speed of an ultrasound examination. Accurate image segmentation and registration are major challenges in image fusion. When intra-procedural motion corrections will be possible and the error in the actual fusion accuracy of images will be below millimetre level (1.9 mm), MR-ultrasound fusion will be a promising technique (32).

Use in active surveillance

An important clinical implication for the incorporation of multiparametric MR imaging in active surveillance protocols is that it should be performed in combination with MR guided biopsies of MR imaging cancer suspicious regions. As we found a substantial number of false-positive imaging results in our application of MR imaging and MR guided biopsy in active surveillance, it is of major importance that histopathological proof of a cancer suspicious region is obtained before it is to be further followed using MR imaging. Not performing biopsy may lead to poor results for MR imaging in predicting active surveillance outcome, due to inclusion of false-positive cancer suspicious regions (16,18,33). Only when ample experience and scientific evidence on the application of MR imaging and MR guided biopsies in active surveillance has been acquired, thresholds for performing MR guided biopsy could be increased.
Future research

Patient tailored MR imaging and MR guided biopsy
To further evaluate the role of MR guided biopsies for prostate cancer diagnosis, future studies, which compare MR guided biopsy detection rates in homogeneous patient populations with identical previous TRUS biopsy protocols and a comparable numbers of previous biopsy sessions, should be performed. Due to inhomogeneous patient populations in current studies, conclusions on when to use MR imaging and MR guided biopsies after a certain type and/or amount of TRUS biopsy sessions cannot be made (Chapter 5). Furthermore, the added value of MR imaging should be measured in nomograms or predictive models, which also include other clinical patient parameters like PSA, clinical stage and prostate volume. These latter study designs will clarify how multiparametric MR imaging and MR guided biopsy can contribute to prostate cancer diagnosis in a specific patient with clinical and/or histopathological parameters. Studies investigating patient-specific added value of multiparametric MR imaging and MR guided biopsy may also enable accurate evaluation of cost-effectiveness of MR imaging and MR guided biopsy for different clinical scenarios.

Validation and implementation of MR guided biopsy prostate cancer diagnosis
MR guided biopsy specimens could be envisioned as a future surrogate for radical prostatectomy specimens. This may certainly hold true given the current shift from radical treatments involving the whole prostate gland to active surveillance or focal image guided therapies (34). Since MR guided biopsy specimen histopathology is image guided and image confirmed, it allows for accurate correlation of MR image parameters to local histopathology. Other advantages are objectivity and accurate delineation in image annotation, which may reduce inter-observer variability and other biases in image-histopathology correlation (35). However, clinical patient parameters, MR guided biopsy specimen outcome and MR guided biopsy maximal cancer core length need to be studied as combined predictors of clinically significant cancers in radical prostatectomy specimens. Results of these investigations are needed to obtain more knowledge on the prognostic value of MR guided biopsy specimen outcome for a specific patient case. This evidence is not only important in the clinical setting of active surveillance, but also for focal therapy.
Our findings on the accurate prediction of radical prostatectomy highest Gleason grade by MR guided biopsy highest Gleason grade should be more extensively studied for their application in prostate cancer screening and active surveillance. One could hypothesize that a more accurate prostate cancer patient risk stratification by multiparametric MR imaging and MR guided biopsy may reduce prostate cancer overdiagnosis in screening and may decrease overtreatment by improved risk stratification of low-risk prostate cancer patients on active surveillance.

**Active surveillance**

In order to evaluate effects of multiparametric MR imaging and MR guided biopsy on secondary active surveillance progression and intervention rates, more follow-up is needed. If multiparametric MR imaging and MR guided biopsy appear to reduce secondary progression rates, cost-effectiveness studies and quality of life studies warrant further investigation. Further follow-up of multiparametric MR imaging and MR guided biopsy in active surveillance (Chapter 7) will also allow for investigation of the added value of an endorectal coil and of MR imaging pelvic node and bone staging. Frequently used pre-treatment nomograms (http://nomograms.mskcc.org) predict probabilities for extracapsular extension ranging from 12-26% and for lymph node invasion ranging from 1.9-2.0% (for a clinical stage cT1c to a cT2a) in a 60-year old man with a PSA of 10 ng/mL and a Gleason score 3+3 cancer in 2 out of 10 cores (36,37). These probabilities mainly reflect the need for accurate evaluation of extracapsular extension of an MR imaging cancer suspicious region in incorrectly included intermediate- to high risk prostate cancer patients on active surveillance. However, as the majority of active surveillance patients will not undergo surgery and the risk of lymph node invasion is small, it should be investigated whether an endorectal coil and pelvic node and bone evaluation can be safely omitted in MR imaging of active surveillance patients.

**Computer-aided diagnosis**

Prostate tissue characteristics form a limitation in multiparametric MR imaging prostate cancer diagnosis, especially for the transition zone. The transition zone includes benign prostatic hyperplasia, in which both glandular and stromal cell proliferation can be present with large variations of tissue cellular density and image signal intensity. Due to this inhomogeneity, prostate cancer differentiation based on quantitative parameters only will be insufficient (1,38). Other
pitfalls in prostate cancer diagnosis, which are inherent to the prostate structure itself, are differentiation of benign conditions, like prostatitis, which, despite the application of multiparametric MR imaging, may still lead to false-positive results. Finally, the lower detection rates of lower Gleason grade (26) or sparsely growing prostate cancers (27) and the inter-patient and intra-patient variability of apparent diffusion coefficient values are other examples of prostate-tissue-related challenges (39). Computer-aided diagnosis holds future promise in helping the radiologist with these pitfalls by combining quantitative parameters with shape and pattern-recognition characteristics in order to differentiate prostate cancer from various benign conditions (40,41). Especially for prostate cancer diagnosis in the transition zone, the added value computer aided diagnosis using pattern recognition combined with tissue characteristics and quantitative MR imaging parameters needs to be a future object of study.

Safeguarding quality: standardization and education

Finally, all results in this thesis were performed in a Prostate Cancer Center of Excellence with highly developed techniques and sophisticated software for simultaneous interpretation. MR imaging data were subsequently read by highly experienced radiologists. The results in this thesis can therefore only become widely clinically applicable when a uniform quality level of the MR imaging techniques and their interpretation can be guaranteed on a larger scale. Multicentre trials, investigating improvement and standardization of prostate MR imaging techniques, are needed (42,43). Uniformity of the quality level of the technique and its interpretation, education of radiologists (44) and development of supporting techniques (40,41) are important requirements for a more general application of prostate MR imaging.

Recently published guidelines containing protocols and instructions to provide a minimal quality level of multiparametric MR imaging of the prostate are a first step in this direction (45). Next to providing technical imaging recommendations, PI-RADS criteria for structured image interpretation were presented (45). The PI-RADS criteria represent an important first step in standardization of multiparametric prostate MR imaging interpretation, however, future studies on validation, inter-observer variation and reliability of PI-RADS warrant further investigation.
Table 3 PI-RADS scoring system

<table>
<thead>
<tr>
<th>Score Criteria</th>
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<tbody>
<tr>
<td>A1. T2WI for the peripheral zone (PZ)</td>
</tr>
<tr>
<td>1 Uniform high signal intensity (SI)</td>
</tr>
<tr>
<td>2 Linear, wedge shaped, or geographic areas of lower SI, usually not well demarcated</td>
</tr>
<tr>
<td>3 Intermediate appearances not in categories 1/2 or 4/5</td>
</tr>
<tr>
<td>4 Discrete, homogeneous low signal focus/mass confined to the prostate</td>
</tr>
<tr>
<td>5 Discrete, homogeneous low signal intensity focus with extra-capsular extension/invasive behaviour or mass effect on the capsule (bulging), or broad (&gt;1.5 cm) contact with the surface</td>
</tr>
<tr>
<td>A2. T2WI for the transition zone (TZ)</td>
</tr>
<tr>
<td>1 Heterogeneous TZ adenoma with well-defined margins: “organised chaos”</td>
</tr>
<tr>
<td>2 Areas of more homogeneous low SI, however well marginated, originating from the TZ/BPH</td>
</tr>
<tr>
<td>3 Intermediate appearances not in categories 1/2 or 4/5</td>
</tr>
<tr>
<td>4 Areas of more homogeneous low SI, ill defined: “erased charcoal sign”</td>
</tr>
<tr>
<td>5 Same as 4, but involving the anterior fibromuscular stroma or the anterior horn of the PZ, usually lenticular or water-drop shaped.</td>
</tr>
<tr>
<td>B. Diffusion weighted imaging (DWI)</td>
</tr>
<tr>
<td>1 No reduction in ADC compared with normal glandular tissue. No increase in SI on any high b-value image (≥b800)</td>
</tr>
<tr>
<td>2 Diffuse, hyper SI on ≥b800 image with low ADC; no focal features, however, linear, triangular or geographical features are allowed</td>
</tr>
<tr>
<td>3 Intermediate appearances not in categories 1/2 or 4/5</td>
</tr>
<tr>
<td>4 Focal area(s) of reduced ADC but iso-intense SI on high b-value images (≥b800)</td>
</tr>
<tr>
<td>5 Focal area/mass of hyper SI on the high b-value images (≥b800) with reduced ADC</td>
</tr>
<tr>
<td>C. Dynamic contrast enhanced (DCE)-MRI</td>
</tr>
<tr>
<td>1 Type 1 enhancement curve</td>
</tr>
<tr>
<td>2 Type 2 enhancement curve</td>
</tr>
<tr>
<td>3 Type 3 enhancement curve +1 For focal enhancing lesion with curve type 2-3</td>
</tr>
<tr>
<td>+1 For asymmetric lesion or lesion at an unusual place with curve type 2-3</td>
</tr>
<tr>
<td>D1. Quantitative MRS for 1.5 T. Diagram references [50, 70]</td>
</tr>
</tbody>
</table>

Figure 1. The PI-RADS scoring system for presence of clinically significant prostate cancer on multiparametric MR imaging as presented by Barentsz et al. European Radiology 2012.
CHAPTER 9

Table 3 (continued)

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Qualitative magnetic resonance spectroscopic imaging (MRSI)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Citrate peak height exceeds choline peak height &gt;2 times</td>
</tr>
<tr>
<td>2</td>
<td>Citrate peak height exceeds choline peak height times &gt;1, &lt;2 times</td>
</tr>
<tr>
<td>3</td>
<td>Choline peak height equals citrate peak height</td>
</tr>
<tr>
<td>4</td>
<td>Choline peak height exceeds citrate peak height &gt;1, &lt;2 times</td>
</tr>
<tr>
<td>5</td>
<td>Choline peak height exceeds citrate peak height &gt;2 times</td>
</tr>
</tbody>
</table>

In qualitative analysis, the relative peak heights of citrate and choline are visually compared (pattern analysis), rather than quantified. The criteria apply for 1.5: for at least three adjacent voxels

Score 1 = Clinically significant disease is highly unlikely to be present
Score 2 = Clinically significant cancer is unlikely to be present
Score 3 = Clinically significant cancer is equivocal
Score 4 = Clinically significant cancer is likely to be present
Score 5 = Clinically significant cancer is highly likely to be present

Figure 1. The PI-RADS scoring system for presence of clinically significant prostate cancer on multiparametric MR imaging as presented by Barentsz et al. European Radiology 2012.
References


17. Ploussard G, Xylinas E, Durand X, et al. Magnetic resonance imaging does not improve the prediction of misclassification of prostate cancer patients eligible for active surveillance when the most stringent selection criteria are based on the saturation biopsy scheme. BJU Int. 2010;10-410X.


Summary / Samenvatting
Summary

3T multiparametric MR imaging and MR guided biopsy: prostate cancer diagnosis and risk-stratification

Current epidemiologic studies show a high prevalence of prostate cancers. Many patients have low-risk cancers and do not develop clinical symptoms during their lifetime. As the majority of prostate cancers behaves as a chronic disease rather than as a lethal cancer, diagnostic tools, which involve an accurate patient risk-stratification as part of a prostate cancer diagnosis are required. This thesis aims to evaluate multiparametric MR imaging and MR guided biopsy in prostate cancer diagnosis and in risk-stratification.

Chapter 2 presents a literature review on state-of-the-art multiparametric MR imaging for detection, localization and staging of prostate cancer. A combination of T1- and T2-weighted MR imaging with diffusion weighted or dynamic contrast-enhanced MR imaging was suggested as a minimal protocol requirement for multiparametric prostate MR imaging. Literature generally shows that addition of functional multiparametric MR imaging to T2-weighted MR imaging may improve prostate cancer localization and staging accuracy. However, as multiparametric MR imaging studies were often incomparable, their reported diagnostic accuracies were inconsistent. Therefore, based on available literature, no definite conclusions on the diagnostic accuracies of (combined) multiparametric MR imaging techniques for a particular clinical prostate cancer problem can be made. In order to improve quality, uniformity, reliability and clinical applicability, guidelines on optimal imaging protocols and combinations of multiparametric MR imaging techniques for different clinical prostate cancer indications are needed.

In chapter 3 a multi-reader study on 3T multiparametric MR imaging versus T2-weighted MR imaging for detection and localization of transition zone prostate cancers is described. Twenty-eight patients with transition zone cancer with a volume >0.5 cm³ in their radical prostatectomy specimen and a pre-prostatectomy endorectal 3T multiparametric MR imaging were retrospectively selected from 197 consecutively performed radical prostatectomy specimens between January 2007 and August 2011. Subsequently, thirty-five patients without transition zone cancer were randomly selected as a control-group. Four radiologists scored transition zone cancer suspicion on T2-weighted MR imaging and on different
multiparametric MR imaging protocols on a 5-point-scale in 6 regions of interest. Transition zone cancer detection accuracy did not differ significantly between T2-weighted- and multiparametric MR imaging for all (68% vs. 66% respectively, p=0.85), for Gleason grade 4-5 (79% vs. 73-75%, p=0.13) and for Gleason grade 2-3 transition zone cancers (66% vs. 62-65%, p= 0.47). In receiver operating characteristic analysis, multiparametric MR imaging (AUC 0.70-0.77) did not significantly improve T2-weighted MR imaging transition zone cancer localization accuracy (AUC 0.72, p>0.05). This study shows that 3T multiparametric MR imaging, consisting of T2-weighted, low-b-value (<1000 s/mm²) diffusion weighted apparent diffusion coefficient maps and dynamic contrast-enhanced MR imaging may not improve transition zone cancer detection and localization accuracy compared to 3T T2-weighted MR imaging alone.

The evaluation of the diffusion weighted magnetic resonance (MR) imaging apparent diffusion coefficient (ADC) for differentiation of transition zone cancer from non-cancerous transition zone and from prostatitis and for differentiation of transition zone cancer Gleason grade is discussed in chapter 4. In this retrospective study, we included 52 patients with 87 transition-zone-cancer-containing MR guided biopsy core specimens and 53 patients with 101 non-cancerous transition zone MR guided biopsy core specimens. MR guided specimen core histopathology was used as a reference standard for median ADC. Median ADC was measured in annotated regions of interest (ROIs) on biopsy sampling locations of MR guided biopsy confirmation scans. In a linear mixed model analysis mean mADC differed significantly for transition zone cancer versus non-cancerous transition zone without and with degree 1-2 prostatitis (p<0.0001-0.05). Exceptions were mixed primary and secondary GG cancers versus a degree 2 of prostatitis (P = 0.06-0.09). No significant differences were found between subcategories of primary and secondary GG cancers (P = 0.17-0.91) and between a degree 1 and 2 prostatitis and non-cancerous transition zone without prostatitis (P = 0.48-0.94). Areas under the receiver operating characteristic curve were 0.84 for mADC to differentiate transition zone cancer versus non-cancerous transition zone, 0.84 and 0.56 to differentiate prostatitis from transition zone cancer and from non-cancerous transition zone. mADC had an AUC of 0.62 to differentiate a primary Gleason grade 4 versus 3 cancer.

Our findings suggest that mADC can differentiate transition zone cancer from non-cancerous transition zone and from a degree 1 and most cases of a degree
2 prostatitis. However, due to substantial overlap, mADC has a moderate accuracy to distinguish between different primary and secondary Gleason grade cancer subcategories and cannot be used to differentiate between non-cancerous transition zone and degrees 1 to 2 of prostatitis.

The study in chapter 5 describes MR guided biopsy prostate cancer detection rates in a large prospective population of patients with an elevated prostate specific antigen and one or more cancer-negative TRUS biopsy sessions. Between March 2008 and February 2011, 438 patients, with a prostatic antigen >4 ng/ml and at least one previous negative TRUS guided biopsy session, were included. In 265 of these patients, MR guided prostate biopsy was performed. Prostate cancer detection rates were 25% for all 438 patients and 41% for the 265 patients, who also underwent MR guided prostate biopsy. The majority of detected cancers were clinically significant (87%). Results of this study show that in patients with an elevated prostate specific antigen and one or more cancer-negative TRUS biopsy sessions, MR guided biopsy has higher prostate cancer detection rates compared to those reported for repeat TRUS biopsy. Furthermore, MR guided biopsy mainly detects clinically significant prostate cancers.

In the study in chapter 6 concordance between highest Gleason grade in MR guided biopsies and the highest Gleason grade in the radical prostatectomy specimen was determined. These concordance rates were compared to similar concordance rates of Gleason grade for random systematic 10 core TRUS biopsies. Between August 2006 and April 2009, 98 out of a total of 123 specimens of radical prostatectomy patients were included based on a prostate cancer diagnosis upon pre-prostatectomy MR guided biopsy (n=34) or upon pre-prostatectomy random systematic TRUS biopsy (n=64). MR guided biopsy was targeted to the lowest apparent diffusion coefficient in cancer suspicious regions on diffusion weighted MR imaging. MR guided biopsy overall highest Gleason grade concordance with radical prostatectomy specimens was significantly higher compared to TRUS biopsy (respectively 88% versus 55%, p=0.001). For highest Gleason grade 3 MR guided biopsy versus TRUS biopsy concordance rates were 100% versus 94% (p=0.41), for a Gleason grade 4 and 5 results were 91% versus 46% (p=0.02) and 73% versus 30% (p=0.01), respectively. In conclusion, MR guided biopsies significantly improve risk-stratification for prostate cancer patients compared with a separate cohort of TRUS biopsies.
In chapter 7, earlier findings of high MR guided biopsy detection rates of clinically significant prostate cancer (chapter 4) and the high concordance rate of MR guided biopsy highest Gleason grade to radical prostatectomy specimen Gleason grade (chapter 6), were clinically applied in prostate cancer patients on active surveillance. In 4 hospitals participating in Prostate Cancer Research International: Active Surveillance (PRIAS), we initiated a side-study (MR-PRIAS) in 66 of 82 consecutively and prospectively included patients. Our purpose was to evaluate 3T multiparametric MR imaging and MR guided biopsy for early risk re-stratification of patients on active surveillance for low-risk prostate cancer. MR imaging of pelvic lymph nodes and bones, prostate multiparametric MR imaging and MR guided biopsy were performed within 3 months after prostate cancer diagnosis. Follow-up comprised repeat multiparametric MR imaging of the prostate, MR guided biopsy and repeat TRUS biopsy at 12 months after diagnosis. Multiparametric MR imaging and MR guided biopsy risk re-stratified 24% at 3 and 10% of patients at 12 months of follow-up in addition to TRUS biopsy. Risk re-stratification was based on histopathologically proven node/bone metastases and/or MR guided biopsy Gleason grade 4 and/or 5 and/or a stage ≥ pT3 (MR guided biopsy specimen with cancer invading (peri-prostatic) fat or seminal vesicles) and/or cancer multifocality (≥ 3 foci, Gleason score ≤3+3 and stage ≤ T2). TRUS biopsy risk re-stratification criteria were according to risk re-stratification criteria used in the PRIAS study. A cancer-negative MR guided biopsy specimen had a negative predictive value of 79% for risk re-stratification at repeat examinations. Furthermore, multiparametric MR imaging cancer suspicious region (CSR) PI-RADS scores ≤2 had a high negative predictive value (84% and 100%), while PI-RADS scores ≥4 had a high sensitivity (75% and 92%) for detection of prostate cancer and Gleason grade (GG) 4-5 prostate cancer at subsequent MR guided biopsy in patients on active surveillance. These initial results indicate that multiparametric MR imaging and MR guided biopsy may contribute in early identification of active surveillance patients with Gleason grade 4-5 cancers, while also improving the selection of active surveillance suitable patients.

Using the research design of chapter 7, we aimed to determine whether diffusion-weighted MR imaging apparent diffusion coefficient (ADC) values can be used to differentiate (high Gleason grade 4-5) prostate cancer in patients on active surveillance for low-risk prostate cancer. This study is discussed in chapter 8. In 54 consecutive patients, cancer suspicious regions were identified on multiparametric
MR imaging at active surveillance inclusion. MR guided biopsy was performed in all cancer suspicious regions to obtain histopathological verification. Regions of interest were annotated on MR guided biopsy apparent diffusion coefficient maps according to needle position. Median apparent diffusion coefficient (mADC) of annotations was related to MR guided biopsy specimen outcome. Upon receiver operating characteristic analysis, mADC had an area under the curve of 0.73 for predicting prostate cancer presence in a cancer suspicious region. Mean mADC in cancer suspicious regions with prostate cancer was $1.04 \times 10^{-3}$ mm$^2$/s (standard deviation (SD) ±0.29), whereas the cancer suspicious regions with no prostate cancer displayed a mean mADC of $1.26 \times 10^{-3}$ mm$^2$/s (SD±0.25; p<0.001). Cancer suspicious regions with a high-grade Gleason component (Gleason grade 4-5) displayed a mean mADC of $0.84 \times 10^{-3}$ mm$^2$/s (SD±0.35) versus a mean mADC for low-grade cancer suspicious regions of $1.09 \times 10^{-3}$ mm$^2$/s (SD±0.25; p<0.05). Our results suggest that diffusion weighted imaging may be a promising technique for risk stratification in patients deemed eligible for active surveillance and may aid in identification and biopsy targeting of prostate cancer on multiparametric MR imaging.

Results of individual studies regarding the value of 3T multiparametric MR imaging and MR guided biopsy in prostate cancer diagnosis and risk-stratification are discussed in chapter 9. Based on the scientific evidence presented in this thesis, the following conclusions can be made:

- **3T MR imaging**, consisting of T2-weighted imaging, diffusion-weighted imaging ADC maps (b-values, 50, 500, and 800 sec/mm$^2$), and dynamic contrast-enhanced MR imaging may not improve TZ cancer detection and localization accuracy compared with T2-weighted imaging alone (Chapter 3).

- Despite overlap, median apparent diffusion coefficient values can differentiate transition zone cancer from non-cancerous transition zone and from a degree 1 and most cases of a degree 2 prostatitis. However, due to substantial overlap, mADC has a moderate accuracy to distinguish between different primary and secondary Gleason grade cancer subcategories and cannot be used to differentiate between non-cancerous transition zone and degrees 1 to 2 of prostatitis. (Chapter 4).
• In patients with elevated prostate specific antigen and one or more negative random systematic TRUS biopsy sessions, MR guided biopsy of multiparametric MR imaging cancer suspicious regions had a prostate cancer detection rate of 41% for predominantly clinically significant cancers (87%) (Chapter 5).

• Diffusion weighted MR imaging directed MR guided biopsies significantly improve pre-treatment patient risk stratification, as MR guided biopsy specimen highest Gleason grade shows high concordance with radical prostatectomy specimen highest Gleason grade (Chapter 6).

• Multiparametric MR imaging and MR guided biopsy may contribute in early identification of incorrectly selected active surveillance patients with Gleason grade 4-5 cancers. Conversely, low Multiparametric MR imaging PI-RADS scores and cancer-negative MR guided biopsy specimens may improve selection of active surveillance suitable patients (Chapter 7).

• As part of a multiparametric MR imaging exam, diffusion weighted MR imaging apparent diffusion coefficient values may contribute in predicting prostate cancer presence in cancer suspicious regions identified by multiparametric MR imaging in patients deemed eligible for active surveillance (Chapter 8).
Samenvatting

De waarde van 3T multiparametrische MRI en MR geleide biopten voor de diagnose en risico-stratifitatie van prostaatkanker.

Hedendaagse epidemiologische studies tonen een hoge prevalentie van klinisch insignificante prostaatkankers. Veel patiënten bij wie de diagnose laag-risico prostaatkanker is gesteld zouden tijdens hun leven geen symptomen ontwikkeld hebben. Prostaatkanker is zich meer gaan gedragen als een chronische ziekte dan als een dodelijke kanker. Dit vraagt om diagnostische instrumenten, welke een nauwkeurige risico-stratifitatie van de patiënt een onderdeel laten zijn van de diagnose. Dit proefschrift heeft als doel om de waarde van multiparametrische MRI en MR geleide biopsie te evalueren voor de diagnose risico-stratifitatie van prostaatkanker.

In Hoofdstuk 2 wordt een overzicht van de literatuur gegeven over state-of-the-art multiparametrische MRI voor de opsporing, de lokalisatie en de stadiëring van prostaatkanker. Dit literatuuroverzicht resulteerde in een combinatie van T1- en T2-gewogen MRI met diffusie-gewogen of contrast versterkende MRI als minimale vereiste binnen een protocol voor multiparametrische prostaat-MRI. In het algemeen laat de literatuur zien dat toevoegen van functionele multiparametrische MRI aan T2-gewogen MRI de nauwkeurigheid voor prostaatkanker lokalisatie en stadiëring kan verbeteren. Echter, omdat studies waarin multiparametrische MRI geëvalueerd werd vaak onvergelijkelijkbaar waren, waren de door deze studies gerapporteerde diagnostische nauwkeurigheden inconsistent. Derhalve kunnen op basis van de huidige beschikbare literatuur geen definitieve conclusies getrokken worden met betrekking tot de diagnostische nauwkeurigheden van (gecombineerde) multiparametrische MRI technieken voor een specifieke klinische probleemstelling bij prostaatkanker. Om de kwaliteit, de uniformiteit, de betrouwbaarheid en de klinische toepasbaarheid te verbeteren zijn er richtlijnen nodig voor optimale protocollen en combinaties van multiparametrische MRI technieken voor diverse klinische prostaatkankerindicaties.

In hoofdstuk 3 wordt een multi-reader studie beschreven waarin 3 tesla multiparametrische MRI wordt vergeleken met T2-gewogen MRI voor de detectie en lokalisatie van transitiezonecarcinoom van de prostaat. Achtentwintig patiënten met transitiezonecarcinoom met een volume >0.5 cm³ in hun
radicale prostatectomie-preparaat en een 3T endorectale multiparametrische MRI voorafgaand aan hun radicale prostatectomie, werden retrospectief geselecteerd uit 197 opeenvolgende preparaten van uitgevoerde radicale prostatectomieën tussen januari 2007 en augustus 2011. Vijfendertig patiënten zonder transitiezonecarcinoom werden vervolgens willekeurig geselecteerd als controlegroep. Vier radiologen scoorden T2-gewogen MRI en multiparametrische MRI op een 5-punts schaal in zes aandachtsgebieden. De nauwkeurigheid voor het opsporen van transitiezonecarcinoom verschilde niet significant tussen T2-gewogen- en multiparametrische MRI voor alle transitiezonecarcinomen (68% vs. 66% respectievelijk, p=0.85). Dit was ook het geval voor voor Gleason graad 4-5 (79% vs. 73-75%, p=0.13) en voor Gleason graad 2-3 transitiezonecarcinomen (66% vs. 62-65%, p= 0.47). In een receiver operating characteristic analyse verbeterde multiparametrische MRI de lokalisatie nauwkeurigheid voor transitiezonecarcinoom niet significant ten opzichte van T2-gewogen MRI (AUC respectievelijk 0.70-0.77 versus 0.72, p>0.05).

Deze studie laat zien dat 3 tesla multiparametrische MRI, bestaande uit T2-gewogen, apparente diffusiecoëfficiënt weergaven van diffusiegewogen-MRI met lage b-waarde (<1000 s/mm²) en dynamische contrastversterkende MRI, de nauwkeurigheid voor opsporing en lokalisatie van transitiezonecarcinoom waarschijnlijk niet kan verbeteren in vergelijking met T2-gewogen MRI alleen.

In hoofdstuk 4 wordt de waarde van de apparente diffusie coëfficiënt (ADC) van diffusie-gewogen MRI besproken voor het onderscheiden van transitiezonekanker van carcinoomvrije transitiezone en van prostatitis en voor het onderscheiden van de verschillende Gleason graden in transitiezonekanker. In een retrospectieve studie werden 52 patiënten met 87 MR geleide biopsie cores met transitiezonecarcinoom en 53 patiënten met 101 cores in de transitiezone zonder carcinoom ingesloten. De histopathologische uitslagen van de MR geleide biopten dienden als gouden standaard voor de mediane ADC (mADC). De mADC werd gemeten in geannoteerde “regions of interest” (ROIs) op de controle-MRI-opnamen voor de naaldpositionering van MR geleide biopten, precies op de plek van het met MR geleide biopsis weggenomen weefsel. In een linear mixed model analyse verschilde de gemiddelde mADC significant voor transitiezonecarcinoom versus carcinoom-vrije transitiezone zonder en met een graad 1-2 prostatitis (p<0.0001-0.05). Uitzonderingen waren prostaatkankers met verschillende Gleason graad componenten versus een graad 2 prostatitis (P=0.06-0.09). mADC verschilde niet
significant tussen de diverse subcategorieën van primaire en secundaire Gleason graad carcinomen \((P=0.17-0.91)\) en tussen een graad 1-2 prostatitis en kanker-vrije transitiezone zonder prostatitis \((P=0.48-0.94)\).

In een receiver operator characteristics analyse was de “area under the curve” \((AUC)\) 0.84 voor mADC om transitiezonecarcinoom te onderscheiden van kanker-vrije transitiezone. Voor het onderscheid van prostatitis van transitiezonecarcinoom en carcinoom-vrije transitiezone waren AUCs respectievelijk 0.84 en 0.56. Voor het onderscheiden van een primaire Gleason graad 4 versus 3 transitiezonecarcinoom op basis van mADC was de AUC waarde 0.62. Deze bevindingen suggereren dat men met behulp van mADC waarden transitiezonecarcinoom kan onderscheiden van carcinoom-vrije transitiezone en van een graad 1, en in de meeste gevallen ook van een graad 2 prostatitis. Echter, ten gevolge van substantiële overlap tussen mADC waarden, heeft mADC een matige nauwkeurigheid voor het onderscheid tussen de verschillende primaire en secundaire Gleason graad subcategorieën, in geval van kanker, en kan mADC niet gebruikt worden om onderscheid te maken tussen carcinoom-vrije transitiezone en graad 1-2 prostatitis.

De studie in hoofdstuk 5 beschrijft prostaatkanker detectiepercentages van 3-tesla MR geleide biopsie in een grote prospectieve populatie van patiënten met een verhoogd PSA en een of meer kanker-negatieve transrectale echografische biopsie sessies. Tussen maart 2008 en februari 2011 werden 438 patiënten met een prostaat-sprecifiek antigeen >4 ng/ml en tenminste één negatieve eerdere transrectale echografische biopsie sessie geïncludeerd. Bij 265 van deze patiënten werd MR geleide biopsie van de prostaat uitgevoerd. Prostaatkanker detectiepercentages waren 25% voor alle 438 patiënten en 41% voor de 265 patiënten die ook MR geleide prostaatbiotypen ondergingen. Het merendeel van de opgespoorde kankers was klinisch significant (87%). De uitkomsten van deze studie laten zien dat bij patiënten met een verhoogd prostaat-specifiek antigeen en een of meer kanker-negatieve transrectale echografische biopsie sessies, prostaatkanker-detectie percentages van MR geleide biotypen hoger zijn in vergelijking met die van eerder beschreven herhaalde transrectale echografische biotypen. Bovendien worden er met MR geleide biopsie voornamelijk klinisch significante prostaatkankers gevonden.

In de studie in hoofdstuk 6 werd de overeenstemming bepaald tussen de hoogste Gleason gradering in MR geleide biotypen en de hoogste Gleason gradering in radicale prostatectomie preparaten. Deze overeenstemming werd vergeleken met eenzelfde
soort overeenstemming voor Gleason gradering van willekeurige systematische 10 core transrectale echografische biopten. Van augustus 2006 tot en met april 2009 werden 98 van een totaal van 123 preparaten van patiënten die een radicale prostatectomie hadden ondergaan geincludeerd op basis van een prostaatkanker diagnose in MR geleide biopten (n=34) of in willekeurige systematische transrectale biopten (n=64). MR geleide biopten werden gericht op de laagste apparente diffusie coëfficiënt waarde van de voor prostaatkanker verdachte gebieden op MRI. De algehele overeenstemming voor hoogste Gleason gradering met radicale prostatectomie preparaten was significant hoger voor MR geleide biopten in vergelijking met transrectale echografische biopten (respectievelijk 88% versus 55%, p=0.001). Voor een hoogste Gleason graad 3 waren overeenstemmingspercentages voor MR geleide versus transrectale echografische biopten 100% versus 94% (p=0.41), voor een Gleason graad 4 en 5 waren de uitkomsten respectievelijk 91% versus 46% (p=0.02) en 73% versus 30% (p=0.01). Concluderend leidt het uitvoeren van MR geleide biopten tot een significante verbetering van de risico-stratificatie voor prostaatkanker-patiënten in vergelijking met transrectale echografische biopten.

In hoofdstuk 7 werden eerdere bevindingen van hogere detectierates van klinisch significant prostaatcarcinoom met MR geleide biopsie (hoofdstuk 4) en een hoge overeenkomst tussen de hoogste Gleason graad in MR geleiden biopten en de hoogste Gleason graad in radicale prostatectomie preparaten (hoofdstuk 6) klinisch toegepast bij prostaatkankerpatiënten onder actieve observatie. Binnen 4 in Prostate Cancer Research International: Active Surveillance (PRIAS) participerende ziekenhuizen werd een sub-studie uitgevoerd (MR-PRIAS) bij 66 van 82 opeenvolgende en prospectief geincludeerde patiënten. De doelstelling was het evalueren van 3T multiparametrische MRI en MR geleide biopsie voor vroege risico-her-stratificatie van patiënten onder actieve observatie voor laag risico prostaatcarcinoom. Multiparametrische MRI van het bekken en van de lokale prostaat en MR geleide biopsie werden uitgevoerd binnen 3 maanden na prostaatkanker diagnose. Follow-up bestond uit herhaling van multiparametrische MRI, MR geleide biopsie en herhaling van de transrectale echografische biopten 12 maanden na prostaatkankerdiagnose. Multiparametrische MRI en MR geleide biopsie her-stratificeerden een additionele 24% van de patiënten op 3 maanden en 10% van de patiënten op 12 maanden follow-up in vergelijking met transrectale echografische biopten. Risico-re-stratificatie werd gebaseerd op histopathologisch bewezen klier- of bot-metastasen en/of een Gleason graad 4 en/of 5 in MR geleide
biopten en/of een stadium ≥pT3 (MR geleide biopsie preparaat: carcinoom met invasie van (peri-prostatisch) vet en/of de zaadblaasjes) en/of kanker multifocaliteit (≥ 3 foci, Gleason score ≤3+3 en stadium ≤T2). Her-stratificatie criteria van transrectale echografische biopten waren conform de PRIAS studie. Een carcinoомн-vrije MR geleide biopsie had een negatief voorspellende waarde van 79% voor risico-her-stratificatie bij herhaal-onderzoeken. Bovendien hadden prostaatkanker-verdachte gebieden met een PI-RADS score ≤2 op multiparametrische MRI een hoge negatief voorspellende waarde (84% and 100%), terwijl prostaatkanker-verdachte gebieden met een PI-RADS score ≥4 op multiparametrische MRI een hoge sensitiviteit hadden (75% and 92%) voor het opsporen van prostaatkanker en Gleason graad (GG) 4-5 prostaatkanker bij MR geleide biopsie in patiënten onder actieve observatie. Deze initiële resultaten tonen aan dat multiparametrische MRI en MR geleide biopsie kunnen bijdragen aan vroege identificatie van patiënten, die met een Gleason graad 4-5 carcinoom ten onrechte actief worden geobserveerd. Tegelijkertijd kan er met behulp van MRI en MR geleide biopsie ook verdere selectie plaatsvinden van patiënten die in aanmerking komen voor actieve observatie.

Gebruik makende van het onderzoeksdesign van hoofdstuk 7, beoogden we te onderzoeken of apparente diffusiecoëfficiënt (ADC) waarden van diffusiegewogen MRI kunnen worden toegepast om prostaatcarcinoom (met een hoge Gleason gradering 4-5) te kunnen onderscheiden in patiënten onder actieve observatie voor laag-risico prostaatkanker. Deze studie wordt besproken in hoofdstuk 8. In 54 opeenvolgende patiënten werden voor prostaatkanker verdachte gebieden (CSR) geïdentificeerd op multiparametrische MRI, welke werd uitgevoerd ten tijde van inclusie in actieve observatie. Van al deze CSRs werd MR geleide biopsie uitgevoerd ter histopathologische verificatie. Op de ADC beelden van de MRI geleide biopten werden “regions of interest” geannoteerd overeenkomstig met de naaldpositie van het weggenomen weefsel. De mediaan van de ADC (mADC) in de annotaties werd gerelateerd aan de histopathologische uitkomst van de MR geleide biopsie. In een receiver operating characteristic analyse had mADC een AUC van 0.73 voor het voorspellen van prostaatkanker in een CSR. De gemiddelde mADC voor de CSRs met prostaatkanker was 1.04x10⁻³ mm²/s (standaard deviatie (SD) ±0.29), terwijl de carcinoомн-vrije CSRs een gemiddelde mADC van 1.26x10⁻³ mm²/s (SD±0.25; p<0.001) lieten zien. CSRs met een hoge Gleason graad (4 of 5 component) toonden een gemiddelde mADC van 0.84x10⁻³ mm²/s (SD±0.35) versus een gemiddelde mADC van 1.09x10⁻³ mm²/s
(SD±0.25; p<0.05) voor CSRs met laaggradige prostaatkanker. Onze resultaten suggereren dat diffusie-gewogen MRI een veelbelovende techniek zou kunnen zijn voor risico-stratificatie van patiënten die geschikt worden geacht voor actieve observatie. Daarnaast kan diffusie-gewogen MRI bijdragen tot de identificatie van en tot het gericht aanprikken van prostaatkanker op MRI bij patiënten onder actieve observatie.

In hoofdstuk 9 worden de resultaten van de verschillende studies naar multiparametrische MRI en MR geleide biopten voor de diagnose en risicostratificatie van prostaatkanker besproken. Op basis van de in dit proefschrift gepresenteerde wetenschappelijke artikelen kunnen de volgende conclusies worden getrokken:

- 3T multiparametrische MRI, bestaande uit T2-gewogen MRI, apparente diffusiecoëfficiënt waarden afgeleid van diffusie-gewogen MRI (b-waarden 50, 500, and 800 sec/mm²) en dynamische contrast-versterkende MRI, laat in vergelijking met T2-gewogen MRI geen verbetering zien voor wat betreft de nauwkeurigheid voor de opsporing en lokalisatie van transitiezonecarcinomen (Hoofdstuk 3).
- Ondanks overlap kan op basis van mediaanwaarden van de apparente diffusiecoëfficiënt transitiezonecarcinoom worden onderscheiden van carcinoom-vrije transitiezone en van graad 1 en meestal ook van een graad 2 prostatitis. Echter, ten gevolge van substantiële overlap tussen mADC waarden, heeft mADC een matige nauwkeurigheid voor het onderscheid tussen de verschillende primaire en secundaire Gleason graad subcategorien, in geval van kanker, en kan mADC niet gebruikt worden om onderscheid te maken tussen carcinoom-vrije transitiezone en graad 1-2 prostatitis. (Hoofdstuk 4).
- Voor patiënten met een verhoogd prostaat-specifiek antigeen en een of meerdere negatieve willekeurige systematische transrectale echografische biopt sessies had MRI geleide biopsie van voor prostaatkanker verdachte gebieden op multiparametrische MRI een detectie-rate van 41% voor voornamelijk klinisch significante prostaatkanker (87%) (Hoofdstuk 5).
- Voorafgaand aan behandeling verbeteren MRI geleide prostaatbiopten op basis van diffusie-gewogen MRI de risico-stratificatie van prostaatkanker-patiënten met prostaatkanker significant, doordat de hoogste Gleason graad in MR geleide biopsie-preparaten hoge correlatie heeft met de hoogste Gleason graad in radicale prostatectomie preparaten (Hoofdstuk 6).
CHAPTER 10

- Multiparametrische MRI en MR geleide biopsie kunnen bijdragen aan een vroege identificatie van patiënten met een Gleason graad 4-5 carcinoom, die ten onrechte actief worden geobserveerd. Omgekeerd kunnen lage PI-RADS scores op multiparametrische MRI en carcinoom-vrije MRI geleide biopten de selectie van voor actieve observatie geschikte patiënten mogelijk verbeteren (Hoofdstuk 7).
- Apparente diffusiecoëfficiënt waarden kunnen, als deel van een multiparametrische MRI onderzoek, bijdragen aan het voorspellen van de aanwezigheid van prostaatkanker in voor prostaatkanker verdachte gebieden, welke gedefinieerd worden door multiparametrische MRI in patiënten die geschikt werden bevonden voor actieve observatie (Hoofdstuk 8).
Appendices
Appendix 1

Multiparametrische MRI bij prostaatkankerscreening

Caroline. M.A. Hoeks,
Jurgen J. Fütterer,
Diederik M. Somford,
Inge M. van Oort,
Henkjan Huisman
Jelle O. Barentsz

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Abstract

• Twee recente onderzoeken naar screening op prostaatkanker lieten tegenstrijdige effecten van screening op de sterfte aan prostaatkanker zien.
• De huidige screeningsmethode van PSA-bepaling in combinatie met transrectale echografische biopten leidt tot een hoog aantal fout-positieve uitslagen en overbehandeling.
• Er is behoefte aan een screeningstest die het aantal onnodige prostaatbiopten vermindert en die minder agressieve vormen van prostaatkanker onderscheidt van agressievere vormen.
• Multiparametrische MRI detecteert prostaatkanker met een hoge specificiteit en geeft informatie over de agressiviteit. De combinatie van PSA en multiparametrische MRI bij 1,5 tesla blijkt een redelijk nauwkeurige screeningstest te zijn.
• Multiparametrische MRI komt vanwege de hoge kosten en de beperkte beschikbaarheid niet in aanmerking als initiële screeningstest, maar zou kunnen dienen als vervolgonderzoek bij een afwijkende uitslag van de PSA test.
• Met multiparametrische MRI als vervolgtest bij prostaatkankerscreening kan men gerichter biopteren, onnodige prostaatbiopten voorkomen en het prostaatcarcinoom beter karakteriseren.
Recent werden resultaten gepubliceerd van de twee grootste internationale studies naar prostaatkancerscreening middels prostaatspecifiek antigeen (PSA). De ‘European randomized study of screening for prostate cancer’ (ERSPC), de grootste studie (n= 182.160 patiënten), liet een sterftereductie zien van 20% (1). De ‘Prostate, lung, colorectal and ovarian cancer screening trial’ (PLCO) bij 76.693 patiënten liet geen effecten zien op de sterfte aan prostaatcarcinoom (2). Ofschoon nu positieve effecten van screening zijn aangetoond is er nog steeds geen consensus over het nut van prostaatkancerscreening (3).

Zowel de European Association of Urology (EAU)(4) als de Nederlandse Vereniging voor Urologie (NVU) hebben gereageerd op de genoemde studies (www.nvu.nl, klik op het logo voor het standpunt van de NVU d.d. 18 maart 2009). In hun reacties uiten ze de behoefte aan ontwikkeling van methoden om de minder agressieve vormen van prostaatkanker, waarbij de kans op overlijden heel laag is, te kunnen herkennen.

De huidige screeningsmethoden bestaan uit een PSA bepaling met een lage specificiteit (circa 60% fout-positieven) in combinatie met transrectale echografische (TRUS) biopten (5). Deze combinatie leidt tot een hoog aantal fout-positieve uitslagen en differentieert onvoldoende tussen klinisch signifieante en insignifieante carcinomen, dat wil zeggen: carcinomen met een relatief lage kans op progressie (6). Bij de invoering van PSA-screening in combinatie met TRUS-biopten zullen patiënten zonder kanker onnodig worden gebiopteerd en zullen patiënten met klinisch insignifieante carcinomen onnodig worden bestraald of geopereerd. Deze overbehandeling kan leiden tot onnodige complicaties als impotentie en incontinentie (7).

In de ERSPC-studie was ook sprake van overbehandeling: om te voorkomen dat 1 patiënt overleed ten gevolge van prostaatcarcinoom, moesten 1410 mannen gescreend worden en 48 van hen ook behandeld (1). De onderzoekers gaven aan dat men overbehandeling kan voorkomen door laag-risico carcinomen of indolente carcinomen niet of niet direct te behandelen. Er is dus behoefte aan een additionele test met een hoge specificiteit, die in combinatie met de PSA-test onnodige prostaatbiopten kan voorkómen en waarmee men de agressieve prostaatkansen better kan onderscheiden van de niet-agressieve. Multiparametrische MRI is een techniek die mogelijk in deze behoefte zou kunnen voorzien. In dit artikel beschrijven wij de mogelijke rol van multiparametrische MRI bij een eventuele screening op prostaatkanker.
Figuur 1. Anatomische T2-gewogen MRI van de prostaat (a), vervaardigd met een endorectale spoel (transversale opname). De perifere zone (P) van de prostaat heeft een hogere intensiteit en is homogener dan de transitiezone (T) en de centrale zone (hier plat gedrukt door de transitiezone). In de linker perifere zone is een gebied zichtbaar met een lagere intensiteit (C); dit gebied is sterk verdacht voor prostaatcarcinoom. Het breidt zich door het kapsel heen uit in de linker neurovasculaire bundel (neurovasculaire bundels: rood omcirkeld). (b) Dynamische contrastversterkte MRI-opname op dezelfde plaats als (a). Het gebied dat voor tumor verdacht is vertoont verhoogde aankleuring met een gadoliniumhoudend contrastmiddel. (c) ‘Apparent diffusion coefficient (ADC) map’ op basis van een diffusiegewogen MRI-opname van dezelfde plaats als (a). Met deze techniek heeft het voor tumor verdachte gebied op de kleurschaal duidelijk een zeer lage ADC-waarde (geel in de verklarende tekening). De gebieden in de transitiezone met een verlaagde ADC-waarde zijn niet verdacht voor prostaatcarcinoom (blauw in de tekening).
Figuur 2. MR-spectroscopie van de prostaat. Het middelste deel van de figuur is een transversale T2-gewogen MRI-opname van dezelfde plaats als figuur 1a. De blauwe voxel (dit is een driedimensionale volume-eenheid) is genomen uit een niet-afwijkend gebied van de prostaat. Het spectrogram (links) vertoont een lage choline-concentratie (pijl a) en een hoge citraat-concentratie (pijl b). De rode voxel is genomen uit een voor tumor verdacht gebied met een lage signaalintensiteit op de T2-gewogen opname. Het spectrogram hiervan (rechts) vertoont een hogere choline-concentratie (pijl a) en een lagere citraat-concentratie (pijl b), met verhoging van de (choline + creatine)/citraatratio. Dit wijst op prostaatkanker.

Figuur 3. Transversale doorsnede van het prostatectomiepreparaat van dezelfde patiënt als in figuur 1. In de linker perifere zone is een witgrijs gebied (groen in de tekening). Bij histopathologisch onderzoek bleek zich hier prostaatcarcinoom te bevinden. De Gleason score was 9 en er was sprake van kapseldoorgroei.
Multiparametrische MRI

Multiparametrische MRI is een combinatie van een anatomische T2-gewogen MRI (figuur 1a) met meerdere functionele MRI-technieken zoals dynamische contrastversterkende MRI (DCE-MRI, figuur 1b), diffusie-gewogen MRI (DWI, figuur 1c), en proton-MR-spectroscopie (MRSI, figuur 2). DWI is een functionele MRI techniek waarbij gedurende enkele tienden van milliseconden de bewegingen van watermoleculen per voxel afgebeeld weefsel worden vastgelegd. Uit diverse diffusiemetingen wordt beeldcontrast verkregen door de ‘apparent diffusion coefficiënt’ (ADC) te berekenen, een kwantitatieve maat voor de diffusie in weefsel (8). Uit onderzoek blijkt dat prostaatkanker op diffusiegegewogen MRI significant lagere ADC-waarden toont dan goedadig prostaatweefsel (vergelijk figuur 1c en figuur 3) (9). Een tweede functionele MRI-techniek, DCE-MRI, berust op het principe dat prostaatcarcinoom met een intraveneus gadoliniumhoudend contrastmiddel sterker aankleurt dan gezond prostaatweefsel, door een toegenomen microvascularisatie en vasculaire permeabiliteit (zie figuur 1b) (10). MRSI, een derde functionele MRI-techniek, geeft kwantitatieve informatie over de concentraties van citraat, creatinine en choline in het prostaatweefsel. In gebieden die prostaatkanker bevatten is de verhouding (choline + creatinine)/citraat toegenomen (vergelijk figuur 2 en figuur 3) (11).

Onderzoek naar MRI bij screening op prostaatcarcinoom

In diverse studies is de combinatie van anatomische T2-gewogen MRI met functionele MRI-technieken onderzocht bij patiënten met een verhoogde PSA waarde. Het grootste recente screeningsonderzoek omvatte 225 patiënten (gemiddelde PSA concentratie: 11,5 ng/ml; uitersten: 0,4-133 ng/ml), die een T2-gewogen MRI (1,5 tesla) in combinatie met MRSI ondergingen. Hiervan was de sensitiviteit voor de detectie van prostaatcarcinoom 72%, met bij een hoge specificiteit (93%) (12).

Andere studies waarbij anatomische MRI werd gecombineerd met functionele MRI-technieken, zoals DCE-MRI, MRSI of DWI(13,14,15,16), gaven betere resultaten dan alleen T2-gewogen MRI (tabel) (17,18). Voor de combinatie van T2-gewogen MRI met functionele MRI-technieken was de sensitiviteit 72-95%, de specificiteit 74-93% en de ‘area under the curve’ (AUC), een maat voor het diagnostisch onderscheidingsvermogen, 0,71-0,86. Als alleen T2-gewogen MRI werd gebruikt, was de sensitiviteit 55-83%, de specificiteit 54-94% en de AUC-waarde 0,67-0,80.
Combinatie PSA-bepaling en multiparametrische MRI
Multiparametrische MRI is niet geschikt als een eerste screeningstest, omdat deze techniek tijdrovend, te duur en niet overal beschikbaar is. Deze techniek zou prostaatkankerscreening wel kunnen ondersteunen als vervolgonderzoek bij patiënten met een verhoogde PSA waarde. Voordat een test als screeningsmethode kan worden ingevoerd, dient deze te voldoen aan de criteria van Wilson en Jungner (19). Een screeningstest moet met name effectief en vervolgens ook kosteneffectief zijn. Voor de multiparametrische MRI bij patiënten met een verhoogde PSA waarde moet dit nog onderzocht worden.
Volgens statistische besluitvormingsanalyses zijn bij screening op prostaatcarcinoom onder meer lage kosten, een maximale specificiteit bij een goede sensitiviteit en een lage interobserver-variabiliteit belangrijke testeigenschappen (20). Uit het eerder genoemde onderzoek bleek dat de combinatie van PSA-bepaling en multiparametrische MRI een hoge specificiteit hebben als men dit als één screeningstest beschouwt. Voor zover ons bekend is er nog geen onderzoek gedaan naar de intra- en interobserver-variabiliteit bij multiparametrische MRI van de prostaat.

Andere diagnostische technieken
Voor de detectie van prostaatkanker zijn naast MRI ook echografische technieken beschikbaar, zoals contrastechografie (CTRUS) en elastografie. CTRUS verhoogt detectiepercentages voor prostaatkanker; hierbij zijn veel minder biopienen nodig dan met conventionele echografie (21). Echter, CTRUS heeft een lagere sensitiviteit (71%) en specificiteit (50%) dan multiparametrische MRI (22). De resultaten van elastografie zijn nog controversieel. Bij een groep patiënten met een Gleason score van 7 of hoger (een graderingschaal voor prostaatcarcinomen) scoorde elastografie redelijk, met een sensitiviteit van 75% en een specificiteit van 77% (23). Echter, in een gerandomiseerd gecontroleerd onderzoek gaf de combinatie van elastografie met TRUS geen verbetering van de detectie van prostaatcarcinoom (24).

Mogelijke toepassingen multiparametrische MRI

Karacterisering prostaatkanker bij screening
In de eerste twee screeningsrondes van de ERSPC-studie had 69% van de gedetecteerde prostaatcarcinomen een Gleason score kleiner dan 7 (25).
APPENDIX 1


Door de heterogeniteit en de onregelmatige begrenzing van de tumoren geeft MRI geen nauwkeurige schatting van het prostaatkankervolume, een mogelijke maat voor de agressiviteit (30). Verder is onderzoek gedaan naar het verband tussen Gleason scores enerzijds en de signaalintensiteit op T2-gewogen MRI, de ADC-waarde in DWI en de metabole ratio’s in MRSI anderzijds (31,32,33), maar een absoluut afkappunt voor deze MRI parameters per Gleason score heeft men nog niet gevonden.
**Tabel 1.** Overzicht van onderzoeken naar de detectie van prostaatcarcinoom met MRI (1,5 tesla) bij patiënten met een verhoogde PSA waarde

<table>
<thead>
<tr>
<th>studie eerste auteur, jaar</th>
<th>Referentie-test*</th>
<th>n</th>
<th>PSA waarde in ng/ml; gemiddelde, tenzij anders aangegeven</th>
<th>techniek</th>
<th>sensitiviteit %</th>
<th>specificiteit %</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langer, 2009[15]</td>
<td>PR</td>
<td>25</td>
<td>5,0 (mediaan)</td>
<td>T2, erc</td>
<td>-</td>
<td>-</td>
<td>0,673</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DWI,ercc</td>
<td>-</td>
<td>-</td>
<td>0,689</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DCE,ercc</td>
<td>-</td>
<td>-</td>
<td>0,592†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0,543‡</td>
<td>0,700§</td>
<td></td>
</tr>
<tr>
<td>Villeirs, 2008[12]</td>
<td>TRUS or PR</td>
<td>225</td>
<td>11,5 ; uitersten: 0,4-133,0</td>
<td>T2, erc</td>
<td>57</td>
<td>94</td>
<td>0,801</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MSRI, erc</td>
<td>60</td>
<td>96</td>
<td>0,857</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2+MSRI</td>
<td>72</td>
<td>93</td>
<td>0,857</td>
</tr>
<tr>
<td>Tanimoto, 2007[11]</td>
<td>TRUS</td>
<td>83</td>
<td>≥4,0</td>
<td>T2</td>
<td>73</td>
<td>54</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2+DWI</td>
<td>84</td>
<td>85</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2+DWI+DCE</td>
<td>95</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>Namimoto, 1998[4]</td>
<td>TRUS or PR</td>
<td>42</td>
<td>≥4,0; uitersten: 5-300</td>
<td>DCE</td>
<td>79</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2+DCE</td>
<td>82</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hara, 2005[16]</td>
<td>TRUS</td>
<td>90</td>
<td>≥2,5</td>
<td>DCE</td>
<td>76</td>
<td>83</td>
<td>-</td>
</tr>
<tr>
<td>Vilanova, 2001[17]</td>
<td>TRUS</td>
<td>81</td>
<td>4-10; 10-20; 4-20</td>
<td>T2, erc</td>
<td>55</td>
<td>80</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>83</td>
<td>65</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>76</td>
<td>-</td>
</tr>
<tr>
<td>Kubota, 2008[18]</td>
<td>TRUS</td>
<td>185</td>
<td>4,0-10,0</td>
<td>T2</td>
<td>79</td>
<td>59</td>
<td>-</td>
</tr>
</tbody>
</table>

PSA = prostaat specifiek antigeen; AUC = oppervlakte onder de ‘receiver operating characteristic’-curve, een waarde voor het diagnostisch onderscheidingsvermogen; PR = histopathologisch onderzoek van prostatectomie-preparaat; TRUS = histopathologisch onderzoek van een transrectaal prostaatbiopt, genomen onder geleide van echografie; T2 = anatomische T2-gewogen MRI; erc = met gebruikmaking van een endorectale coil om het MRI-signal uit de prostaat op te vangen; DCE = dynamische contrastversterkende MRI; DWI = diffusiegewogen MRI; MRSI = proton-MR-spectroscopie; : = waarde niet bekend. *De referentietest is de gouden standaard aan de hand waarvan de sensitiviteit en specificiteit van de onderzochte test werd afgemeten. † AUC van $K_{trans}$, een parameter van DCE-MRI. ‡ AUC van Ve, een parameter van DCE-MRI. § AUC van T2 + $K_{trans}$ (een parameter van DCE-MRI) + ADC, een parameter van DWI. || Patiënten werden in dit onderzoek geïncludeerd voorafgaand aan het uitvoeren van transrectale biopten.

**Vervolgtest bij screening op prostaatkanker**

De combinatie van een PSA-bepaling en multiparametrische MRI (bij 1,5 tesla) is redelijk nauwkeurig als screeningstest. Er zijn echter een beperkt aantal studies met multiparametrische MRI als screeningsmethode verricht. Bij de meeste hiervan gebruikte men een suboptimale gouden standaard voor de detectie van prostaatkanker, namelijk TRUS-biopten in plaats van een prostatectomie-preparaat. Daarom dient prostatectomie de standaard te zijn bij toekomstig onderzoek naar de waarde van MRI als vervolgtest bij patiënten met een verhoogde PSA-waarde. Aspecten als interobserver-variabiliteit en kosteneffectiviteit zijn onvoldoende.
onderzocht om MRI nu te kunnen inzetten bij screening. Het verband tussen parameters op MRI-beelden en de agressiviteit van prostaatkanker is nog niet duidelijk genoeg. Ook dit vraagt om nader onderzoek. De klinische praktijk is nog niet geheel rijp voor toepassing van multiparametrische MRI bij screening omdat apparatuur, software en ervaren personeel daarvoor te beperkt beschikbaar zijn. Momenteel hebben slechts enkele centra ervaring met multiparametrische MRI van de prostaat bij een veldsterkte van 1,5 tesla. In Nederland kan momenteel alleen het Universitair Medisch Centrum (UMC) St. Radboud het volledige arsenaal van DCE-MRI, DWI en MRSI bij een veldsterkte van 3 tesla uitvoeren, maar technisch gezien kan men met de meeste MRI apparaten een goed multiparametrisch MRI onderzoek doen. Richtlijnen voor de uitvoering van functionele MRI bij verschillende specifieke klinische vraagstellingen zijn nog in ontwikkeling. Ook standaardisatie van de verslaglegging is belangrijk. Een MRI verslag is immers vrij subjectief, omdat de uitslag mede afhankelijk is van de ervaring van de radioloog.

Samengevat heeft multiparametrische MRI de volgende voordelen: gerichtere biopstering en verminderen van het aantal onnodige TRUS biopsten, karakterisering van prostaatkanker en informatie over uitbreiding en stadiëring van de tumor. Hierdoor is een optimale therapeutische keuze mogelijk. Echografie heeft het voordeel dat het beter beschikbaar is dan MRI en sneller een uitslag geeft, maar de sensitiviteit en specificiteit zijn lager, en die van multiparametrische MRI. Bovendien geeft echografisch onderzoek toegepast als screeningsmethode, geen bruikbare informatie over het stadium en de agressiviteit van prostaatkanker, in tegenstelling tot MRI. Als uit de eindresultaten van de ERSPC- en de PLCO studie blijkt dat PSA-screening effectief en kosteneffectief is, zou men multiparametrische MRI als een vervolgonderzoek op de screening kunnen overwegen. Deze techniek zou zowel het aantal onnodige TRUS biopsten als de over- of onder-behandeling van prostaatkanker in gescreende populaties aanzienlijk kunnen beperken. Voordat MRI hiervoor kan worden ingezet dient men echter aspecten zoals prostaatkanker-characterisatie, kosteneffectiviteit en interobserver-variatie verder te onderzoeken.
Literatuur

APPENDIX 1


Appendix 2

Dankwoord
APPENDIX 2

Dit proefschrift was niet tot stand gekomen zonder het enthousiasme, het vertrouwen en de bereidwilligheid van vele mensen, waaronder collega’s, vrienden en familie. Een mooie ervaring in mijn tijd als arts onderzoeker was dat mensen, waarvan een zeker aantal mij nauwelijks kenden, mij belangeloos en bereidwillig hebben geholpen.

Beste Jelle, professor dr. Barentsz, ik ben je bijzonder dankbaar voor de kans die je me hebt gegeven. Door jou heb ik geleerd hoe ver je het kan schoppen met de nodige dosis overtuigingskracht en positieve energie (yes, we scan!). Ik heb me verwonderd over hoe jij complexe wetenschappelijke materie op een heldere en luidieke manier kan overbrengen in presentaties. Het vertrouwen dat je in me had en de vrijheid die je me tijdens dit promotieonderzoek hebt gegeven, heb ik erg gewaardeerd. Als ik weer met een idee of opzet voor een studie kwam, kreeg ik altijd de mogelijkheid om ermee aan de slag te gaan.


Beste Christina, dr. Hulsbergen-van de Kaa, ik wil je bedanken voor de grote hoeveelheden radicale prostatectomieën en biopten die je binnen de studies in dit proefschrift hebt (her)beoordeeld. Door je nauwkeurigheid en inzicht kun jij voor velen op wetenschappelijk gebied het verschil maken. In mijn geval leidden je revisies zonder uitzondering tot een substantiële verbetering van de artikelen.

Beste Inge, dr. van Oort, jij was vanaf het begin betrokken bij de implementatie van MRI in active surveillance. Bedankt voor je geloof in het nieuwe project en je hulp bij het opzetten van de MR-PRIAS studie. Ook je kritische blik bij revisies van artikelen en je efforts voor de patiëntinclusie bleken onmisbaar.
Dankwoord

Beste leden van de manuscriptcommissie, beste prof. dr. Maroeska Rovers, prof.dr. Geert Villeirs en dr. Michiel Sedelaar, dank voor het beoordelen van mijn manuscript.

Beste Thomas, ik ken geen enkele klinische onderzoeker met zoveel bevlogenheid en inzicht in MR techniek als jij. Bovendien was jij ook “onze” eerste prostaatonderzoeker die zich begaf op het gebied van MR geleide biopten.
Wat een geluk had ik dat jij me vanaf dag 1 onder je hoede nam en me veel leerde. Uiteraard ging dit laatste niet zonder de nodige hoeveelheid chaos en zonder me wijs te maken dat perfluorocarbon radioactief was (haha). Samen hebben we als eerste/tweede auteurs een aantal mooie publicaties neergezet. Jouw inspiratie, enthousiasme en inzicht hebben hieraan wezenlijk bijgedragen. Ik ben dan ook trots dat je naast me zult staan als paranimf.

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APPENDIX 2

Last but not least: de onderzoekers van het PRIAS project binnen de afdeling Urologie in het Erasmus MC. In het bijzonder zijn dit professor dr. Chris Bangma, dr. Monique Roobol, dr. Roderick van den Bergh en dr. Meelan Bul. Bedankt voor de kans die jullie mij hebben gegeven om binnen het PRIAS project een MRI studie te starten. Ik hoop dat het project waardevolle nieuwe inzichten zal genereren in de rol die MRI binnen active surveillance zal kunnen spelen.

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Dear Gorjan,
Words on paper, like those written above, cannot express what you mean to me. Thanks for being my best friend and support. I love you.
Appendix 3

CV, publications, presentations
Curriculum Vitae

Caroline Hoeks was born on as the oldest of three sisters on January 26th 1981 in Maarheeze, the Netherlands. She graduated from secondary school in 1999 (Gymnasium, S.G. Augustinianum, Eindhoven). After obtaining a propaedeuse Health Sciences in 1999, she studied medicine at Maastricht University from 2000-2006. During her subsequent position as a medical doctor at the department of Internal Medicine at the Amphia Hospital in Breda her interest and enthusiasm for Radiology started to grow. July 2008 she started her research on prostate MRI at the Department of Radiology Nijmegen Medical Centre supervised by professor dr. J.O. Barentsz. Next to performing the research presented in this thesis, she gained clinical experience in MRI and MR guided biopsy of the prostate. During this period she also started living together with Gorjan Nikolik in Utrecht. From January 2013 Caroline started her Radiology residency at the Department of Radiology, Meander Medical Centre Amersfoort.
Publications


Presentations


**Hoeks CM**. MRI (and ultrasonography): which lesions to biopsy, and how? European School of Oncology, Active surveillance for low-risk prostate cancer as Faculty member, 2012 Rotterdam, the Netherlands.

Emberton M, **Hoeks CM**. Application of emerging technology and biomarkers for Screening and Surveillance European School of Oncology, Active surveillance for low-risk prostate cancer as Faculty member, 2012 Rotterdam, the Netherlands.


**Hoeks CM**, Somford DM, van Oort IM, Vergunst H, Bangma C, Barentsz JO. Value of 3T multiparametric MR Imaging and MR guided biopsy in patient selection for active surveillance within the PRIAS study: initial results of the MRPRIAS study, a prospective single arm multicenter cohort study. RSNA 2010, Chicago, USA.
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