Prerequisites for patient-tailored treatment in localized prostate cancer

Muller, B.G.

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Prerequisites for patient-tailored treatment in localized prostate cancer

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om 11.00
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Oude Lutherse Kerk,
Singel 411 (hoek Spui),
Amsterdam

Na afloop bent u van harte
welkom op de receptie
En 's avonds vanaf 20:00
voor het promotiefeest
in bar The Tara
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Prerequisites for patient-tailored treatment in localized prostate cancer

BERREN MULLER
Prerequisites for patient-tailored treatment in localized prostate cancer

Berrend Gustian Muller
Prerequisites for patient-tailored treatment in localized prostate cancer

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit
op vrijdag 20 december 2019, te 11.00 uur

door

Berrend Gustian Muller
geboren te Weesp
## PROMOTIECOMMISSIE

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Faculteit der Geneeskunde
“Probeer, elke keer als je tegen de lamp loopt, een beetje licht mee te nemen”
- Harrie Jekkers -
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Chapter 1

General introduction, aims, and thesis outline
ABBREVIATIONS (IN ALPHABETICAL ORDER)

4M: Met prostaat-MRI Meer Mans
AS: Active Surveillance
DRE: digital rectal examination
ESUR: European Society of Urogenital Radiology
FLA: focal laser ablation
GS: Gleason score
HIFU: high intensity focused ultrasound
IRE: irreversible electroporation
ISUP: international society of urological pathology
mpMRI: multiparametric magnetic resonance imaging
OCT: Optical coherence tomography
PI-RADS: prostate imaging – reporting and data system
PRECISION: Prostate Evaluation for Clinically Important Disease: Sampling using image Guidance or Not?
PSA: prostate specific antigen
PDT: photodynamic therapy
RFA: radio frequency ablation
TPM: transperineal (template) prostate mapping
TRUS: transrectal ultrasound

BACKGROUND

Clinical dilemma of intermediate risk prostate cancer

Approximately 8% of the male population will develop a clinically significant prostate cancer during their lifetime. Since the discovery of prostate specific antigen (PSA), the prevalence of prostate cancer increased substantially [1]. The incidence rates have increased mainly due to intensified use of PSA testing, improved prostate biopsy techniques and improved imaging technologies. However, cancer specific mortality remained more or less unchanged [2]. In the Netherlands, 12,646 men were diagnosed with prostate cancer in 2018, and 2865 died of prostate cancer in 2017 [3]. The workup for prostate cancer includes clinical staging based on digital rectal examination (DRE) by an experienced urologist, the pretreatment serum PSA and the Gleason Score (GS) based on microscopic cellular architecture in the initial biopsy. (Table 1) Nowadays, in approximately 80% of men with prostate cancer, a clinically localized stage is identified at diagnosis. Current treatment options for localized prostate cancer depending on d’Amico risk group (Table 2) include: 1) active surveillance (AS) and 2) curative treatment: radical whole-gland re-
moval through radical prostatectomy +/- lymphadenectomy or radiation (external beam or brachytherapy) in combination with short, or long-term androgen deprivation therapy. In the intermediate risk group, active treatment is advised [4, 5].

**Table 1:** ISUP grading [6]

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>ISUP grade group</th>
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<tbody>
<tr>
<td>6 (3+3)</td>
<td>1</td>
</tr>
<tr>
<td>7 (3+4)</td>
<td>2</td>
</tr>
<tr>
<td>7 (4+3)</td>
<td>3</td>
</tr>
<tr>
<td>8 (4+4 or 3+5 or 5+3)</td>
<td>4</td>
</tr>
<tr>
<td>9 - 10</td>
<td>5</td>
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**Table 2:** d’Amico prostate cancer risk classification [6] Abbreviations: GS; Gleason score, PSA; prostate-specific antigen; TNM; clinical stage of the tumor

<table>
<thead>
<tr>
<th>Low-Risk</th>
<th>Intermediate-Risk</th>
<th>High-Risk</th>
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<td>Gleason Score</td>
<td>GS &lt; 7 (ISUP 1)</td>
<td>GS 7 (ISUP 2-3)</td>
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<tr>
<td>PSA</td>
<td>PSA ≤10 ng/mL</td>
<td>PSA 10-20 ng/mL</td>
</tr>
<tr>
<td>TNM</td>
<td>cT1-2a</td>
<td>cT2b</td>
</tr>
<tr>
<td>Localized</td>
<td></td>
<td></td>
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<tr>
<td>Locally advanced</td>
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The ideal treatment would provide oncological cure and preserving urological and sexual functioning with few side effects. Although radical therapy offers treatment with curative intent, there can be a high rate of associated complications, with erectile dysfunction seen in 24-90%, urinary incontinence in 2-72% and rectal toxicity in 2-15% [7]. These complications have a serious impact on quality of life [8, 9]. Low-, but also intermediate-risk prostate cancer is usually slowly growing, with a long preclinical phase before progressing to clinically significant disease (if at all) [10-12]. This suggests that a significant number of low-risk prostate cancer patients have no gain from treatment and that for intermediate-risk prostate cancer patients, there is a long window of opportunity for treatment, before clinical progression especially if pathology shows no cribriform growth pattern [13]. In patients with low-, and intermediate-risk prostate cancer, active treatment may not improve disease related survival, but can cause complications and side effects, which impair the quality of life significantly and are, therefore, prone for overtreatment.

**The rationale for focal therapy**

Focal therapy can offer an alternative minimal invasive treatment option in some low-risk and especially in intermediate-risk patients. It aims to achieve oncological control and reduction of anxiety (of living with a cancer) on the one hand, without the side effects of radical treatment on the other hand and preserving functional outcome. With focal
therapy, individual cancer areas are targeted while sparing important functional and anatomical urological structures (e.g. neurovascular bundle, urinary sphincter and rectal wall) [14]. Focal therapy can be performed on either a targeted or segmental basis (quadrant, hemi- or hockey-stick ablation). The fact that only the cancer lesion is targeted, and the rest of the prostate remains untreated, highlights the importance of adequate imaging/mapping of the cancer before initiating treatment, as tumors will reside and/or progress within the prostate if they are missed [14].

A variety of ablative technologies have been introduced for the focal treatment of localized prostate cancer: brachytherapy, cryotherapy, high intensity focused ultrasound (HIFU), radiofrequency ablation (RFA), focal laser ablation (FLA), photodynamic therapy (PDT), interstitial laser thermotherapy and irreversible electroporation (IRE) [15]. Since focal therapy is relatively new to the armamentarium of prostate cancer treatment with no long-term follow-up data, the European Association of Urology considers all focal treatment modalities still experimental technologies and patients should only be treated within the framework of a trial [5].

Index lesion
Prostate cancer is multifocal but usually consists of a dominant focus and one or more separate, secondary foci of smaller volume [16, 17]. This dominant tumor is measured by tumor volume and deemed the index lesion. In lesions other than the index lesion Gleason grade 4 or higher is very rare and, therefore, are considered to be insignificant [17]. Furthermore, gene fusions, found in prostate cancer metastases are only found in the index lesion, but not in small, low grade, satellite lesions [18]. This finding suggests that these small satellite lesions do not metastasize. Following this reasoning, it is hypothesized that by targeting the index lesion, a patient can be “cured” from significant prostate cancer [19]. A recent study nuanced these findings and found a percentage of 23% of prostate cancer metastases that did not arise from the “index” lesion [20].

Existing tumor mapping technologies
In order to successfully execute focal therapy of prostate cancer, it is essential that all clinically significant tumors in the prostate are reliably identified and that the physician is certain that the ablative energy is guided towards these areas in the prostate. Finally, the ablated areas have to be monitored to determine treatment success of failure. Not a single modality meets all these requirements by itself. Today, a combination of imaging modalities and biopsy is considered gold standard [14].

Template saturation biopsies
Until recently, transperineal template mapping (TPM) biopsies were considered gold standard for patient selection in focal therapy [14,21]. It has a sensitivity and negative
predictive value of approximately 95% for detection and ruling out of clinically significant cancer [14,22]. Disadvantages are that this method is time consuming, requires anesthetics and is not seldomly followed by a urinary retention in 2-11% of the cases [14].

**Ultrasound**

Ultrasound based technologies are not widely implicated in clinical practice of imaging for prostate cancer detection and are mainly in a research phase [23]. Examples of these technologies are elastography, tissue characterization imaging modalities and contrast enhanced ultrasound (multiparameter ultrasound); these have shown variable degrees of certainty in the identification of clinically significant cancer in specialized centers. However, ultrasound and ultrasound fusion with other imaging technologies (MRI) seem to be a useful technology for detection and treatment guidance, since it is easily performed in an office or operating room setting and the technology is real-time [24].

**Multiparametric MRI (mpMRI)**

The imaging modality that has been studied most widely is mpMRI and has shown reasonable sensitivity for the detection of cancers in the prostate of GS 7 or more (Table 3) [25, 26]. MpMRI uses functional parameters such as dynamic contrast enhanced, diffusion weighted, or magnetic resonance spectroscopy, combined with anatomical parameters (T2 weighted imaging). In mpMRI before focal treatment of prostate cancer, the index lesion is defined as the lesion(s) with the highest cancer suspicion score based on initial mpMRI of a patient, irrespective of size [27]. In order to establish uniformity in mpMRI acquisition, interpretation and reporting, the prostate imaging – reporting and data system (PI-RADS) was created in 2012 by the European Society of Urogenital Radiology (ESUR) [28]. For detection of clinically significant prostate cancer (GS ≥ 4+3 or cancer core length ≥ 6 mm), mpMRI showed a significantly higher sensitivity than systematic 12 core transrectal ultrasound (TRUS) guided biopsies, compared to template prostate mapping biopsy as a gold standard [29]. Recently, two studies were published, suggesting that mpMRI with targeted biopsy only if mpMRI is positive, is superior to systematic 12 core TRUS biopsies in the biopsy naïve population (PRECISION and 4M studies) [30, 31].

| Table 3: Prostate cancer detection rates (%) by mpMRI for tumor volume and Gleason Score in radical prostatectomy specimens [25]. |
|---------------------------------|----------------|----------------|----------------|
| **Gleason Score**              | **Tumor volume (mL)** | **<0.5** | **0.5 - 2.0** | **>2.0** |
| 6                              | 21 - 29%         | 43 - 54%    | 67 - 75%      |
| 7                              | 63%              | 82 - 88%    | 97%           |
| >7                             | 80%              | 93%         | 100%          |
Optical coherence tomography (OCT) as a novel imaging modality in prostate cancer

OCT is a technology that allows for minimal invasive and microscopic imaging of structures in biological tissues. Huang et al described the first application of OCT in the retina and the coronary artery in 1991 [32]. The contrast in the OCT images is based on differences in the back-scattering properties of the tissue, which are visualized as gray-scale levels. The principle is similar to ultrasonography, except that, in OCT, light waves provide the back-scattered information, rather than acoustic waves. Using near infrared light with very short wavelengths (1300 nm), a detailed image can be produced with a penetration depth of approximately 1–2 mm and resolutions as low as 10 µm [33]. Consequently, images that are comparable to histopathology can be created. Thin fiber optic helical scanning OCT probes were built into needles, which allow the introduction of the OCT probe into solid tissue such as the prostate [34]. As the light penetrates the tissue, the optical properties of tissue, such as scattering and absorption, limit the imaging depth. In other words, the optical attenuation coefficient, which defines the decay of OCT signal with depth, can be used to quantitatively differentiate between tissues. Recent studies indicate that OCT can aid in the discrimination of neoplastic and cancerous tissue over normal tissue by using Lambert-Beer's law of exponential attenuation [35], by quantitative measurement of the attenuation coefficient [36-40].

There is a good rationale for using OCT in the detection of prostate cancer. Within urology, most research has been performed to assess the potential of OCT to accurately diagnose bladder cancer [41-43]. In the kidney, OCT was successful in discriminating between benign and malignant renal tissue [36]. In the prostate, OCT has been used to identify neurovascular bundles and assessment of surgical margins during robotic radical prostatectomy [44]. However, until now, the interpretation of OCT images of the prostate is solely based on the qualitative image interpretation, without further quantitative analysis of the OCT signal. The attenuation coefficient is expected to provide valuable clinical information, because it quantitatively determines changes of the tissue that may be disease related. The OCT images can be analyzed on visible qualitative tissue structures [45] or more quantitatively on light scattering parameters [46] and/or measured size of visible structures [47], which can be compared to histopathology of tissue. The detection of prostate cancer with OCT would enable a digital biopsy of the prostate with instant results, creating the possibility of cancer diagnosis and treatment in the same session. Moreover, the technology would not be prone to interpretation bias, since the results are quantifiable. One could imagine a clinical pathway in which suspicious lesions on mpMRI will be confirmed with targeted OCT and instantaneously treated through the same fiber-based probe, enabling super-fast diagnosis and treatment.
**PROBLEM DESCRIPTION**

Prostate Cancer is among the leading causes of cancer-related death in men [2]. Recommended therapies by guidelines for localized prostate cancer are radical prostatectomy, radiotherapy using either brachytherapy or external beam radiotherapy +/- hormonal therapy or active surveillance depending on risk group classification. Side effects of radical treatments (erectile dysfunction and urinary incontinence) have a severe impact on the quality of patients’ life [8, 48]. In selected patients, focal therapy can be applied. In focal therapy, treatment is directed only at the tumorous part of the prostate, leaving the remaining prostate unharmed, and, therefore, reducing the side effects of radical treatments. Focal therapy is a relatively new, experimental form of treatment for a highly selected group of patients. Accurate localization of the target lesion in the prostate gland before starting focal therapy is of paramount importance.

The most widely investigated and promising imaging technology for the prostate is mpMRI. As with any new form of diagnosis or treatment, it is essential to develop guidelines for imaging and treatment technologies. Guidelines for the detection of localized prostate cancer, but also for patient selection, treatment guidance, and patient follow-up in focal therapy. Only with uniform data acquisition, substantial uniform data can be generated to support or reject the use of new forms of treatment or imaging.

The suspicion of prostate cancer by rise in PSA, on prostate imaging or DRE must always be confirmed by prostate biopsies. A relatively new imaging technology in the field of oncology is OCT. Using back-scattered light, it can produce high-resolution images of tissue at even cellular levels (optical biopsy). In other organs, it has proven its value for the detection of malignancy. We hypothesize that this imaging technology can play a role in the detection of prostate cancer and in guiding and monitoring focal therapy for prostate cancer.

**THE AIMS OF THIS THESIS**

1) To advance the development and standardization of imaging and treatment protocols for focal therapy and prostate cancer imaging for focal therapy planning, guidance and follow-up (chapters 2 - 7)

2) Explore the role of Optical Coherence Tomography as a novel imaging modality for prostate tissue and detection of prostate cancer (chapters 8 - 11)
As an introduction to this thesis, we assessed the current state of imaging technologies for prostate cancer. **Chapter 2** provides an overview of novelties in patient selection for focal therapy, treatment guidance and follow-up and underlines that standardization of conduct in imaging for focal therapy in prostate cancer is essential for development of uniform data and guidelines.

The process of standardized data and guideline formation starts with expert opinion. **Chapters 3 and 4** describe structured consensus projects between urologic, radiologic and research experts in the field on the utility of mpMRI in treatment planning, treatment guidance and follow-up in focal therapy.

Since focal therapy of prostate cancer is a relatively new concept, little is known about patient follow-up after treatment. Standardization of follow-up is of utmost importance for the creation of uniformly comparable data in clinical trials. Therefore, we conducted a structured consensus project on this topic in **chapter 5**.

In 2016, the PI-RADS steering committee published PI-RADS V2.0 guidelines for the conduct and interpretation of prostate mpMRIs. In **chapter 6**, we assessed the accuracy and inter-observer variability of this new PI-RADS v2.0 in a biopsy naive population.

Following radical treatment, patients can develop a local recurrence of their prostate cancer. It is important to diagnose these recurrences in an early stage to improve the outcomes of salvage treatment. **Chapter 7** describes the results of a study that investigated the use of mpMRI/TRUS fusion biopsy to detect recurrent prostate cancer after radical prostatectomy at an early stage.

The second part of the thesis explores the potential of OCT as a novel imaging modality for the imaging of prostate tissue. In order to ensure accurate measurements, the system needed to be calibrated. **Chapter 8** describes calibration measurements of the OCT system. A customized computer program was designed to automatically analyze OCT pullbacks.

With a calibrated system, we were ready to perform measurements in prostate tissue. In **chapter 9**, we assessed the diagnostic accuracy of the optical attenuation coefficient for the detection of prostate cancer in 6 prostates.

In chapter 9 we discovered that our histopathology matching method was not accurate enough to reliably validate needle-based OCT as an imaging technology for prostate tissue. This challenge was solved in **chapter 10** by the development of a customized device that matches OCT data to histopathology.

In **chapter 11**, we analyzed the results of 106 OCT datasets measured in 20 patients with the customized tool for pathology matching. Results were quantitatively as well as qualitatively analyzed.
Chapter 12 provides concluding remarks on the thesis and a summary of the most important findings. It also contains a critical discussion and considers future perspectives. In chapter 13, a summary of the topics addressed in the previous chapters is provided.
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Part I

Standardization of imaging and treatment protocols for focal therapy in prostate cancer
Chapter 2

Imaging modalities in focal therapy: patient selection, treatment guidance, and follow-up

BG Muller, W van den Bos, PA Pinto, JJMCH de la Rosette

Published in Current Opinion in Urology, 2014 May;24(3):218-24
ABSTRACT

Purpose of review
Focal therapy for prostate cancer is emerging as a management option between active surveillance and radical treatments. In this article, we present two of the most important imaging modalities in focal therapy, multiparametric MRI (mpMRI) and ultrasonography. We review the recent advances within these two platforms.

Recent findings
State-of-the-art imaging in all phases of focal therapy is essential for treatment safety. In patient selection, treatment guidance, and follow-up, different aspects of imaging are important. mpMRI is an imaging technology with high imaging resolution and contrast. This makes it an excellent technology for patient selection and treatment planning and follow-up. Ultrasound has the unique property of real-time image acquisition. This makes it an excellent technology for real-time treatment guidance. There are multiple novelties in these two platforms that have increased the accuracy considerably. Examples in ultrasound are contrast-enhanced ultrasonography, elastography, shear-wave elastography, and histoscanning. In mpMRI, these advantages consist of multiple sequences combined to one image and magnetic resonance thermometry.

Summary
Standardization of multiparametric transrectal ultrasound and mpMRI is of paramount importance. For targeted treatment and follow-up, a good negative predictive value of the test is important. There is much to gain from both of these developing fields and imaging accuracy of the two platforms is comparable. Standardization in conduct and interpretation, three-dimensional reconstruction, and fusion of the two platforms can make focal therapy the standard of care for prostate cancer.

Keywords
focal therapy, MRI, prostate cancer, ultrasonography
INTRODUCTION

Following the discovery of prostate-specific antigen (PSA), the incidence of prostate cancer increased drastically, whereas cancer-specific mortality rate remained unchanged at 5% [1]. Concerns have especially been raised about the increasing detection of low-risk and intermediate-risk prostate cancer, as active treatment may not improve disease-related survival, but on the other hand may impair the quality of life significantly. Consequently, deferred treatments such as active surveillance or watchful waiting are appealing management solutions which maximize the quality of life [2]. However, these management options have their disadvantages. Biopsy sampling errors, particularly those leading to missed anterior tumors, and consequently undergrading of the tumor, is the biggest limitation of active surveillance [3]. Furthermore, repeat biopsies can result in increased costs, pain, and infections associated with increased hospitalizations [4]. A cancer diagnosis is stressful for the patient and not actively treating the disease may, in susceptible individuals, cause additional anxiety [5]. Finally, compliance is also an issue, with some studies showing as few as 53% of patients in specific subgroups comply with protocol mandated biopsy at 1 year [6]. Focal therapy can offer an alternative in patients with low-risk and intermediate-risk prostate cancer, as it offers cancer control on the one side without the side-effects of radical treatments on the other side [7,8,9,10]. For focal therapy, high-end imaging is of paramount importance. The clinician has to be positive that the targeted tumor is low-risk or intermediate risk prostate cancer and that there is no extracapsular extension. During treatment, the clinician should be certain that the targeted tumor is being totally ablated and that outside the targeted area, no significant tumor resides. In the follow-up period, recurrences or residual tumor should be clearly recognized on imaging. The two most important imaging modalities for imaging in focal therapy are mpMRI and multiparametric ultrasound (mpUS) [11]. In focal therapy, roughly three phases can be distinguished, each demanding a different aspect from imaging modalities. These phases include patient selection and treatment planning, treatment guidance, and follow-up after focal therapy. Definitions of these phases differ among literature, therefore we defined the definitions as used in this review:

1. Patient selection: selection of a patient with low or intermediate prostate cancer ($\leq$T2W, Gleason Score $\leq$4+3, and PSA <20 ng/ml), with a target lesion confined to one lobe of the prostate.
2. Treatment guidance: real-time guidance of the focal treatment modality to the targeted lesion.
3. Follow-up: after treatment control that there is no residual tumor, or after a period of time, no recurrent tumors.
The review focuses on imaging for focal therapy in these three different phases of this treatment form.

IMAGING FOR PATIENT SELECTION

The requirements of imaging in patient selection are to identify patients with low-to-intermediate risk prostate carcinoma. Moreover, the targeted area should be identifiable (the tumor should be clearly visible on imaging). Furthermore, outside the targeted area, there should not be a significant other lesion. It is, therefore, essential to have a high resolution three-dimensional (3D) imaging technology available that identifies in high accuracy the location, size, grade, and stage of the tumor. Moreover, negative predictive value of the non-affected prostate lobe should be high.

MRI has the potential to fulfill the strong imaging requirements for patient selection in focal therapy. MRI works with a magnetic field varying between 0.5 and 7 Tesla (T). Most systems for prostate scanning use 1.5 or 3 T. The technology relies on the detection of a radiofrequency signal emitted by excited hydrogen atoms in the body, using the energy from an oscillating magnetic field applied at the appropriate resonant frequency [12]. Until recently, the diagnostic performance of MRI was too low to implement the technology into the diagnostic workup leading to focal therapy of prostate cancer. However, evidence coming from the centers of excellence support an accurate diagnostic performance of MRI, provided that multiple sequences are used and that their outputs are combined in a mpMRI. These sequences include T2-weighted (T2W) imaging, dynamic contrast-enhanced (DCE) imaging, diffusion-weighted imaging (DWI), and sometimes proton spectroscopic imaging (MRSI) (Fig. 1). Disagreement among experts in the field of uro-radiology about the conduct, interpretation, and reporting of mpMRI have prohibited the formation of uniformly comparable literature on diagnostic accuracy and hence the formation of guidelines. Various consensus projects have therefore been initiated to standardize the conduct and reporting of mpMRI in prostate cancer [13–15,16]. The key difficulty in medical imaging research is the comparison of images to histopathology. It can be challenging to relate the images on MRI to the histopathology specimens, because of shrinkage and freehand slicing. Several solutions have been posed to overcome these challenges. Orczyk et al.[17] developed deformable histopathology mpMRI fusion computer software based on 22 landmarks in the specimens. They managed to reach an improvement in matching accuracy of 32% over rigid comparison methods. Trivedi et al. [18] developed a 3D histopathology analysis tool using 3D printed customized moulds based on preoperative mpMRI data, corrected for shrinkage, for slicing of the histopathological specimens in exactly the same plane as the mpMRI scanning. Using these methods, Turkbey et al. [19] determined the diagnostic accuracy for the separate
sequences used in mpMRI (T2W, DWI, DCE, and magnetic resonance spectroscopy) in a prospective study including 45 patients. The results are depicted in Table 1. By using advanced histopathology matching, the validity of mpMRI accuracy research improved substantially. The same research group demonstrated that 3 T mpMRI could accurately estimate tumor volume independent of Gleason score, using this method, in 135 patients.

Figure 1: A mpMRI image of a prostate in a 70-year-old patient with Gleason 3+3 prostate carcinoma. (A) T2-weighted image, with hypodense lesion (arrow). (B) Diffusion-weighted image. The arrow indicates an area with diffusion restriction. (C) Dynamic contrast-enhanced image. The arrow indicates an enhancing lesion.

These results are valuable in focal therapy treatment planning as well as follow-up after therapy [24]. Another way to improve the diagnostic performance of MRI is to increase MRI field strength. In the prostate, only few studies have yet been done regarding 7 T mpMRI. The advantage of a higher field strength is a higher signal-to-noise ratio. Rosenkrantz et al. [25] demonstrated the feasibility of 7 T MRI in two patients with biopsy-proven prostate cancer. They demonstrated a signal-to-noise ratio gain of 2.1 at 7 T MRI vs. 3 T MRI and images showed excellent visual correlation with the radical prostatectomy specimens. Several studies demonstrated the safety and feasibility of magnetic resonance (MR) spectroscopic imaging at 7 T in patients with biopsy-proven prostate cancer. 7 T MRI rendered a well-tolerated and promising technology [26,27]. Another promising novelty is correlated diffusion imaging (CDI). CDI takes the advantage of multiple gradient pulse strengths and timings. This not only reduces dependency on the way diffusion gradient pulses are applied, but also improves delineation between cancerous and healthy tissue. One study demonstrated an impressive improvement in area under the receiver operator characteristic (ROC) curve for CDI over normal DWI (0.9789 vs. 0.9183) in 20 patients with prostate cancer [28]. The future of mpMRI lies also in standardization of conduct and interpretation and quantification of the results.
These aspects will make the technology more comparable, more reproducible, and less operator dependent. Maas et al. [29] demonstrated good performance with quantitative evaluation of computed high b value diffusion-weighted MRI of the prostate. Artan et al. [30] proposed the first mechanism of automated prostate cancer localization on mpMRI. The results in the first eight patients look promising, but have to be investigated in larger trials.

Ultrasonography works with oscillating sound pressure waves that move through the body and reflect on surfaces in between dense and soft structures. In the last decennia, there were multiple advances in the field of ultrasound, which increased sensitivity and specificity of the technology for the detection of prostate carcinoma [31]. The major benefit of ultrasound is that the technology is real time, so that information can be interpreted during the investigation. Frequency varies between 2 and 60MHz with as a general rule: the higher the frequency, the higher the imaging resolution. However, image penetration depth decreases with increasing frequency. In the field of ultrasound, similar developments as with MRI are emerging. Detection rates of prostate cancer in greyscale ultrasound are low, but when the outputs of several sequences are combined, the accuracy would presumably go up. Advances in the field of ultrasound imaging of the prostate include contrast-enhanced ultrasonography (CEUS) (Fig. 2), elastography, shear-wave elastography, power Doppler, and histoscanning.

Figure 2: A Contrast enhanced Ultrasonography (CEUS) image in the apex of the prostate. On the right, we can see the greyscale TRUS image. On the left, the contrast enhanced picture is visible, 28 s after the injection of contrast medium. An area of enhancement is seen on the right apex indicating suspicion for tumor.
A consensus meeting about the use of ultrasound modalities in focal therapy concluded that the ultrasonography alone was insufficiently accurate for patient selection in 2011 [32]. In the last years, however, much research has been done into different modalities of ultrasound, which gives the technology a multiparametric character. In the past, it has been suggested that end-fire ultrasonography probes have a higher detection rate than side-fire probes. A recent article by Rom et al. [33] showed that the cancer detection rate in transrectal ultrasound (TRUS) does not depend on the type of ultrasound probe used (end-fire probe 34.3% or side-fire probe 34.4%) in 300 patients. Contrast-enhanced ultrasonography with contrast-tuned imaging technology has a greater sensitivity (73.1%) and accuracy (83.7%) than conventional greyscale ultrasound (50.9 and 78.8%), and power Doppler (48.3 and 77.7%). This study was performed in 150 patients with targeted biopsy as an endpoint [20]. Another prospective study investigated the hypothesis whether pretreatment with dutasteride would improve the detection rate of CEUS-guided biopsies. ROC analysis showed that CEUS increased the detection of cancer compared with greyscale ultrasound (sensitivity went up from 0.60 to 0.64 for all lesions). For high-grade lesions, however, sensitivity improved from 0.74 to 0.80. These numbers were even higher for high-grade lesions with more than 50% core involvement (0.83–0.90). Dutasteride pretreatment did not improve the detection rate [34]. Zalesky et al. [35] described an area under the ROC curve of 0.776 for power Doppler compared to 0.67 for normal greyscale, indicating that the sensitivity and specificity for power Doppler is significantly higher than greyscale ultrasound. This prospective study consisted of 146 patients. Brock et al. [22] described in 2012 in a prospective study of 353 patients that real-time elastography guided biopsies revealed more prostate cancer (sensitivity 60.8 and specificity 68.4) than greyscale ultrasound-guided biopsies (sensitivity 15 and specificity 92.3). Simmons et al. [21] described the diagnostic accuracy of histoscanning. A total of 31 patients were included and the results were compared to radical prostatectomy. Sensitivity of 93% was found. A novelty in the field of elastography is the invention of shear-wave elastography. In shear-wave elastography, the ultrasound probe automatically generates standardized pressure waves, instead of depending on the pressure wave manually generated by the physician. In a prospective study of 53 patients, Barr et al. [23] demonstrated a sensitivity of 96.2% with a specificity of 96.2%, positive predictive value (PPV) of 69.4, and negative predictive value (NPV) of 99.6 in patients with elevated PSA and abnormal digital rectal examination (DRE). Combining the outputs of these different ultrasound modalities into a standardized, automated multiparametric TRUS (mpTRUS) can be very promising for the diagnostic accuracy of ultrasound. Combined data on sensitivity and specificities of the different ultrasonography modalities can be found in Table 1.
The goal of imaging during treatment guidance is to get the modality of focal therapy to the targeted area. For this, real-time orientation is essential. An ideal combination would be the high resolution and contrast of mpMRI with the real-time feedback of ultrasound.

There have been some recent advances in the field. Traditionally, ultrasound is the technology most used as a treatment-guidance modality in focal therapy. However, MRI-guided technologies are used more and more frequently. In 2012, Lindner et al. [36] described the first case of MRI-guided high-frequency focused ultrasound (HIFU) ablation of prostate cancer. The major advantage of the procedure is that the tumor can be accurately targeted with small margins on MRI and the ablation zone can be accurately monitored during treatment. Disadvantage is that the technique is time-consuming. Bomers et al. [37] provided an overview of MRI-guided focal technologies.
in 2012. Conclusions of this review article were that currently MRI-guided laser ablation and MRI-guided HIFU are the most promising options for focal treatment of the prostate in patients with prostate cancer. Other techniques – that is, cryosurgery, microwave ablation, and radiofrequency ablation are, for several and different reasons, less suitable for MRI-guided focal therapy of the prostate. A relatively new technology for image-guided thermal focal therapy is MR thermometry. With this technology, the temperature of tissue can be exactly monitored during ablative therapy. Partanen et al. [38] investigated the technology in dogs using transurethral focused ultrasound monitored by MR thermometry. The technology rendered well tolerated and promising for use in humans. In 2013, Kuru et al. [39] demonstrated the accuracy of TRUS–MRI fused transperineal prostate biopsies. They proved a high detection rate of clinically significant tumors using this technology. A TRUS–MRI elastic fusion technology with excellent accuracy was also demonstrated by Ukimura et al. [40] in 2012. It is expected that TRUS–MRI fusion will gain field not only in targeted biopsy, but also in focal therapy treatment guidance in future. Results of the first use of TRUS–MRI fusion in focal therapy guidance are already emerging [41].

**IMAGING FOR FOLLOW-UP**

Imaging for follow-up after focal therapy should ideally be fast, accurate, insensitive to treatment artifacts, and should be able to distinguish ablated area from tumorous tissue. The images should be comparable to previous imaging, to accurately detect recurrent and residual lesions. Ideally, the technology is minimally invasive, because imaging for follow-up has to be done repetitively.

There is little evidence about imaging in the follow-up after focal therapy of the prostate. Last year, a consensus project was set up along a 45-member panel of urologists and radiologists, and it was decided that follow-up of focal therapy should start with a mpMRI after 6 months, followed by a yearly mpMRI. mpMRI findings should be confirmed by targeted biopsy before retreatment [16]. Few studies have been done on imaging modalities in the follow-up after focal therapy. One of these studies is a retrospective work by Punwani et al. [42] in 2012, in which 26 patients had a DCE-MRI and targeted biopsy of the prostate after whole-gland HIFU treatment. Sensitivity ranged between 73 and 87% among three readers, whereas specificity ranged between 73 and 82%. These results were comparable with pre-biopsy PSA levels. A retrospective study with MRSI showed that most recurrences after focal radiation therapy occur at the same site as the dominant primary tumor at baseline. This suggests that supplementary focal therapy aimed at enhancing the lesions would be a rational addition to management [43]. Del Vescovo et al. [44] evaluated DCE-MRI in a prospective study in 25 patients.
In all patients, a rim of enhancement alongside the targeted area was observed on DCE-MRI, 1 month after treatment, which typically disappeared on later DCE-MRIs. Four months after treatment, the prostate had significantly reduced volume (average 61% volume reduction). Decision support systems (DSS) for mpMRI of the prostate are being designed to make reading more standard and less objective. The DSS provides a probability map for peripheral zone prostate tumors based on endorectal mpMRI. These probability maps may aid in reaching a higher accuracy and more comparable outcomes in the follow-up of focal therapies [45].

CONCLUSION

State-of-the-art imaging in all phases of focal therapy is essential for treatment safety. In patient selection, treatment guidance, and follow-up, different aspects of imaging are important. Not only a high PPV is required, but also a high NPV to rule out significant cancer in other parts of the prostate. mpMRI is an imaging technology with high imaging resolution and contrast. This makes it an excellent technology for patient selection and treatment planning and follow-up. Ultrasound has the unique property of real-time image acquisition. This makes it an excellent technology for real-time treatment guidance. There are multiple novelties in these two platforms that have increased the accuracy considerably. Examples in ultrasound are CEUS, elastography, shear-wave elastography, and histoscanning. In mpMRI, these advantages consist of multiple sequences combined to one image (mpMRI) and MR thermometry. Standardization of mpTRUS and mpMRI is of paramount importance. There is much to gain in these two fields. Imaging accuracy of the two platforms is comparable. Standardization in conduct and interpretation, 3D reconstruction, and fusion of the two platforms can bring focal therapy a step closer to the standard of care.

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CONFLICTS OF INTEREST:

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23. Barr RG, Memo R, Schaub CR. Shear wave ultrasound elastography of the prostate: initial results. Ultrasound Q 2012; 28:13–20. A first trial on shear-wave elastography in the prostate. By using a standardized device generated pressure wave, the accuracy of shear-wave elastography is higher than real-time elastography, making it an ultrasound modality with very high accuracy.


Chapter 3

The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer: recommendations from a consensus panel

BG Muller, JJ Fütterer, RT Gupta, A Katz, A Kirkham, J Kurhanewicz, JW Moul, PA Pinto, AR Rastinehad, Cary Robertson, JJMCH de la Rosette, R Sanchez-Salas, JS Jones, O Ukimura, S Verma, H Wijkstra, M Marberger

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ABSTRACT

Objectives

- To establish a consensus on the utility of multiparametric magnetic resonance imaging (mpMRI) to identify patients for focal therapy.

Methods

- Urological surgeons, radiologists, and basic researchers, from Europe and North America participated in a consensus meeting about the use of mpMRI in focal therapy of prostate cancer.
- The consensus process was face-to-face and specific clinical issues were raised and discussed with agreement sought when possible. All participants are listed among the authors.
- Topics specifically did not include staging of prostate cancer, but rather identifying the optimal requirements for performing MRI, and the current status of optimally performed mpMRI to (i) determine focality of prostate cancer (e.g. localizing small target lesions of ≥0.5 mL), (ii) to monitor and assess the outcome of focal ablation therapies, and (iii) to identify the diagnostic advantages of new MRI methods.
- In addition, the need for transperineal template saturation biopsies in selecting patients for focal therapy was discussed, if a high quality mpMRI is available. In other words, can mpMRI replace the role of transperineal saturation biopsies in patient selection for focal therapy?

Results

- Consensus was reached on most key aspects of the meeting; however, on definition of the optimal requirements for mpMRI, there was one dissenting voice.
- mpMRI is the optimum approach to achieve the objectives needed for focal therapy, if made on a high quality machine (3T with/without endorectal coil or 1.5T with endorectal coil) and judged by an experienced radiologist.
- Structured and standardized reporting of prostate MRI is paramount.
- State of the art mpMRI is capable of localizing small tumors for focal therapy.
- State of the art mpMRI is the technique of choice for follow-up of focal ablation.

Conclusions

- The present evidence for MRI in focal therapy is limited.
- mpMRI is not accurate enough to consistently grade tumor aggressiveness.
- Template-guided saturation biopsies are no longer necessary when a high quality state of the art mpMRI is available; however, suspicious lesions should always be confirmed by (targeted) biopsy.
The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer

KEYWORDS

prostate cancer, focal therapy, consensus, multiparametric magnetic resonance imaging, prostate biopsies.
INTRODUCTION

Current treatment in prostate cancer aims at systemic or whole gland/radical procedures, with significant side-effects, i.e. erectile dysfunction and/or incontinence [1]. Consistent with rising awareness and new and improved imaging methods, small tumors occupying <5–10% of the prostate volume are detected earlier than in the past. Concerns have been raised about the diagnosis and over-treatment of these small tumors. These concerns led to the concept of focal therapy, a selective ablation targeted to specific sites in the prostate gland, reducing lifetime morbidity and side-effects without compromising life expectancy for patients with low- and selected patients with intermediate-risk prostate cancer [2]. These techniques include cryotherapy, high-intensity focused ultrasound (HIFU), laser ablation therapy, radiofrequency ablation, irreversible electroporation (IRE) and photodynamic therapy (PDT). The first two methods have emerged as alternative therapeutic options in patients with clinically localized prostate cancer by the European Association of Urology (EAU) and the American Urological Association (AUA). The others are still considered experimental.

Imaging criteria in focal therapy for prostate cancer differ from imaging criteria for whole gland treatment. Eligible patients who are offered focal treatment are already diagnosed with prostate cancer, which has been confirmed by TRUS-guided prostate biopsies. The objective of imaging is therefore accurate location and contour (boundary) of the target lesion, rather than just identifying or staging of a lesion. However, several key issues remain to be addressed for successful focal therapy: (i) Can cancers of clinical significance be reliably identified? (ii) Can such lesions be accurately localized? (iii) Can these lesions be targeted and ablated with lower morbidity than that associated with whole-gland therapy? iv) Can complete ablation be monitored to determine treatment success and what are the optimal parameters to measure success? [2]. Considering morbidity and potential pitfalls of repeated multiple core prostate biopsies, imaging technology that enables reduction or replacement of these invasive interventions is always advantageous. Moreover, there is a paucity of information about the concept of focal therapy in the current urological guidelines. Therefore, a meeting was organized to achieve consensus among experts on the use of mpMRI in focal therapy for prostate cancer. The objectives of this meeting were to establish a consensus on: (i) the utility of mpMRI to identify patients for focal therapy (e.g. can mpMRI accurately localize small target lesions of ≥0.5 mL), (ii) to determine criteria for monitoring of focal therapy and follow-up after focal therapy, and finally (iii) whether mpMRI can replace the need for invasive transperineal template saturation biopsies. The topic of prostate cancer diagnosis by mpMRI, was specifically not discussed, as patients eligible for focal therapy already have biopsy confirmed prostate cancer. This subject was recently discussed in a meta-analysis by Moore et al. [3] and is therefore not further covered in this article.
METHODS

The consensus meeting was held 6 June 2012 (Durham, NC, USA: http://www.focaltherapy.org). The meeting focused on optimizing methods and indications of mpMRI in the localization and follow-up of prostate cancer in patients eligible for focal therapy. A multidisciplinary board of international contributors was selected based on their expertise in the topics discussed. Professor Michael Marberger (Vienna, Austria) chaired the meeting; participants are listed among the authors.

The conduct of the meeting conformed to an informal consensus process, for which no formal scoring system to measure the level of agreement was used [4]. However, the process did conform to generally accepted stages of a consensus process [5]. Items for discussion were preselected beforehand and discussed by three individual groups. These topics were assigned a specific time for general discussion during the meeting. A representative of each group gave a brief presentation. A moderated discussion took place using the presentation as a basis (Level 1). Discussed issues were resolved within this session of the meeting (Level 2). A consensus was established by noting any individuals who did not agree to the general view on specific items (Level 3). Items selected for discussion are shown in the headlines of the results section. All contributors to the consensus process have read and approved the present manuscript and, by agreeing to authorship, concur with the essential contents of this article. Dr Peter Pinto chaired the discussion on item number 1, Dr Jurgen Fütterer chaired the discussion on item number 2, and Professor Osamu Ukimura chaired the discussion on item number 3.

RESULTS

1. What are the optimal mpMRI requirements for selecting patients for focal therapy in prostate cancer, and can this technology replace template saturation biopsies?

Over the last 6 years, several studies have been published comparing preoperative MRI to histopathological specimens from radical prostatectomies (RPs) for definition of the diagnostic accuracy [6–19]. Reports of similar consensus meetings about imaging and focal therapy for prostate cancer have been previously published [2,20]. However, these were mainly directed at diagnosing and staging prostate cancer, and not so much on locating small lesions amenable to focal therapy. Therefore, the results from these meetings were still unsuited for use in clinical practice [21]. The most reliable approach to assess the diagnostic accuracy of mpMRI is by comparing mpMRI results with histological finding in whole mounted and close step-sectioned RP specimens. As prostate cancer is often multifocal in nature, correlation of mpMRI is not straightforward, e.g. differentiation of
index lesions from other smaller lesions is often difficult. Limitations in studies assessing accuracy of MRI with histopathology arise from free-hand slicing of the specimens (deformation and variable slice thickness) and non-uniform shrinkage during fixation (distortion). It was therefore difficult to determine the true accuracy of mpMRI for localization of lesions [16,22,23]. Turkbey et al. [24] found a potential solution for this problem in 2011 by slicing the histopathological specimen exactly according to the mpMRI images by using a customized three-dimensional mold. This mold, for standardized slicing, enabled accurate comparison of RP specimen with histopathology. Good positive predictive values for mpMRI at 3T were found (98%, 98%, and 100% in the overall prostate, peripheral zone and central zone, respectively). According to the consensus meeting, this study represents an accurate representation of the available evidence for validation of mpMRI in focal therapy of the prostate. The results of the study are shown in Table 1 [6–24]. This data was supported by the data from a study by Villers et al. [23]. These mpMRI data, which were acquired on a 1.5 T device, instead of the 3 T device in the study of Turkbey et al. [24], and compared with whole-mount histopathology without a customized mold, showed a sensitivity, specificity and positive and negative predictive values for detection of prostate cancer by mpMRI of 77%, 91%, 86% and 85% for foci of >0.2 mL, and 90%, 88%, 77%, and 95% for foci of >0.5 mL, respectively.

Given the variation of sensitivity and specificity for different quality mpMRIs, the general opinion in the consensus meeting was that optimal MRI technology and protocols should be defined to select patients for focal therapy, rather than defining minimal criteria. The optimum approach to achieve the objectives needed for focal therapy was considered a 3T mpMRI, regardless of use of a transrectal or whole body coil. The highest signal-to-noise ratio is achieved using 3T MRI with an endorectal coil (Figure 1). This is about five-times higher than when solely a surface coil is used. There is currently no data showing equivalent signal strengths between the two different approaches. The clinical difference between the two approaches may be minimal. However, a 1.5T system can only be used considered an optimal alternative if used with a transrectal coil. One person (Dr Kirkham) was opposed to this motion, as in his opinion 1.5T devices have enough diagnostic accuracy for focal therapy. However, the others strongly disagreed on this point and felt that with less than optimum technology, additional measures, i.e. template biopsies are absolutely needed. Spectroscopy at this time is still under investigation and suffers from the inability of multiple institutions being able to perform it reproducibly. As the decision for focal therapy relies on the mpMRI examination, only better developed technology should be used for decision making in focal therapy.

Considering artefacts induced by previous biopsies, it was decided that any previous biopsies should have been taken at least 8 weeks before mpMRI, as biopsy artefacts disturb tumor visibility.
The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer

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Table 1: Outcomes of studies from paragraph 1 summarized. (-) means that no data on this variable was provided in the study.
Figure 1: Prostate cancer in a 67-year-old patient with a PSA level of 6.23 ng/mL and Gleason 7(A). Axial T2-weighted MRI of the prostate showing a low signal intensity area in the left peripheral zone. (B) ADC and the high b-value (C) images show restriction and high signal in the left peripheral zone, respectively. The perfusion MRI shows high Ktrans (transfer constant) in the left peripheral zone (D). The whole-mount section histopathology slide on the same level as (a–d) shows Gleason 7 cancer in this MRI-positive area (E).
There was consensus that mpMRI and 12-core TRUS-guided biopsies, do not show contradictory findings, when exporting TRUS images to MRI [25]. It can therefore be concluded that template biopsy is not a strong prerequisite, as long as there is a high quality mpMRI available. Consequently, consensus was reached on the following topic: in presence of any doubt on the MRI image, a MRI-guided biopsy should be considered instead of a template biopsy. However, due to clinical importance of mpMRI, the consensus meeting decided that it should preferably be assessed by two ‘blinded’ readers with a minimum experience of 50 studies under appropriate monitoring each. Furthermore, elastically fused MRI-TRUS can also be performed to guide lesion biopsy [26], but on this topic no consensus was reached. Important information from this paragraph is summarized in Table 1.

2. What is the diagnostic accuracy of mpMRI defined as necessary for answering the demand for focal therapy for localizing focal cancer, predicting the progressive potential of small lesions and what are the limitations from previous biopsies?

Focal therapy is defined as treatment to a segment of tissue; ideally patients have low-volume, unilateral, preferentially unifocal disease. However, multifocal prostate cancer is common, present in 67–87% of all pathological specimens after a RP, even among men with small cancer volumes (<0.5 mL) [27]. Multifocal prostate cancer does not necessarily represent a contraindication for focal therapy. An index lesion (defined as the largest and usually considered the highest grade) is frequently identified and may represent the most important determinant of prognosis. Even when the cancer is multifocal, most non-index lesions appear to be biologically indolent on the basis of small size and low grade. Eggener et al. [28] found that among patients with multifocal disease, 80% of the total tumor volume was present in the index lesion. In 92% of patients, extracapsular extension arose only from the largest lesion [28]. It is generally accepted that tumor progression is usually mediated by index lesions of larger volume (>0.5 mL) and higher grade (Gleason score ≥7). For effective treatment, accurate localization and characterization of the index lesion in candidates for focal therapy on mpMRI is a prerequisite. Therefore, diagnosis of evident high-volume lesions, as well as small lesions on mpMRI is paramount. According to the Epstein criteria of significant prostate cancer, a tumor of >0.5 mL is already significant [29]. Consequently, MRI must be accurate in diagnosing tumors of ≥0.5 mL, particularly those with a primary or secondary Gleason pattern 4.

Recent studies that compare mpMRI to whole-mount histopathology for disease detection report maximum sensitivities and specificities of 80–88% and 96–100%, respectively, with 3T MR systems. However, only tumors of >0.5 mL were included in the analyses [13,30]. The accuracy of mpMRI for detecting tumors of <0.5 mL is less well established. MRI information using a four prostate quadrants localization showed low
sensitivity of 2–20%, but high specificity (91–95%) [31]. MRI improved the prediction of minimal disease that included clinical and pathological preoperative data. These data do not support the use of T2-weighted (T2w) endorectal MRI without functional parameters to localize small tumors for focal therapy as a single sequence compared with mpMRI. However, this suggests that T2w MRI is useful to exclude patients for focal therapy trials based on radiological evidence of more extensive disease [31].

T2w MRI without functional parameters, i.e. diffusion weighted imaging (DWI) or dynamic contrast material enhanced MRI (DCE-MRI), is not sufficient for accurate diagnosis and measurement of small tumors eligible for focal therapy [31]. Tumor volume measurements made based only on T2w MRI are not reliable for clinical decision making [32–35]. As a result, functional MR methods, i.e. DWI [36], MR-spectroscopic imaging (MRSI) [37] and DCE-MRI [23] have been investigated for their capability to improve prostate tumor volume measurement. DWI is a noninvasive technique that is sensitive to random thermal movement of water molecules and is capable of probing the structure of biological tissue at a microscopic level [36]. Several studies [33,38–41] report on the added value of apparent diffusion coefficient (ADC) maps calculated from DWI on clinical decision making in prostate cancer diagnosis. Using an ADC threshold value at 0.0016 mm², the analysis showed a sensitivity of 95% and specificity of 65% [42]. DWI and MRSI have shown significant incremental value to clinical variables in predicting organ-confined and insignificant prostate cancer [43,44].

As the diagnostic accuracy of only T2w imaging is too low for use in focal therapy, the incremental value of mpMRI such as DCE-MRI, DWI, and MRSI has been investigated. Studies reporting on the combination of these techniques describe the additional value in diagnostic yield [9,16,45–51]. Fütterer et al. [9] reported an area under the curve (AUC) of 0.90 when T2w, DWI and DCE-MRI were combined in localizing prostate cancer. The meeting therefore recommended performing mpMRI, using T2w, DCE-MRI, and DWI (Figure 1). Especially for less experienced readers of MRI in staging prostate cancer, DCE-MRI could be of added diagnostic value [52].

The consensus meeting decided that 3T mpMRI (T1, T2, DCE, DWI), regardless of use of a transrectal or whole body coil, should be used. A 1.5T system can only be considered an alternative when performed with a transrectal coil. However, compared with a 3T device there is a clear limitation in signal that results in a relative decrease in cancer detection of 40% [16]. Spectroscopy suffers from the inability of multiple institutions being able to perform it reproducibly, and therefore the consensus was to not discuss it at this time.

Although studies that report on comparison of Gleason grade with MRI are limited, a significant negative correlation between Gleason grade and ADC value has been found with DWI [53–55]. Furthermore, choline plus creatine-to-citrate ratios determined by MRSI have also been correlated with Gleason grade [56,57]. One study even reported on
The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer

the correlation of signal intensities on T2w imaging with Gleason grade [58]. Correlation can be found, but Gleason grade can still not be accurately determined by mpMRI, as ADC values overlap between different Gleason grades. Therefore, more research needs to be done with regard to what role mpMRI can play in the differentiation of small high-grade cancers (target lesions) in contrast to small low-grade lesions (insignificant lesions).

For the diagnostic accuracy of small tumors, the consensus meeting decided that mpMRI has sufficient potential to detect a lesion of ≈0.5 mL with sensitivity as well as specificity of ≈90% (Tables 2 [24] and 3 [23]). For smaller tumors of ≈0.2 mL, the sensitivity of MRI decreased from 90.0 to 76.0% compared with tumors of >0.5 mL, but specificity remained in the same range (87.9 and 91.2%, respectively). This means that detection rate decreases as the size of the tumor decreases. For these very small tumors, mpMRI can only be used to exclude patients from focal therapy.

<table>
<thead>
<tr>
<th></th>
<th>PZ</th>
<th>CG</th>
<th>A&amp;CG</th>
<th>Overall gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Sensitivity (p-value)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2W</td>
<td>0.65 (0.04)</td>
<td>0.15 (0.08)</td>
<td>0.38 (0.07)</td>
<td>0.58 (0.04)</td>
</tr>
<tr>
<td>ADC</td>
<td>0.57 (0.04)</td>
<td>0.22 (0.09)</td>
<td>0.44 (0.07)</td>
<td>0.53 (0.04)</td>
</tr>
<tr>
<td>MRS</td>
<td>0.17 (0.04)</td>
<td>0.08 (0.06)</td>
<td>0.15 (0.05)</td>
<td>0.16 (0.04)</td>
</tr>
<tr>
<td>DCE</td>
<td>0.39 (0.05)</td>
<td>0.22 (0.09)</td>
<td>0.31 (0.07)</td>
<td>0.38 (0.05)</td>
</tr>
<tr>
<td>%Specificity (p-value)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2W</td>
<td>0.9 (0.02)</td>
<td>1 (0)</td>
<td>0.98 (0.01)</td>
<td>0.93 (0.01)</td>
</tr>
<tr>
<td>ADC</td>
<td>0.93 (0.02)</td>
<td>0.97 (0.01)</td>
<td>0.97 (0.01)</td>
<td>0.95 (0.01)</td>
</tr>
<tr>
<td>MRS</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>DCE</td>
<td>0.97 (0.01)</td>
<td>0.99 (0)</td>
<td>0.99 (0)</td>
<td>0.98 (0.01)</td>
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<tr>
<td>%PPV (p-value)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2W</td>
<td>0.69 (0.05)</td>
<td>0.87 (0.1)</td>
<td>0.73 (0.09)</td>
<td>0.7 (0.05)</td>
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<tr>
<td>ADC</td>
<td>0.74 (0.04)</td>
<td>0.63 (0.13)</td>
<td>0.75 (0.06)</td>
<td>0.73 (0.04)</td>
</tr>
<tr>
<td>MRS</td>
<td>0.94 (0.04)</td>
<td>0.89 (0.1)</td>
<td>0.96 (0.04)</td>
<td>0.93 (0.04)</td>
</tr>
<tr>
<td>DCE</td>
<td>0.86 (0.05)</td>
<td>0.86 (0.07)</td>
<td>0.89 (0.04)</td>
<td>0.86 (0.04)</td>
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<tr>
<td>%NPV (p-value)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2W</td>
<td>0.89 (0.02)</td>
<td>0.92 (0.02)</td>
<td>0.93 (0.01)</td>
<td>0.9 (0.01)</td>
</tr>
<tr>
<td>ADC</td>
<td>0.87 (0.02)</td>
<td>0.92 (0.02)</td>
<td>0.94 (0.01)</td>
<td>0.89 (0.01)</td>
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<tr>
<td>MRS</td>
<td>0.8 (0.02)</td>
<td>0.91 (0.02)</td>
<td>0.91 (0.01)</td>
<td>0.83 (0.01)</td>
</tr>
<tr>
<td>DCE</td>
<td>0.84 (0.02)</td>
<td>0.92 (0.02)</td>
<td>0.92 (0.01)</td>
<td>0.87 (0.01)</td>
</tr>
</tbody>
</table>

Table 2: The individual sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) of the four MRI sequences for the peripheral zone (PZ), central gland (CG), anterior horns of the peripheral zone and central gland (A&CG), and overall prostate gland (from [24]).

Upon the issue of reporting of the results, the consensus meeting decided the following: Structured reporting of the results is of utmost importance to increase sensitivity and specificity and to diminish inter-observer variability. The lack of consensus in imaging
protocols (i.e. with/without endorectal coil, field strengths, b-values, post-processing methods) makes defining guidelines for mpMRI troublesome. The PI-RADS classification, which resulted from the 2011 consensus meeting among uro-radiologists, is a useful tool for standardized reporting of mpMRI. Using this classification as a guideline is strongly recommended [59]. There is little evidence about learning curves for mpMRI reading, but the consensus panel agreed on a number of 50 patients.

3 WHAT IS THE ROLE OF MRI IN MONITORING AND DEFINING SUCCESSFUL FOCAL THERAPY AND FOLLOW-UP?

MRI could have a potential role in real-time monitoring of thermal focal ablation, namely MR thermometry [60]. The technology is based on temperature sensitive MR parameters, i.e. proton resonance frequency, diffusion coefficient, T1, T2 relaxation times, magnetization transfer, proton density, as well as temperature-sensitive contrast agents [60]. This non-invasive way of monitoring thermal focal therapies is fairly accurate provided that the target does not move. With transrectal ablation this is virtually impossible to avoid. The technique is validated both with image-guided focal laser therapy of the prostate [61], and transurethral HIFU of the prostate [62]. Siddiqui et al. [63] showed in 2010 that MR thermometry could show excellent results in real-time treatment monitoring for thermal therapy in the canine prostate. Preliminary results of this monitoring option in humans look promising. However, these results were only achieved when the prostate is secured in place, i.e. by using a transurethral probe. The challenges of movement in MR thermometry have not been resolved for transrectal ablation technologies and to date no data have been published. Until these issues have been resolved, the meeting does not recommend this technology for monitoring focal therapy.

<table>
<thead>
<tr>
<th>MRI Performance for detecting 56 cancer foci according to tumor volume in regions</th>
<th>% foci (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 0.2 mL</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>76.6 (68.5-85.3)</td>
</tr>
<tr>
<td>Specificity</td>
<td>91.2 (85.5-96.9)</td>
</tr>
<tr>
<td>PPV</td>
<td>85.7 (78.7-92.7)</td>
</tr>
<tr>
<td>NPV</td>
<td>85.2 (78.1-92.3)</td>
</tr>
</tbody>
</table>

Table 3 Sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) of small and large tumor detection on DCE-MRI correlated with whole gland histopathology (from [23])

In the follow-up of focal treatment, mpMRI can also be an accurate diagnostic tool. Vargas et al. provided an extensive review about how an ablated lesion in the prostate...
The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer

can appear on mpMRI [64]. In the following paragraph we summarize the most important findings. Thickening of the prostatic capsule, fibrosis (in the prostate and peri-prostatic), thickening of the prostatic capsule and scarring can be apparent on mpMRI after focal therapy, depending on the extent of the ablation, the ablative energy source and timing of imaging after treatment.

At 6 months after treatment, usually the prostate is low in signal on T2w imaging and there is a significant volume reduction of the prostate [65]. PSA nadir 6 months after treatment correlated with initial volume of enhancing tissue (pre-treatment) and with the prostate volume reduction at 6 months [65]. DCE imaging is the most sensitive parameter to detect recurrences/residual tumors after treatment, and any enhancing lesion should be suspicious for recurrence. Due to treatment artefacts, T2w imaging and DWI become less reliable for the detection of recurrent lesions [66]. Recurrent lesions after HIFU showed similar characteristics on DCE imaging as untreated lesions. These characteristics include a short time to peak enhancement, and early washout of the contrast [67]. Initially after HIFU treatment however, a 3-8 mm rim of enhancement will show on DCE T1w imaging, that typically resolves within 3-5 months after HIFU treatment [68]. This rim may be mistaken for a recurrence, when prostate imaging is performed to early after treatment. This phenomenon was also witnessed after photodynamic therapy. Irregularity at the treatment boundary was seen on contrast enhanced T1w images, with areas of enhancement (viable tissue) between non-enhancing low-signal-intensity regions (necrosis) [69]. After cryotherapy, these areas of heterogeneous enhancement were also seen, in combination with thickening of the prostatic capsule, urethra, and rectal wall [66]. After HIFU, diffuse or multifocal areas of low signal intensity on T2w imaging can be present, hindering the detection of recurrent/residual prostate cancer [68]. There are some authors that claim that there is a role for MRSI in the differentiation of prostate cancer from necrosis [67]. However, MRSI is not widely used and therefore evidence is too little to make a conclusive statement.

Rouvière et al. [72] showed in 2010 that in men with PSA elevation after whole gland HIFU-MR targeted biopsy detected more cancer than when the biopsies were taken by someone who was ‘blinded’ from the MRI images. The odds ratio of the probability of finding viable cancer at MRI targeted vs routine biopsy was 3.35. Punwani et al. [73] showed that DCE-MRI has similar sensitivity and specificity and receiver operating characteristic performance to serial PSA. They support surveillance with serial PSA measurements, then in cases of biochemical recurrence, use of MRI to detect local recurrence and guide biopsy. The trend is that with the increasing use of focal therapies, the significance of PSA is decreasing, although the percentage decrease of PSA from before and after focal therapy may have a role in predicting successful ablation of the index lesion. The role of DCE-MRI in focal therapy for prostate cancer is becoming more and more important [73]. Ahmed et al. [74] showed in 2012 with mpMRI after HIFU that cancer can be reliably
be detected. Kim et al. [71] showed in 2008 that for prediction of local tumor progression after HIFU ablation, DCE-MRI was more sensitive than T2w MRI with DWI, but T2w MRI with DWI was more specific than DCE-MRI. For above reasons, the conclusion of the consensus panel was that the diagnostic accuracy of loss of enhancement in MRI immediately after treatment, could suggest ‘Technical successful’ targeting, but there is yet too little evidence to correlate histological success to MRI images. Therefore, more data are required of post-MRI findings in the long term, namely after 6 months, to draw solid conclusions about MR follow-up of focal therapy. The consensus panel decided also that preoperative MRI is mandatory, to compare with focal therapy results. This MRI should ideally be taken before biopsy, but MRI before focal therapy is acceptable, if done 8 weeks after the last biopsy. Finally, the consensus panel agreed that follow-up MRI of the prostate should be taken 6 months after therapy. Some voices also opted for a MRI immediately after surgery, ≤2 weeks, for comparison, but in this topic no consensus was reached.

CONCLUSIONS

Focal therapy in prostate cancer is a new and developing field of research. The present evidence for MRI in focal therapy is limited, as studies are not uniformly executed with different technologies (1.5–3T), different protocols (mpMRI, DCE-MRI, DWI, MRSI, T1-T2) and MRI results are not uniformly reported. Therefore, limited evidence is available to make firm statements. mpMRI is the optimum approach to achieve the objectives needed for focal therapy, if made using a high-quality machine (3T with/without endorectal coil or 1.5T with endorectal coil) and judged by an experienced radiologist. Structured and standardized reporting of prostate MRI is paramount. However, when mpMRI is compared with Gleason grade, the technology is not yet accurate enough to consistently grade tumor aggressiveness. Template-guided saturation biopsies for selecting patients for focal therapy can be discarded if a high-quality MRI is available; however, suspicious lesions should always be confirmed by (targeted) biopsy. In this rapidly developing field, most research is based on expert opinion and performed only in centers of excellence. Therefore there is a need for large standardized studies.

CONFLICT OF INTEREST

Stephen Jones received an unrestricted research grant from Health Tronics.
The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer

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Chapter 4

Role of multiparametric magnetic resonance imaging (MRI) in focal therapy for prostate cancer: a Delphi consensus project

BG Muller, W van den Bos, M Brausi, F Cornud, P Gontero, A Kirkham, PA Pinto, TJ Polascik, AR Rastinehad, TM de Reijke, JJMCH de la Rosette, O Ukimura, A Villers, J Walz, H Wijkstra, M Marberger

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ABSTRACT

Objective
To define the role of multiparametric MRI (mpMRI) for treatment planning, guidance and follow-up in focal therapy for prostate cancer based on a multidisciplinary Delphi consensus project.

Materials and Methods
An online consensus process based on a questionnaire was circulated according to the Delphi method. Discussion points were identified by literature research and were sent to the panel via an online questionnaire in three rounds. A face-to-face consensus meeting followed the three rounds of questions that were sent to a 48-participant expert panel consisting of urologists, radiologists and engineers. Participants were presented with the results of the previous rounds. Conclusions formulated from the results of the questionnaire were discussed in the final face-to-face meeting.

Results
Consensus was reached in 41% of all key items. Patients selected for focal therapy should have biopsy-proven prostate cancer. Biopsies should ideally be performed after mpMRI of the prostate. Standardization of imaging protocols is essential and mpMRIs should be read by an experienced radiologist. In the follow-up after focal therapy, mpMRI should be performed after 6 months, followed by a yearly mpMRI. mpMRI findings should be confirmed by targeted biopsies before re-treatment. No consensus was reached on whether mpMRI could replace transperineal template saturation biopsies to exclude significant lesions outside the target lesion.

Conclusions
Consensus was reached on a number of areas related to the conduct, interpretation and reporting of mpMRI for use in treatment planning, guidance and follow-up of focal therapy for prostate cancer. Future studies, comparing mpMRI with transperineal saturation mapping biopsies, will confirm the importance of mpMRI for a variety of purposes in focal therapy for prostate cancer.

Keywords
prostate cancer, focal therapy, multiparametric MRI, consensus
INTRODUCTION

Two decades ago, imaging of breast tumors had significant limitations and was unreliable for organ-preserving surgical treatments. Scoring protocols for breast x-ray imaging and, at a later stage, breast MRI were developed through formal attempts to establish agreement among experts on areas of uncertainty [1–3]. These attempts resulted in reduced inter observer variability and improved the positive predictive value of pathology from breast biopsy, which paved the way for lumpectomy (focal therapy of the breast). Nowadays, this is the most prevalent treatment for breast cancer, with an oncological survival rate similar to that obtained with radical treatment [4]. We are currently witnessing a similar development in prostate cancer care. Localized prostate cancer is traditionally managed by radical treatment of the complete organ or by active monitoring. The first option may result in undesirable side effects such as erectile dysfunction and urinary incontinence, whereas active surveillance may cause anxiety about tumor progression and under-treatment [5].

Improved imaging techniques and biopsy protocols have led to the early detection of small tumors, characterized by small cancer volume and low grade [6]. Concerns regarding over-treatment of these small tumors have introduced the concept of focal therapy, using a variety of selective ablation technologies. Focal therapy is defined as a treatment that aims to eradicate known cancer within the prostate and preserve uninvolved healthy prostatic tissue, and consequently genitourinary function, without compromising cancer control [7]. Currently, focal therapy techniques in prostate cancer include cryotherapy [8], high-intensity focused ultrasonography [9], laser ablation therapy [10], radiofrequency ablation [11], irreversible electroporation [12] and photodynamic therapy [13].

For these forms of treatment, the accurate identification, localization, demarcation and, ideally, grading of a lesion are essential. MRI has the potential to fulfill these basic requirements for focal therapy in prostate cancer, but until recently, the diagnostic performance of MRI was too low to implement the technology into the diagnostic evaluation leading to focal therapy; however, there is increasing evidence, coming from centers of excellence, to support an accurate diagnostic performance of MRI, provided that multiple sequences are used and that their outputs are combined in a so-called multiparametric MRI (mpMRI) [14]. These sequences include T1-weighted and T2-weighted imaging, dynamic contrast-enhanced (DCE) imaging, diffusion-weighted imaging (DWI) and magnetic resonance spectroscopic imaging (MRSI). Disagreement among experts in the field of uro-radiology about the conduct, interpretation, and reporting of mpMRI prohibited the reproduction of results and the formation of uniformly comparable literature on diagnostic accuracy and, hence, the formation of standardized guidelines [15]. Consensus projects were therefore initiated to reach consensus on recommendations for standardization of conduct, interpretation and reporting of prostate mpMRI for prostate cancer detection and localization [16–18]. These studies and their recommendations...
aimed to address the lack of guidelines and consensus by increasing the uniformity and diagnostic accuracy of mpMRI in prostate cancer. Imaging criteria in focal therapy for prostate cancer differ from the regular criteria in prostate cancer because the histological diagnosis has usually already been established, and imaging is therefore used to identify cancers amenable for focal therapy. The main diagnostic objective of mpMRI is the identification of the precise location of the tumor within the prostate and any other cancerous lesions other than the targeted tumor and, in particular, other high grade lesions. As the majority of the patients who undergo MRI have had a previous biopsy, biopsy artifacts are also an important issue. The other applications of mpMRI in focal therapy are the monitoring of the treatment itself, and follow-up to document treatment efficacy. The present paper reports the recommendations of a panel of experts who participated in a formal consensus process that was conducted according to the Delphi method. The consensus project aimed to define when prostate mpMRI should be applied and how it should be conducted and reported when used in focal therapy for prostate cancer.

**MATERIALS AND METHODS**

**Delphi Method**

The essence of the Delphi consensus method is to derive quantitative estimates through the qualitative assessment of evidence. Studies of widely different design and quality can be assessed. When published information is scarce, experts can make inferences using other data from similar contexts. Experts’ estimates are aggregated and fed back anonymously to all participants, who then review their initial responses in view of group-wide choices. This practice confers anonymity and allows opinions to be expressed free from peer group pressure. The Delphi consensus method was considered to be the most appropriate for our objectives. The method is most suited to topic areas when there is limited quality evidence to enable a ‘gold standard’ recommendation to be made. The Delphi method used for the present study included a series of three online surveys, in which panelists were presented with the results of the previous survey and in which the participants could add, modify, or delete questions for the next round. A face-to-face discussion panel followed this series of questionnaires. The Delphi method was applied in accordance with the reported literature [19–21].

**Panel Selection**

On the basis of a systematic literature review on [Prostate Cancer] AND [Focal Therapy] AND [Multiparametric MRI] (and synonyms), experts in the field were selected. All experts published in the field of focal therapy for prostate cancer and/or mpMRI were selected by their peers. Fifty experts were approached, one declined and one retracted after the
first round, resulting in 48 panelists (urologists, radiologists and engineers) from Europe, North America, Asia and Australia (Tables 1,2). Commercial bias was excluded through the use of institutional funds.

**Table 1: Delphi consensus panel**

<table>
<thead>
<tr>
<th>Selected Participants</th>
<th>Profession</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashim Ahmed</td>
<td>Urologist</td>
<td>University College Hospital London, London, UK</td>
</tr>
<tr>
<td>Jelle Barentsz</td>
<td>Radiologist</td>
<td>Radboud University Hospital, Nijmegen, the Netherlands</td>
</tr>
<tr>
<td>Maurizio Brausi</td>
<td>Urologist</td>
<td>Estense S.Agostino Hospital, Modena, Italy</td>
</tr>
<tr>
<td>Peter Carroll</td>
<td>Urologist</td>
<td>University of California, San Francisco, USA</td>
</tr>
<tr>
<td>Jean-Yves Chapelon</td>
<td>Engineer</td>
<td>National Institute of Health and Medical Research, Paris, France</td>
</tr>
<tr>
<td>Peter Choyke</td>
<td>Radiologist</td>
<td>National Cancer Institute, Bethesda, USA</td>
</tr>
<tr>
<td>François Cornud</td>
<td>Radiologist</td>
<td>Cochin Hospital, Paris, France</td>
</tr>
<tr>
<td>Sébastien Crouzet</td>
<td>Urologist</td>
<td>Edouard Herriot Hospital, Lyon, France</td>
</tr>
<tr>
<td>Theo de Reijke</td>
<td>Urologist</td>
<td>AMC University Hospital, Amsterdam, the Netherlands</td>
</tr>
<tr>
<td>Bob Djavan</td>
<td>Urologist</td>
<td>New York University, New York, USA/ University of Vienna, Vienna, Austria</td>
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<tr>
<td>Scott Eggener</td>
<td>Urologist</td>
<td>University of Chicago, Chicago, USA</td>
</tr>
<tr>
<td>Mark Emberton</td>
<td>Urologist</td>
<td>University College Hospital London, London, UK</td>
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<td>Marc Engelbrecht</td>
<td>Radiologist</td>
<td>AMC University Hospital, Amsterdam, the Netherlands</td>
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<td>Masoom Haider</td>
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<td>Sunnybrook Hospital, Toronto, Canada</td>
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<tr>
<td>Mukesh Harisinghani</td>
<td>Radiologist</td>
<td>Harvard Medical School, Boston, USA</td>
</tr>
<tr>
<td>Stijn Heijmink</td>
<td>Radiologist</td>
<td>Dutch Cancer Institute, Amsterdam, the Netherlands</td>
</tr>
<tr>
<td>Hedvig Hricak</td>
<td>Radiologist</td>
<td>Memorial Sloan Kettering Cancer Center, New York, USA</td>
</tr>
<tr>
<td>Didier Jacqmin</td>
<td>Urologist</td>
<td>University Hospital of Strasbourg, Strasbourg, France</td>
</tr>
<tr>
<td>J Stephen Jones</td>
<td>Urologist</td>
<td>Cleveland Clinic, Cleveland, USA</td>
</tr>
<tr>
<td>Aaron Katz</td>
<td>Urologist</td>
<td>Wythop Urology Hospital, New York, USA</td>
</tr>
<tr>
<td>Kirkham</td>
<td>Radiologist</td>
<td>University College Hospital London, London, UK</td>
</tr>
<tr>
<td>Laurence Klotz</td>
<td>Urologist</td>
<td>Sunnybrook Hospital, Toronto, Canada</td>
</tr>
<tr>
<td>John Kurhanewicz</td>
<td>Radiologist</td>
<td>University of California, San Francisco, USA</td>
</tr>
<tr>
<td>Nathan Lawrentschuk</td>
<td>Urologist</td>
<td>University of Melbourne, Melbourne, Australia</td>
</tr>
<tr>
<td>Constantino Leonardo</td>
<td>Urologist</td>
<td>University of Rome, Rome, Italy</td>
</tr>
<tr>
<td>Uri Lindner</td>
<td>Urologist</td>
<td>Princess Margaret Hospital, Toronto, Canada</td>
</tr>
<tr>
<td>Vibeke Legager</td>
<td>Radiologist</td>
<td>Copenhagen University, Hospital Herlev, Herlev, Denmark</td>
</tr>
<tr>
<td>Michael Marberger</td>
<td>Urologist</td>
<td>Medical University of Vienna, Vienna, Austria</td>
</tr>
<tr>
<td>Alessandro Napoli</td>
<td>Radiologist</td>
<td>Sapienza University of Rome, Rome, Italy</td>
</tr>
<tr>
<td>David Penson</td>
<td>Urologist</td>
<td>Vanderbilt-Ingram Cancer Center, Nashville, USA</td>
</tr>
</tbody>
</table>
### Table 1: Delphi consensus panel (continued)

<table>
<thead>
<tr>
<th>Selected Participants</th>
<th>Profession</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 Peter Pinto</td>
<td>Urologist</td>
<td>National Cancer Institute, Bethesda, USA</td>
</tr>
<tr>
<td>36 Thomas Polascik</td>
<td>Urologist</td>
<td>Duke University Medical Center, Durham, USA</td>
</tr>
<tr>
<td>37 Ardeshir Rastinehad</td>
<td>Urologist/ Radiologist</td>
<td>Smith Institute for Urology, New York, USA</td>
</tr>
<tr>
<td>38 Jean de la Rosette</td>
<td>Urologist</td>
<td>AMC University Hospital, Amsterdam, the Netherlands</td>
</tr>
<tr>
<td>39 Olivier Rouvière</td>
<td>Radiologist</td>
<td>Edouard Herriot Hospital, Lyon, France</td>
</tr>
<tr>
<td>40 Georg Salomon</td>
<td>Urologist</td>
<td>University of Hamburg Martini Clinic, Hamburg, Germany</td>
</tr>
<tr>
<td>41 Peter Scardino</td>
<td>Urologist</td>
<td>Memorial Sloan Kettering Cancer Center, New York, USA</td>
</tr>
<tr>
<td>42 Michiel Sedelaar</td>
<td>Urologist</td>
<td>Radboud University Hospital, Nijmegen, the Netherlands</td>
</tr>
<tr>
<td>43 Samir Taneja</td>
<td>Urologist</td>
<td>NYU Langone Medical Center, New York, USA</td>
</tr>
<tr>
<td>44 Joachim Thüroff</td>
<td>Urologist</td>
<td>University Medical Center, Johannes Gutenberg University, Mainz, Germany</td>
</tr>
<tr>
<td>45 Osamu Ukimura</td>
<td>Urologist</td>
<td>Keck Medical Center of USC, Los Angeles, USA</td>
</tr>
<tr>
<td>46 Sadna Verma</td>
<td>Radiologist</td>
<td>University of Cincinnati, Cincinnati, USA</td>
</tr>
<tr>
<td>47 Arnauld Villers</td>
<td>Urologist</td>
<td>Lille University Hospital, Lille, France</td>
</tr>
<tr>
<td>48 Jochen Walz</td>
<td>Urologist</td>
<td>Institut Paoli-Calmettes, Marseille, France</td>
</tr>
</tbody>
</table>

### Table 2: Panel Characteristics

**Panel Characteristics:**

#### Specialties:

<table>
<thead>
<tr>
<th>Profession</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urologist</td>
<td>62,50%</td>
</tr>
<tr>
<td>Radiologist</td>
<td>33,30%</td>
</tr>
<tr>
<td>Engineer</td>
<td>2,10%</td>
</tr>
<tr>
<td>Urology-Radiology</td>
<td>2,10%</td>
</tr>
</tbody>
</table>

#### Experience with the following focal therapies:

<table>
<thead>
<tr>
<th>Focal Therapy</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIFU</td>
<td>59,60%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>46,80%</td>
</tr>
<tr>
<td>Laser Therapy</td>
<td>31,90%</td>
</tr>
<tr>
<td>Irreversible Electroporation</td>
<td>12,80%</td>
</tr>
<tr>
<td>Photodynamic Therapy</td>
<td>29,80%</td>
</tr>
<tr>
<td>Radiofrequency Ablation</td>
<td>12,80%</td>
</tr>
<tr>
<td>Other</td>
<td>12,80%</td>
</tr>
</tbody>
</table>

#### Patients treated with focal therapy on a yearly basis:

<table>
<thead>
<tr>
<th>Range</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varying from - to 0 - 300</td>
<td></td>
</tr>
<tr>
<td>Mean estimated number of patients</td>
<td>38,15</td>
</tr>
<tr>
<td>Total estimated number of patients treated on a yearly basis by the panel</td>
<td>1793</td>
</tr>
</tbody>
</table>
**Construction of the Questionnaire**

An online questionnaire, operated and designed using an online questionnaire program (http://www.SurveyMonkey.com), containing 41 items was constructed between 28 January and 15 April 2013. This online questionnaire was presented to the panelists in three rounds between 15 April and 29 April 2013, each time with a 1-week interval used for analysis and construction of the subsequent round. Items discussed can be found in Tables 3–5. B.G.M. and W.v.d.B. designed the first round of questionnaires, under the supervision of M.M. and J.d.l.R., using the literature review as described in item 2.2. Questions were based on controversial items in the studies, or items on which evidence was lacking. All subsequent rounds were designed by the feedback from the participating panelists. Each round was analyzed and graphically presented to the participants in the next round. Participants were asked to clarify per question whether they considered themselves sufficiently knowledgeable to answer.

### Table 3: Results regarding treatment planning

<table>
<thead>
<tr>
<th>Question</th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Which diagnostic tool do you recommend for focal therapy treatment planning?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>26,10%</td>
<td>35,71%</td>
<td>23,30%</td>
</tr>
<tr>
<td>mpMRI</td>
<td>80,40%</td>
<td>92,86%</td>
<td>73,30%</td>
</tr>
<tr>
<td>TRUS</td>
<td>23,90%</td>
<td>14%</td>
<td>30,00%</td>
</tr>
<tr>
<td>Histoscanning</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>3D plotting</td>
<td>6,50%</td>
<td>0%</td>
<td>10,00%</td>
</tr>
<tr>
<td>Transperineal Saturation biopsies</td>
<td>19,60%</td>
<td>7,14%</td>
<td>26,70%</td>
</tr>
<tr>
<td>Other</td>
<td>15,20%</td>
<td>0%</td>
<td>16,70%</td>
</tr>
<tr>
<td><strong>With mpMRI, which field strength do you recommend for use in focal prostate cancer treatment planning?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Tesla</td>
<td>80,90%</td>
<td>81,25%</td>
<td>79,31%</td>
</tr>
<tr>
<td>1.5 Tesla</td>
<td>4,30%</td>
<td>0%</td>
<td>6,90%</td>
</tr>
<tr>
<td>There is no significant difference between the 2</td>
<td>12,80%</td>
<td>18,75%</td>
<td>10,34%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>2,10%</td>
<td>0%</td>
<td>3,45%</td>
</tr>
<tr>
<td><strong>Do you recommend the use of an endorectal coil in prostate mpMRI at 1.5 Tesla?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63,80%</td>
<td>87,50%</td>
<td>48,28%</td>
</tr>
<tr>
<td>No</td>
<td>29,80%</td>
<td>12,50%</td>
<td>41,38%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>6,40%</td>
<td>0%</td>
<td>10,34%</td>
</tr>
<tr>
<td><strong>Do you recommend the use of an endorectal coil in prostate mpMRI at 3.0 Tesla?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34%</td>
<td>31,25%</td>
<td>34,48%</td>
</tr>
<tr>
<td>No</td>
<td>59,60%</td>
<td>62,50%</td>
<td>58,62%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>6,40%</td>
<td>6,25%</td>
<td>6,90%</td>
</tr>
<tr>
<td><strong>Is an endorectal coil indicated if the mpMRI is used for diagnosis of prostate cancer?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42,60%</td>
<td>62,50%</td>
<td>31,03%</td>
</tr>
<tr>
<td>No</td>
<td>55,30%</td>
<td>37,50%</td>
<td>65,52%</td>
</tr>
<tr>
<td>Table 3: Results regarding treatment planning (continued)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Radiologists</td>
<td>Urologists</td>
<td></td>
</tr>
<tr>
<td>I don't know</td>
<td>2,10%</td>
<td>0%</td>
<td>3,45%</td>
</tr>
</tbody>
</table>

Is an endorectal coil indicated if the mpMRI is used for localization of small lesions for focal therapy treatment planning?

| Yes | 51,10% | 75% | 37,93% |
| No | 46,80% | 25% | 58,62% |
| I don't know | 2,10% | 0% | 3,45% |

Are there any EXCLUSION criteria for use of an endorectal coil in prostate mpMRI? (multiple options possible)

| No, ERC is always indicated | 12,80% | 12,50% | 13,79% |
| In patient who are eligible for Radiation Therapy (since it deforms the prostate) | 27,70% | 37,50% | 20,69% |
| When localizing small tumors for focal treatment targeting (since it deforms the prostate) | 17,00% | 18,75% | 17,24% |
| In patients on active surveillance | 23,40% | 31,25% | 20,69% |
| When patients do not tolerate the endorectal coil (hemorrhoids, colorectal surgery) | 23,40% | 68,75% | 51,72% |
| Other | 12,80% | 18,75% | 10,34% |
| I don't know | 8,50% | 0% | 13,79% |

Is the use of a pelvic phased array coil indicated for prostate mpMRI, in focal therapy treatment planning (localizing small lesions)

| Yes, always (with or without endorectal coil) | 72,30% | 75,00% | 68,79% |
| Yes, and always without an endorectal coil | 14,90% | 12,50% | 17,24% |
| Yes and always in combination with an endorectal coil | 6,40% | 12,50% | 3,45% |
| No, never | 0% | 0% | 0% |
| I don’t know | 6,40% | 0% | 10,34% |

Which mpMRI sequences do you recommend for prostate MRI?

| T1W | 85,10% | 93,75% | 79,31% |
| T2W | 93,60% | 100% | 89,66% |
| DCE | 85,10% | 81,25% | 86,21% |
| DWI | 90% | 100% | 83,33% |
| MRSI | 10,60% | 18,75% | 6,90% |
| I don’t know | 6,40% | 0% | 3,40% |

In Gleason 6 tumors, what are the lower limits of detection on mpMRI, with respect to tumor size?

| 0,2 cc | 8,50% | 6,25% | 6,90% |
| 0,5 cc | 68,10% | 75% | 69,00% |
| 0,7 cc | 4,30% | 0% | 6,90% |
| 1,0 cc | 8,50% | 6,25% | 10,30% |
| 1,2 cc | 2,10% | 6,25% | 0% |
| I don’t know | 8,50% | 6,25% | 6,90% |

In Gleason 7 tumors, what are the lower limits of detection on mpMRI, with respect to tumor size?

| 0,2 cc | 23,40% | 50,00% | 6,90% |
### Table 3: Results regarding treatment planning (continued)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 cc</td>
<td>66.00%</td>
<td>50.00%</td>
<td>75.90%</td>
</tr>
<tr>
<td>0.7 cc</td>
<td>2.10%</td>
<td>0%</td>
<td>3.40%</td>
</tr>
<tr>
<td>1.0 cc</td>
<td>4.30%</td>
<td>0%</td>
<td>6.90%</td>
</tr>
<tr>
<td>1.2 cc</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>4.30%</td>
<td>0%</td>
<td>6.90%</td>
</tr>
</tbody>
</table>

**Does tumor location within the prostate influence the accuracy of prostate MRI?**

<table>
<thead>
<tr>
<th>Does tumor location within the prostate influence the accuracy of prostate MRI?</th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>95.20%</td>
<td>92.86%</td>
<td>96.20%</td>
</tr>
<tr>
<td>No</td>
<td>4.80%</td>
<td>7.14%</td>
<td>3.80%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Is the detection rate of prostate tumors on mpMRI dependent on prostate volume? (multiple answers possible)**

<table>
<thead>
<tr>
<th>Is the detection rate of prostate tumors on mpMRI dependent on prostate volume?</th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>63.80%</td>
<td>62.50%</td>
<td>69.00%</td>
</tr>
<tr>
<td>Yes, with increasing prostate size detection rate decreases</td>
<td>29.80%</td>
<td>37.50%</td>
<td>24.10%</td>
</tr>
<tr>
<td>Yes, with large amount of BPH, false positive rate increases</td>
<td>12.80%</td>
<td>18.75%</td>
<td>10.30%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>2.10%</td>
<td>6.25%</td>
<td>6.90%</td>
</tr>
</tbody>
</table>

**Is there a minimal time span between prostate biopsies and MRI to facilitate reliable images?**

<table>
<thead>
<tr>
<th>Is there a minimal time span between prostate biopsies and MRI to facilitate reliable images?</th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, 3 weeks</td>
<td>4.30%</td>
<td>12.50%</td>
<td>0%</td>
</tr>
<tr>
<td>Yes, 6 weeks</td>
<td>66.00%</td>
<td>56.25%</td>
<td>69.00%</td>
</tr>
<tr>
<td>Yes, 8 weeks</td>
<td>19.10%</td>
<td>12.50%</td>
<td>24.10%</td>
</tr>
<tr>
<td>Yes 12 weeks</td>
<td>10.60%</td>
<td>18.75%</td>
<td>6.90%</td>
</tr>
</tbody>
</table>

**Do you consider mpMRI of the prostate an adequate alternative to systematic template saturation biopsies in patient selection for focal therapy?**

<table>
<thead>
<tr>
<th>Do you consider mpMRI of the prostate an adequate alternative to systematic template saturation biopsies in patient selection for focal therapy?</th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>54.30%</td>
<td>57.14%</td>
<td>40.00%</td>
</tr>
<tr>
<td>No</td>
<td>39.10%</td>
<td>21.43%</td>
<td>53.30%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>6.50%</td>
<td>21.43%</td>
<td>6.70%</td>
</tr>
</tbody>
</table>

**Do you consider prostate mpMRI at least as adequate as template saturation biopsies in patient selection for focal therapy?**

<table>
<thead>
<tr>
<th>Do you consider prostate mpMRI at least as adequate as template saturation biopsies in patient selection for focal therapy?</th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, always</td>
<td>23.40%</td>
<td>18.75%</td>
<td>27.60%</td>
</tr>
<tr>
<td>Yes, but only in patients with Gleason 7 tumors, or higher</td>
<td>8.50%</td>
<td>18.75%</td>
<td>3.40%</td>
</tr>
<tr>
<td>Yes, but only if targeted biopsy confirms the diagnosis</td>
<td>46.80%</td>
<td>50.00%</td>
<td>41.40%</td>
</tr>
<tr>
<td>No, never</td>
<td>21.30%</td>
<td>12.50%</td>
<td>27.60%</td>
</tr>
</tbody>
</table>

**If tumor location within the prostate influences the accuracy of mpMRI, then the**

<table>
<thead>
<tr>
<th>If tumor location within the prostate influences the accuracy of mpMRI, then the</th>
<th>Lowest</th>
<th>Intermediate</th>
<th>Highest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection rate for tumors in the Transition Zone is</td>
<td>46.20%</td>
<td>35.90%</td>
<td>2.60%</td>
</tr>
<tr>
<td>Detection rate for tumors in the Peripheral Gland is</td>
<td>0.00%</td>
<td>4.80%</td>
<td>88.10%</td>
</tr>
<tr>
<td>Detection rate for tumors in the Anterior Gland is</td>
<td>20.50%</td>
<td>59.00%</td>
<td>10.30%</td>
</tr>
</tbody>
</table>
Table 4: Results regarding treatment guidance

<table>
<thead>
<tr>
<th>Question</th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which imaging modality is used in your hospital for focal therapy guidance, during treatment?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRUS</td>
<td>59.50%</td>
<td>35.71%</td>
<td>66.70%</td>
</tr>
<tr>
<td>MRI</td>
<td>35.70%</td>
<td>50.00%</td>
<td>36.70%</td>
</tr>
<tr>
<td>MRI-TRUS Fusion</td>
<td>26.20%</td>
<td>14.29%</td>
<td>23.30%</td>
</tr>
<tr>
<td>We don’t do focal therapy</td>
<td>7.10%</td>
<td>14.29%</td>
<td>0.00%</td>
</tr>
<tr>
<td>Is there a MRI modality suitable for real time focal treatment monitoring?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>89.40%</td>
<td>93.75%</td>
<td>86.20%</td>
</tr>
<tr>
<td>No</td>
<td>6.40%</td>
<td>0%</td>
<td>10.30%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>4.30%</td>
<td>6.25%</td>
<td>3.40%</td>
</tr>
<tr>
<td>If there is a possibility for real time MR focal treatment monitoring, which one do you prefer?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI-Thermometry</td>
<td>85.10%</td>
<td>87.50%</td>
<td>82.80%</td>
</tr>
<tr>
<td>TRUS-MRI fusion</td>
<td>12.80%</td>
<td>12.50%</td>
<td>10.30%</td>
</tr>
<tr>
<td>No preference</td>
<td>4.30%</td>
<td>6.25%</td>
<td>3.40%</td>
</tr>
<tr>
<td>I do not believe that there is a MRI modality suitable for real time monitoring</td>
<td>4.30%</td>
<td>0%</td>
<td>6.90%</td>
</tr>
<tr>
<td>Do you recommend the use of TRUS-MRI fusion for use in focal therapy for prostate carcinoma? (multiple answers possible)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, TRUS-MRI fusion for treatment planning</td>
<td>42.60%</td>
<td>43.75%</td>
<td>41.40%</td>
</tr>
<tr>
<td>Yes, TRUS-MRI fusion for real-time treatment guidance</td>
<td>40.40%</td>
<td>31.25%</td>
<td>44.80%</td>
</tr>
<tr>
<td>Yes, TRUS-MRI fusion for targeted biopsy</td>
<td>85.10%</td>
<td>87.50%</td>
<td>82.80%</td>
</tr>
<tr>
<td>No</td>
<td>10.60%</td>
<td>6.25%</td>
<td>13.80%</td>
</tr>
<tr>
<td>Do you think it is important that standardized protocols are used for reporting of prostate MRIs?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>No</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>What is your opinion about deformation artifacts in TRUS-MRI fusion?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Existent, but always acceptable</td>
<td>8.50%</td>
<td>12.50%</td>
<td>3.40%</td>
</tr>
<tr>
<td>Only acceptable when data are elastically fused (software correction for tissue deformation)</td>
<td>72.30%</td>
<td>75.00%</td>
<td>72.40%</td>
</tr>
<tr>
<td>Only acceptable for lesions in the peripheral zone</td>
<td>2.10%</td>
<td>0%</td>
<td>3.40%</td>
</tr>
<tr>
<td>Not acceptable</td>
<td>2.10%</td>
<td>0%</td>
<td>3.40%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>17.00%</td>
<td>18.75%</td>
<td>17.20%</td>
</tr>
<tr>
<td>Do you use a standardized acquisition/reporting protocol for prostate mpMRIs in your hospital?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, ESUR / PI-RADS Guidelines</td>
<td>34.00%</td>
<td>42.68%</td>
<td>30.77%</td>
</tr>
<tr>
<td>Yes, Likert Score</td>
<td>4.80%</td>
<td>7.14%</td>
<td>3.80%</td>
</tr>
<tr>
<td>Yes, self-developed protocol</td>
<td>40.50%</td>
<td>50.00%</td>
<td>34.60%</td>
</tr>
<tr>
<td>No</td>
<td>7.10%</td>
<td>0%</td>
<td>11.50%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>11.90%</td>
<td>0%</td>
<td>19.20%</td>
</tr>
<tr>
<td>Do you consider it important that all prostate mpMRIs are made and reported by a specialized radiologist?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>No</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
### Table 4: Results regarding treatment guidance (continued)

<table>
<thead>
<tr>
<th>How many prostate mpMRIs should a radiologist report on a yearly basis to remain experienced?</th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>&gt;50</td>
<td>55,30%</td>
<td>56,25%</td>
<td>55,20%</td>
</tr>
<tr>
<td>&gt;75</td>
<td>12,80%</td>
<td>25,00%</td>
<td>6,90%</td>
</tr>
<tr>
<td>&gt;100</td>
<td>27,70%</td>
<td>18,75%</td>
<td>31,00%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>4,30%</td>
<td>0,00%</td>
<td>6,90%</td>
</tr>
</tbody>
</table>

### Table 5: Results regarding treatment follow-up

<table>
<thead>
<tr>
<th>Which modality (modalities) do you recommend for focal therapy follow-up? (multiple options are possible)</th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>mpMRI</td>
<td>95,70%</td>
<td>100%</td>
<td>93,10%</td>
</tr>
<tr>
<td>TRUS</td>
<td>8,50%</td>
<td>0%</td>
<td>13,80%</td>
</tr>
<tr>
<td>Prostate Biopsies</td>
<td>48,90%</td>
<td>31,25%</td>
<td>58,60%</td>
</tr>
<tr>
<td>MRI-TRUS fusion</td>
<td>31,90%</td>
<td>18,75%</td>
<td>34,50%</td>
</tr>
<tr>
<td>Contrast Enhanced Ultrasound (CEUS)</td>
<td>8,50%</td>
<td>0%</td>
<td>10,30%</td>
</tr>
<tr>
<td>PSA</td>
<td>51,10%</td>
<td>43,75%</td>
<td>55,20%</td>
</tr>
<tr>
<td>DRE</td>
<td>19,10%</td>
<td>12,75%</td>
<td>24,10%</td>
</tr>
</tbody>
</table>

**Is mpMRI a reliable tool for follow-up after focal therapy for prostate carcinoma?**

- Yes: 76,60% | 81,25% | 72,40%
- No: 17,00% | 12,50% | 20,70%
- I don’t know: 6,40% | 6,25% | 6,90%

**After focal therapy of prostate cancer, when should the first follow-up mpMRI be done?**

- 0-7 days after treatment (baseline): 17,00% | 12,50% | 17,20%
- 3 months after treatment: 14,90% | 12,50% | 17,20%
- 6 months after treatment: 63,80% | 68,75% | 62,10%
- 1 year after treatment: 2,10% | 0% | 3,40%
- I don’t know: 2,10% | 6,25% | 0%

**At which intervals should mpMRI be performed in the follow-up of focal therapy of prostate cancer?**

- mpMRI every 6 months: 51,10% | 68,75% | 37,90%
- mpMRI every year: 42,60% | 25% | 55,20%
- no routine mpMRI, only based on clinical indications: 6,40% | 6,25% | 6,90%

**Immediately after treatment, how does definitive tissue destruction present on a prostate mpMRI? (multiple answers possible)**

- Low signal on T2W images (scar): 10,60% | 18,75% | 6,90%
- Loss of enhancement on DCE-MRI: 89,40% | 100% | 82,80%
- ADC above a certain cut-off value (dependent on b-value of the scanner): 4,30% | 6,25% | 0%
- Increased Choline/citrate ratio on MRSI: 0% | 0% | 0%
- Other: 4,30% | 6,25% | 3,40%
Face-to-face meeting format

The face-to-face meeting took place on 29 May 2013, in Noordwijk, the Netherlands. Participants from the online questionnaire were invited to join. Fifteen experts in urology and uro-radiology attended the meeting and are listed among the authors of this manuscript. All panel members also participated in the online series of questionnaires. During the meeting, the results from the online questionnaire were discussed in plenary sessions to draw conclusions from the acquired data. No new input was taken into consideration. A chairman (B.G.M.), with no financial disclosures to declare, was chosen to preside the meeting.

Interpretation of the results

Consensus on a topic was defined as >80% unanimity on the question regarding this topic in the online questionnaire. The participants in the discussion are listed in Table 1.

---

Table 5: Results regarding treatment follow-up (continued)

<table>
<thead>
<tr>
<th>Question</th>
<th>Overall</th>
<th>Radiologists</th>
<th>Urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months after treatment, how does definitive tissue destruction present on a prostate mpMRI? (multiple answers possible)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low signal on T2W images (scar)</td>
<td>19.60%</td>
<td>18.75%</td>
<td>21.40%</td>
</tr>
<tr>
<td>Loss of enhancement on DCE-MRI</td>
<td>67.40%</td>
<td>68.75%</td>
<td>64.30%</td>
</tr>
<tr>
<td>ADC above a certain cut-off value (dependent on b-value of the scanner)</td>
<td>2.20%</td>
<td>0%</td>
<td>3.60%</td>
</tr>
<tr>
<td>Increased Choline/citrate ratio on MRSI</td>
<td>0%</td>
<td>0%</td>
<td>0.00%</td>
</tr>
<tr>
<td>Other</td>
<td>6.50%</td>
<td>6.25%</td>
<td>7.10%</td>
</tr>
<tr>
<td>I don't know</td>
<td>4.30%</td>
<td>6.25%</td>
<td>3.60%</td>
</tr>
<tr>
<td>Which is the best biopsy strategy for follow-up biopsies after focal therapy?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systematic biopsies</td>
<td>15.20%</td>
<td>6.25%</td>
<td>21.40%</td>
</tr>
<tr>
<td>Targeted biopsies</td>
<td>82.60%</td>
<td>93.75%</td>
<td>75.00%</td>
</tr>
<tr>
<td>Template saturation biopsies</td>
<td>2.20%</td>
<td>0%</td>
<td>3.60%</td>
</tr>
<tr>
<td>How should biopsies in the follow-up of focal therapy be guided?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRUS guided based on mpMRI images</td>
<td>17.00%</td>
<td>18.75%</td>
<td>17.20%</td>
</tr>
<tr>
<td>MRI guided</td>
<td>4.30%</td>
<td>6.25%</td>
<td>3.40%</td>
</tr>
<tr>
<td>Either TRUS or MRI guided</td>
<td>8.50%</td>
<td>12.50%</td>
<td>6.90%</td>
</tr>
<tr>
<td>TRUS-MRI fusion guided</td>
<td>70.20%</td>
<td>62.50%</td>
<td>72.40%</td>
</tr>
</tbody>
</table>
RESULTS

The results of the questionnaires are shown in Tables 3–5. During the meeting, final conclusions were formulated based on the acquired data from the questionnaires. Questionnaire results were not altered and no new data were taken into account during the meeting. A summary of the questionnaire results and items discussed in the meeting is given below. Consensus was reached on 41% of the items.

Patient selection and treatment planning
The panel agreed that mpMRI is currently the ideal imaging tool for focal therapy of prostate cancer. For patient selection, histologically proven prostate cancer is still considered crucial. In other words, the prostate cancer should be biopsy-proven before receiving any focal therapy. These biopsies should preferably be done after mpMRI. The panel reached a consensus that 3 Tesla is the recommended field strength for use in focal therapy. An endorectal coil is increasingly recommended at low field strengths (63.8% for 1.5 Tesla compared with high field strengths (34% for 3 Tesla). There was a strong consensus that a pelvic phased array coil was indispensable in prostate mpMRI. The panelists recommended the following sequences: T1-weighted, T2-weighted and DCE imaging, and DWI. The conclusion of MRSI in mpMRI was not supported by a large group (only 10.6%). The majority of the panel (68.1%) defined 0.5 mL as the lower limit of a reliable detection rate in Gleason 6 tumors. In Gleason 7 tumors, 23.4% of the panel defined 0.2 mL as the lower limit for detection, but still most participants (65.96%) defined 0.5 mL as the lower limit. On this topic there was a remarkable difference between urologists and radiologists (6.9 vs 50%, respectively, defined the lower limit as 0.2 mL). The panel strongly agreed that tumor location within the prostate influenced the diagnostic accuracy of mpMRI. The detection rate is most accurate for tumors in the peripheral zone. The detection rate of tumors on mpMRI seemed to be independent of prostate volume. There was a strong consensus that ideally, the MRI should be performed before prostate biopsies. If this was not possible, a post-biopsy interval period of 6–8 weeks should be considered to facilitate reliable images on mpMRI. No consensus could be reached on the question of whether mpMRI was an adequate alternative for transperineal template saturation biopsies for the exclusion of significant lesions outside the target lesion. A study comparing the diagnostic performance of mpMRI to template saturation biopsies should first be executed, with sufficient power to adequately demonstrate the ability of mpMRI to replace the role of template saturation mapping biopsies.

Treatment Guidance
Most panel members use TRUS as guidance for focal therapy. Of all panel members, 35.7% use MRI-guided focal therapy. Consensus was reached that, where real-time MRI
monitoring of focal therapy is used, magnetic resonance thermometry is the best suitable technology (restricted to thermal ablation technologies). The panel stated that the standardization of conduct and reporting protocols was of paramount importance (100% consensus), but 40.5% of the panel members worked with a self-developed protocol, and 7.1% did not even use a standardized protocol for MRI reporting. This illustrates that standardization between centers is essential. Finally, the need for a specialized radiologist to report on prostate mpMRI was debated. All of the panel members agreed that a specialized radiologist was necessary for image acquisition, reading and reporting of prostate mpMRI. To become expert and to remain experienced, the radiologist should read at least 50 prostate mpMRI scans with pathological feedback per year.

**Treatment follow-up**

It was found that mpMRI was the preferred method of focal therapy follow-up (95.7% consensus). Furthermore, the majority of the panel supported the use of PSA, prostate biopsies and MRI-TRUS-guided biopsies in the follow-up of focal therapies for prostate cancer. Of the panel members 76.6% indicated that mpMRI could accurately identify tumor recurrence in the prostate. Regarding the follow-up schedule of mpMRI after focal therapy, no consensus was reached; nonetheless, 63.83% indicated that the first mpMRI should be performed 6 months after focal treatment. The performance of a baseline mpMRI immediately or 3 months after treatment was discussed, but this did not receive much support (17.0%). Equal support for both mpMRI every 6 months (51.1%) and every year (42.6%) was found for imaging intervals after initial imaging after focal therapy. In the face-to-face meeting, the panel agreed that mpMRI every year after treatment was sufficient. There was a strong agreement (89.4%) that definitive tissue destruction immediately after focal therapy results in a loss of enhancement on a DCE MRI. Furthermore, 67.4% of the panelists defined definitive tissue destruction as a loss of enhancement on DCE MRI, 6 months after treatment. Moreover, 6 months after treatment, scarring might be observed on T2-weighted images (19.6%). There was a strong consensus that mpMRI findings could be an indication for biopsies in the follow-up of focal therapy. Targeted biopsy was the best strategy to perform biopsies and 70% of panelists indicated that TRUS-MRI fusion was the best way to guide the targeted biopsies in the follow-up of focal therapy.

**Recommendations of the Panel**

- mpMRI was the recommended diagnostic tool for treatment planning in focal therapy for prostate cancer. The panel stated that ideally, this mpMRI should be made on a 3-Tesla device. When a 1.5-Tesla device was the only device available, an endorectal coil was deemed to be essential. A minimum of the following sequences should be included: T1-weighted, T2-weighted and DCE imaging and DWI. The location of
the tumor within the prostate could influence the accuracy of the mpMRI, which the clinician should keep in mind.

- Magnetic resonance thermometry was regarded as a possible technology for real-time monitoring of thermal ablation. The panel preferred this technology. TRUS-MRI fusion was recommended by the panel for targeting biopsies. Standardized protocols for the acquisition and reporting of mpMRIs were considered of paramount importance and should be used. Furthermore, a specialized and experienced radiologist should report all mpMRI results.

- mpMRI was concluded to be the best suitable technology for follow-up after focal therapy and should therefore be used in the follow-up schedule of focal therapy. Immediately after treatment, a successful ablation was defined as a loss of enhancement in the DCE sequence. Targeted biopsies should be carried out if follow-up MRI indicated suspected recurrent/residual tumor.

- No consensus could be reached on the topic of template saturation biopsies for patient selection. Forty-six percent of the panel stated that mpMRI was not yet an adequate alternative for template saturation biopsies.

**DISCUSSION**

The use of the Delphi method produced consensus in 41% of the key items (14 out of 34). On some questions there was a considerable difference in opinions between radiologists and urologists (Tables 2–4). Although the panel reached a consensus for 3 Tesla as the ideal field strength in prostate mpMRI, some panelists mentioned that 1.5 Tesla might have the same diagnostic accuracy. This is supported by a recent publication by Bratan et al. [22]. The panel agreed that, with increasing Gleason score, smaller tumors could be detected on mpMRI. Substantiation of this topic was provided in studies by Bratan et al. [22] and Turkbey et al. [23]. As a tool for the real-time guidance of thermal focal therapy, magnetic resonance thermometry is a suitable technology. Although not widely implemented, magnetic resonance thermometry results seem promising for future application [24]. Furthermore, the panel agreed that TRUS-MRI fusion is a promising technology for targeted biopsies of the prostate. Deformation errors can arise, but these are minimal and therefore acceptable. TRUS-MRI-fusion-guided biopsies have shown similar results to those of MRI-guided biopsies [25]. In the follow-up section, the panel agreed that PSA should be part of the follow-up after focal therapy, but the literature has not yet determined, nor has a consensus been reached on, how to interpret PSA kinetics after focal therapy. Face-to-face consensus methods or expert group discussions are prone to biases. Dominant personalities are known to be capable of influencing the opinion of the group to a significant extent [26]. The Delphi method is very well suited to reduce
this type of bias. All panelists were given the opportunity to actively contribute and share their opinions anonymously. During the face-to-face meeting, conclusions were only formulated from the anonymously acquired data; no new input was given. The Delphi method also implies that the group is presented with questions, which are formulated based upon the latest literature, resulting in a high level of validity. Based on their knowledge, the panelists were given the opportunity to add discussion points, questions and amendments to the series of questions, to achieve consensus about what is important in the view of the group as a whole. Because panelists from Europe, North America, Asia and Australia were participating in the panel, all topics were viewed within this broad perspective. The panel reached a consensus at a unanimity level of $\approx 80\%$. This may be considered a limitation, since experts were selected on the basis of their expertise in prostate cancer. For focal therapy of prostate cancer, state-of-the-art imaging is of utmost importance. The physician should be able to target the tumor and has to ensure that, outside the targeted area, no other significant tumor is missed. Through incorporation of the recommendations reported in the present paper, the conduct, interpretation and reporting of mpMRI in treatment planning, treatment guidance and treatment follow-up of focal therapy will be more consistent and standardized. With pooled analyses, the clinical diagnostic accuracy of mpMRI will increase. The panel concluded that mpMRI for treatment planning should ideally be carried out before biopsy; however, limitations such as costs, lack of availability of MRI, lack of standardization and reproducibility, mean that this approach cannot always be applied in daily practice. Previous studies have also recommended such an approach [27]. Imaging criteria for mpMRI are stricter in tissue-preserving strategies such as active surveillance and focal therapy. For focal therapy, it is not only important to be able to see the target lesion, but also to exclude significant tumors elsewhere in the prostate. If the accuracy of mpMRI is great enough to exclude significant tumor sufficiently, template saturation mapping biopsies in patients undergoing focal therapy can potentially be avoided in the future. Additionally, the detection and localization components of mpMRI could assist in targeting biopsies. A large meta-analysis recently published by Nelson et al. [28] showed that MRI-guided biopsies potentially have a detection rate equivalent to transperineal template saturation biopsies; however, these findings are yet to be validated in prospective studies. TRUS-mpMRI fusion can fulfill a significant role in this respect and was also recommended by the panel. It is important to note that most of the literature is generated in high-volume expert centers. Consequently, panel members were also from these centers. It might therefore be challenging to extrapolate these results to settings outside of these expert centers. The relatively low amount of consensus (41% of the topics) indicates that there are many uncertainties in the field. The results of the consensus project are, therefore, not immediately to be used as guidelines for clinical practice. Nevertheless, given the numerous studies that have been performed in this area of research, we anticipate that
these consensus statements will be meaningful and that other research groups will implement the recommendations in new study protocols on focal therapy and imaging. Dickinson et al. [16] already pointed out in 2011 that transperineal saturation biopsies are the optimum reference standard for studies on the diagnostic accuracy of mpMRI, because they overcome random and systematic sampling errors by sampling the gland every 5 mm, provide three-dimensional coordinates for correlation to imaging and can be applied to all men. It is anticipated that future studies, comparing mpMRI with transperineal saturation mapping biopsies, will confirm the important role of mpMRI in a variety of purposes in focal therapy for prostate cancer. In conclusion, focal therapy is an emerging technique for prostate cancer treatment. For this treatment optimum imaging is paramount and mpMRI has the potential to meet these strict imaging requirements. Through a structured consensus method, our panel agreed on several key issues regarding mpMRI for use in focal therapy. Before these recommendations can be implemented in clinical protocols, they first have to be validated in prospective clinical trials.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

A.R. received non-financial research support from Philips during the study period. J.d.l.R. reports grants and personal fees from Angiodynamics during the conduct of the study. U.U. is an advisory board member at SonaCare Medical LLC. A.V. was a consultant at Janssen Pharmaceutica, Astellas and Ferring during the study period. Furthermore, he received research grants from Ipsen and Takeda.
REFERENCES

Chapter 5

Follow-up modalities in focal therapy for prostate cancer: results from a Delphi consensus project

BG Muller, W van den Bos, M Brausi, JJ Fütterer, S Ghai, PA Pinto, IV Popeneciu, TM de Reijke, C Robertson, JJMCH de la Rosette, S Scionti, B Turkbey, H Wijkstra, O Ukimura, TJ Polascik

ABSTRACT

Introduction
Focal therapy can offer the middle ground for treatment between active surveillance and radical therapy in patients with low- and intermediate-risk prostate cancer. Factors that prohibit focal therapy from being standard of care are numerous. Several consensus projects have been conducted to position the utilization of imaging and trial design in focal therapy. However, the literature is still scarce on patient follow-up after focal therapy. For these reasons, an international multidisciplinary consensus project was established in order to reach consensus about a uniform follow-up protocol after focal therapy.

Objective
To standardize patient follow-up after focal therapy.

Materials and methods
A literature study was performed, and a questionnaire was constructed. The questionnaire was sent out to 76 participants (70 % urologists, 28 % radiologists and 2 % biomedical engineers) in three consecutive rounds according to the Delphi method. In each round, the panelists were presented with the results of the previous round. Participants each had the opportunity to adapt, delete or add questions. The topics discussed pertaining to follow-up after focal therapy were as follows: (1) general,(2) biopsies, (3) PSA, (4) digital rectal examination (DRE), (5) imaging, (6) quality of life (QoL) and (7) registration and pooling of data. The project was concluded with a face-to-face meeting in which final conclusions were formulated.

Results
The follow-up after focal therapy should be a minimum of 5 years. The following modalities should be included in assessing post-treatment outcomes: multiparametric MRI (mpMRI), biopsies, assessment of erectile function, QoL, urinary symptoms and incontinence. A systematic 12-core TRUS biopsy combined with 4–6 targeted biopsy cores of the treated area and any suspicious lesion(s) should be performed after 1 year, and thereafter only when there is suspicion on imaging. The ideal way to perform targeted biopsies is to use TRUS–MRI fusion technology. PSA should be performed for research purposes, in the first year, every 3 months, and after the first year, every 6 months. mpMRI is the optimal imaging modality for follow-up after focal therapy. On a 1.5T scanner, an endorectal coil is strongly advised by the panel, whereas on a 3T machine, it is optional, however, it will improve image quality. The following sequences should be included: T2WI, DWI including high b values of >1,000 and ADC maps of DWI, DCE and T1WI. Imaging should be performed at 6 months and at 1 year following treatment; after the first year
post-treatment, it should be performed every year until 5 years following treatment. All data should ideally be pooled in a common global database.

**Conclusion**

Focal therapy is a relatively new form of treatment for prostate cancer. In order to include focal therapy as a standard of care treatment, consistent follow-up is necessary. By implementing the results of this consensus study, focal therapy users will be able to provide important and standardized outcome data.

**Keywords**

Focal therapy, Follow-up, Consensus, Prostate cancer
INTRODUCTION

Focal therapy offers a middle ground approach as a disease management strategy in a select group of men with low- and intermediate-risk prostate cancer (PCa), positioned between active surveillance on one side and radical treatment on the other side [1]. The factors that prohibit focal therapy from becoming standard of care are multiple: a lack of clear definitions of what constitutes focal therapy [2], a wide variety of ablative technologies available and lack of substantial standardized studies, and consequently reliable outcome data. Cryotherapy and high-intensity focused ultrasound (HIFU) are mentioned by the guidelines of the European Association of Urology as management options in patients with clinically localized PCa [3–5]. The following other technologies also belong to the armamentarium of focal therapies for prostate cancer: laser ablation therapy [6], radiofrequency ablation [7], irreversible electroporation [8], photodynamic therapy [9] and focal brachytherapy [10], among others. In order to advance the field and render focal therapy a standard of care, uniformly comparable outcome data have to be produced. Various consensus meetings among experts have led to protocols for both focal therapy trial design and the utilization of imaging in focal therapy [2, 11–14]. However, the literature on follow-up strategies following focal therapy is still scarce. For these reasons, an international multidisciplinary consensus project was established to reach consensus about a uniform follow-up protocol following focal therapy. The project was executed according to an adapted Delphi method. The Delphi method has been used for many years to reach consensus on topics with minimum bias. By implementation of the results of this consensus project, scientific results can be generated which may allow focal therapy to evolve as an accepted means of prostate cancer care for the appropriate patient.

MATERIALS AND METHODS

The project was conducted according to the Delphi method, derived from the 1950s that proved to be effective in reaching consensus on economic and political issues. More recently, this method has been used regularly in the medical field [15–17]. A systematic literature search was performed on “prostate cancer” (and synonyms) and “focal therapy” (and synonyms) and “follow-up”(and synonyms) (see search strategy below):

Follow-up modalities in focal therapy for prostate cancer: results from a Delphi consensus project


This search yielded 378 articles, of which only a limited number was useful. The panel members were selected as authors of clinical trials from the literature study, or recommended as expert in the field by their peers. The systematic literature search was also used to select controversial topics in the field and to design a questionnaire to resolve these issues. BM and WvdB designed the questionnaire under the supervision of OU and TP.

The web-based questionnaire was constructed by the use of www.surveymonkey.com (accessed between July 1, 2014, and August 15, 2014). The panel members were sent the questionnaire in three consecutive rounds. For each new round, the panelists were presented with the results of the previous rounds. They were encouraged to adapt the questions or indicate when they disagreed with a question/topic. In this way, a structured academic discussion was held in order to reach consensus about a variety of subtopics. The whole questionnaire can be found in Appendix 1 of supplementary material. The pertinent topics related to follow-up after focal therapy discussed were as follows: (1) general, (2) biopsies, (3) PSA, (4) DRE, (5) imaging, (6) QoL and (7) registration and pooling of data. Consensus was defined as 75 % agreement on a topic.

The project was concluded with a final meeting on August 21, 2014, for which every participant received an invitation. In this final meeting, the results of the questionnaires were presented to the panelists, and conclusions were formulated.1 The meeting was recorded for documentation purposes.

RESULTS

Seventy-six experts were invited to participate in the project, 51 agreed, 3 declined and 22 did not reply. Questionnaires were sent out in 3 rounds, to each person who did not
Results from the consensus project

General
The follow-up period following focal therapy should be defined as the period needed to determine the efficacy of the treatment. It is reasonable to expect that after a period of 5 years, the chance that residual disease will become apparent is low and therefore the follow-up period following focal therapy should be defined as a minimal period of 5 years. Oncological treatment success has to be defined as negative biopsies of the treated area. Functional treatment success should be defined as the absence of treatment-related functional change, after a period of healing. Therefore, the various functional parameters have to be assessed, each at their own intervals. Erections and ejaculations have to be assessed for 24 months, QoL for 24 months and urinary symptoms for 12 months. The most important parameters for functional treatment success are QoL and erections, continence and prostate symptoms. The following modalities should be evaluated in the follow-up following focal therapy: histology (prostate biopsies), serum PSA, prostate imaging, and assessment of erectile function, QoL, urinary symptoms and incontinence. Although there was no consensus (71 %) about the inclusion of an objective assessment of incontinence using a 24-h pad weight test, it is advised by the panel. There was no consensus about assessment of bowel symptoms by a bowel symptom score. The panel agreed that assessment of ejaculation should be part of the follow-up, by the addition of Q9 and Q10 (orgasmic function) of the IIEF-15 to the shortened IIEF-5 score.

Biopsies
At 1 year after treatment, a biopsy of the treated area should be performed, combined with a systematic 12× TRUS biopsy of the whole prostate (also untreated areas). After the first biopsy at 1-year post-treatment, re-biopsy of the treated area should be done only when there is suspicion on imaging. The best way to take a biopsy of the treated area is to take 4–6 targeted cores from the margins of the ablation zone including at least one sample from within the area of ablated/fibrosed tissue. These 4–6 cores from the treated area are essential to account for: (1) fibrosis-related gland deformity and (2)
the possible slight degree of misregistration even when using a fusion device. After the initial biopsy at 1 year, the panel advised only to perform rebiopsies if suspect imaging findings are demonstrated. The untreated area of the prostate should be biopsied at 1 year after treatment for surveillance purposes. When the treated area is sampled, a 12-core systematic TRUS biopsy of the remainder of the prostate should be performed. Afterward, biopsy of the untreated area should be performed only when there is suspicion on imaging. When performing a targeted biopsy of a suspicious lesion, it is advised to also perform a systematic 12-core random TRUS biopsy. The optimal modality for follow-up biopsy of suspicious lesions is TRUS–MRI fusion guided biopsy technology. With the rising awareness of molecular characterization being predictive with outcome of prostate biopsies, the biological effects of focal therapy could be documented by molecular analysis of post-therapy biopsies. The pathologist who reads the biopsy material should have an understanding of focal therapy and interpreting tissue after a particular ablative intervention.

**PSA**
PSA should be included in the follow-up following focal therapy. The first PSA should be taken 3-month post-treatment. After the first measurement, PSA should be taken every 3 months during the first year; after the first year, PSA should be taken every 6 months. Although PSA doubling time seems the most important parameter that could indicate treatment failure, no consensus could be reached about a definition of biochemical recurrence. Since there is no consensus on the role of PSA, the data should be collected for research purposes.

**DRE**
DRE should still be part of the follow-up after focal therapy. Although it does not have much added value for prostate evaluation, it may have some value in the evaluation of bowel-related symptoms, especially in ablative procedures performed by a transrectal approach.

**Imaging**
mpMRI is the optimal imaging modality for follow-up following focal therapy. mpMRI can be performed at 1.5T, but only with the use of an endorectal coil. When a 3T mpMRI is available, the endorectal coil is not a strict prerequisite, but it will enhance image quality by improving the signal-to-noise ratio. For optimal imaging, the following sequences should be included: T2WI, DWI including high b values of >1,000 and ADC maps of DWI, DCE and T1WI. T1WI is required for assessment of hemorrhage and lymph nodes. MRSI is not beneficial and should not be performed in the follow-up following focal therapy. The first imaging should be performed at 6-month post-treatment as a baseline to evalu-
ate recurrence or residual disease. Before that time, imaging may still be distorted by treatment-related hemorrhage, artifact or the expected inflammatory process after an intervention. Follow-up imaging should be performed every year after the initial imaging at 6 and 12 months, or in the case of a biochemical suspicion of progression (although no consensus could be reached about a clear definition of this). DCE is considered the most important sequence to detect a recurrence or residual disease. Suspicion for treatment failure is defined as one or a combination of the following features: early focal enhancement on DCE, focal area with diffusion restriction on ADC maps and focal area with high signal intensity on DWI with a b value >1,000 after 6 months. Treatment success on imaging is defined as the absence of treatment failure in the targeted area, after 1 year. Curve type analysis for DCE may also help following focal treatment, since fibrosis would show gradual increased enhancement rather than rapid wash-in. When mpMRI findings are positive, they always have to be confirmed by targeted biopsy of the suspicious area.

Quality of life and functional outcome
QoL, urinary symptoms, incontinence, erections and ejaculations should be assessed in the follow-up following focal therapy. Each aspect should be evaluated every 3 months in the first year and every 6 months in the second year. IPSS/ AUA score combined with uroflowmetry/residual urine measurement should be used to evaluate urinary symptoms, incontinence should ideally be evaluated by a 24-h pad weight test, or a question about the number of pads used per day. IIEF-5 scores should be used to evaluate erections. Ejaculations should be evaluated by the addition of two questions to the IIEF-5 questionnaire that are pertinent to orgasmic function [Q9 (When you had sexual stimulation or intercourse, how often did you ejaculate?) and Q10 (When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax)] taken from the IIEF-15 questionnaire. However, no consensus was reached on the best overall QoL assessment tool, as several are available. Each individual question should be entered as a data point. For example, using the IIEF-5, the second question [With sexual stimulation, how often have your erections been sufficient for penetration (entering your partner)?] is the most important.

Data pooling and complication registration
100 % of the panel members agreed that adverse events and complications should be registered. Moreover, there was a strong consensus (84 %) that it is important to pool data on focal therapy in a common database, on the condition that all focal therapy data will be gathered in a standardized way. Based on the results of this meeting, we constructed a flow diagram for surveillance after focal therapy that aims to standardize follow-up (Fig. 1).
Figure 1: Follow-up scheme as proposed by the panel: Patient selection for focal therapy is not a topic of this consensus project. When biopsies in the follow-up proof recurrent or residual disease, the treating physician should evaluate the treatment options again. *Assessment of incontinence by either 24-h pad weight test (most objective test and advised as optimum), or number of pads used per day.
DISCUSSION

The majority of panel members agreed that all findings on follow-up should be registered in a common database. It is important to establish such a database and clinicians who perform focal therapy should use it. An online platform would be most suitable. The Cryo On-Line Database is an example of such a registry that reports on outcome after cryotherapy for prostate cancer. When setting up a global registry for focal therapy, one needs to take into account the following possible pitfalls: funding of the project (ideally, the database should be independent of any public company), authorships for publication, monitoring/auditing of the data, quality control, selection bias (every patient needs to be registered) and different methods/energy sources of focal therapy that could be compared. Although constructing an international database could be costly and challenging, it is deemed essential. We demonstrated earlier that most centers with expertise currently only treat 10–30 patients a year. In order to form strong, uniform data, such a database is of paramount importance. In the proposed follow-up diagram (Fig. 1), biopsies will be performed 1 year after treatment. After this initial pathological evaluation of the treatment, biopsies will only be performed when there is suspicion on imaging. Pitfalls of (repeated) prostate biopsies include: (1) infections appear in 2–5 % of patients [4], (2) after focal ablation, the treated area will contract and eventually will be partially reabsorbed and replaced by fibrotic tissue, surrounded by normal prostate tissue, therefore, the treated area might be challenging to target, (3) due to fibrosis, the prostate tissue can be firm and biopsies can be painful and (4) interpretation of PSA can be challenging because of biopsy induced damage/inflammation/infection of the prostate [18, 19]. A study which evaluated biopsies of the treated area as early as 6 months following HIFU showed no difficulty in diagnostics using microscopy or immunohistochemistry [20]. There is consensus that PSA does not currently offer any reliable, reproducible data in the follow-up following focal therapy. PSA is not cancer specific, it is volume dependent on glandular tissue and when the prostate is damaged or inflamed, serum PSA will increase. Since a significant amount of functional prostate tissue is still in situ after focal therapy, PSA could indicate a need for imaging, but as an indicator for biopsy, PSA is unreliable. PSA is expected to temporally rise right after treatment as a consequence of treatment-related damage to and inflammation of the prostate. Since the PSA half-life is approximately 2–3 days, values should normalize approximately within 1 month following treatment [21]. For this reason, it is advised to measure the first PSA 3 months after treatment and in the first year every 3 months. Although PSA doubling time might appear to be an important parameter that could indicate treatment failure, no consensus could be reached about a definition of biochemical recurrence. For the evaluation of functional outcome, objective and standardized evaluation is very important. Although no consensus could be reached about the best QoL assessment tool, any
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validated instrument would be suitable. Various questionnaires have been published, each with their own purpose [22, 23]. The FACT-P questionnaire has been validated for assessment of QoL after radiotherapy for prostate cancer [24]. The panel agreed that this tool is suitable and advised its use in the follow-up following focal therapy. Preservation of ejaculation is an important reason why men may opt for focal therapy. The panel agreed it should be evaluated by the addition of Q9 and Q10 (orgasmic function) of the IIEF-15, to the shortened IIEF-5 version commonly used when evaluating focal therapy outcomes [25].

Limitations
By implementing an adapted Delphi method, objective results were reached without dominant personalities being able to influence the results. The questions were formulated from the literature and by the selected expert panel. A bias could be that the panelists were all experts in focal therapy and might therefore be enthusiastic about its abilities. A second limitation is that not every panelist completed all the questionnaires, and not every panelist was able to attend the face-to-face meeting.

CONCLUSION

Focal therapy is a relatively new form of localized prostate cancer treatment. In order to enable focal therapy becoming a standard of care, standardization of patient follow-up is essential. A specific roadmap is given for the middle- and long-term follow-up of currently available focal therapy approaches. By implementing the results of this Delphi-based consensus study, standardized literature may be generated that accelerates a broader implementation of focal therapy.

CONFLICT OF INTEREST

The following authors declare no conflict of interest: B.G. Muller, W. van den Bos, M. Brausi, J.J. Fütterer, S. Ghai, P.A. Pinto, I.V. Popeneciu, T.M. de Reijke, B. Turkbey and H. Wijkstra.

C. Robertson is consultant/PI at EDAP TMS Inc., S. Scionti is consultant at SonaCare Medical, T.J. Polascik receives a research grant from Endocare, O. Ukimura is advisory board member at SonaCare Medical, J.J.M.C.H. and de la Rosette is consultant to AngioDynamics.
ETHICAL STANDARD

The manuscript does not contain clinical studies or patient data.
REFERENCES

Chapter 6

Prostate cancer: interobserver agreement and accuracy with the revised prostate imaging reporting and data system at multiparametric mr imaging

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ABSTRACT

Purpose:
To evaluate accuracy and interobserver variability with the use of the Prostate Imaging Reporting and Data System (PI-RADS) version 2.0 for detection of prostate cancer at multiparametric magnetic resonance (MR) imaging in a biopsy-naïve patient population.

Materials and methods:
This retrospective HIPAA-compliant study was approved by the local ethics committee, and written informed consent was obtained from all patients for use of their imaging and histopathologic data in future research studies. In 101 biopsy-naïve patients with elevated prostate-specific antigen levels who underwent multiparametric MR imaging of the prostate and subsequent transrectal ultrasonography (US)–MR imaging fusion–guided biopsy, suspicious lesions detected at multiparametric MR imaging were scored by five readers who were blinded to pathologic results by using the newly revised PI-RADS and the scoring system developed in-house. Interobserver agreement was evaluated by using κ statistics, and the correlation of pathologic results with each of the two scoring systems was evaluated by using the Kendall τ correlation coefficient.

Results:
Specimens of 162 lesions in 94 patients were sampled by means of transrectal US-MR imaging fusion biopsy. Results for 87 (54%) lesions were positive for prostate cancer. Kendall τ values with the PI-RADS and the in-house-developed scoring system, respectively, at T2-weighted MR imaging in the peripheral zone were 0.51 and 0.17 and in the transitional zone, 0.45 and -0.11; at diffusion-weighted MR imaging, 0.42 and 0.28; at dynamic contrast material-enhanced MR imaging, 0.23 and 0.24; and overall suspicion scores were 0.42 and 0.49. Median κ scores among all possible pairs of readers for PI-RADS and the in-house-developed scoring system, respectively, for T2-weighted MR images in the peripheral zone were 0.47 and 0.15; transitional zone, 0.37 and 0.07; diffusion-weighted MR imaging, 0.41 and 0.57; dynamic contrast-enhanced MR imaging, 0.48 and 0.41; and overall suspicion scores, 0.46 and 0.55.

Conclusion:
Use of the revised PI-RADS provides moderately reproducible MR imaging scores for detection of clinically relevant disease.
INTRODUCTION

To bring uniformity and standardization to reporting of multiparametric magnetic resonance (MR) imaging of the prostate, the European Society of Urogenital Radiology published a unified Prostate Imaging Reporting and Data System (PI-RADS) in 2012 [1]. Several research groups have validated the original PI-RADS, mostly by using a PI-RADS sum score (on a scale of 3–15) for summation of the single scores for the three different pulse sequences (T2-weighted imaging, diffusion-weighted imaging [DWI], and dynamic contrast material–enhanced [DCE] MR imaging). However, several developments prompted reconsideration of the original PI-RADS. For instance, there was consensus that a single score system (on a scale of 1–5), similar to that used with the Breast Imaging Reporting and Data System, would improve communication among clinicians of different disciplines [2]. Moreover, new data suggested that different weightings should be used depending on the location of the lesion in the peripheral zone (PZ) or transitional zone (TZ). For instance, Baur et al [3] reported that assigning a PI-RADS score on the basis of DWI for PZ lesions and a PI-RADS score on the basis of T2-weighted imaging for TZ lesions was sufficient for stratification of patients for further diagnostic workup. Furthermore, the contribution of DCE MR imaging curve-type analysis was reported to be of questionable value [3,4].

For these reasons, the European Society of Urogenital Radiology prostate MR imaging expert group and the PIRADS steering committee of the American College of Radiology have developed PI-RADS, version 2.0 [5]. This version includes the following changes: (a) The concept of a dominant sequence depending on the location of the lesion was introduced. For example, in the PZ, the dominant sequence is DWI; in the TZ, the dominant sequence is T2-weighted imaging. (b) The consensus group reported that DCE imaging results should be scored as positive when there is early focal enhancement and as negative when there is no early focal enhancement or diffuse enhancement, instead of using curve-type analysis as described in the original version of PI-RADS. (c) For positive DCE imaging results, the overall PI-RADS suspicion score should be increased by one point, but only if it makes a clinically relevant difference (ie, when the PI-RADS score will increase from 3 to 4). (d) Finally, an overall score on a scale of 1–5 is assigned according to the revised rules in the second version of PI-RADS. The suggested modifications to PI-RADS also were proposed by Bomers et al (6) and Baur et al [3]. Critical to the success of PI-RADS is the ability to show consistency in scores among readers, which, after all, is the primary goal of the guideline. The goal of this study was to evaluate both the accuracy and interobserver variability with the use of the PI-RADS, version 2.0, for detection of prostate cancer at multiparametric MR imaging in a biopsy-naïve patient population.
MATERIALS AND METHODS

Study design and patient population
This Health Insurance Portability and Accountability Act-compliant retrospective study was approved by the local ethics committee, and written informed consent was obtained from all patients for use of their imaging and histopathologic data in future research studies. Between December 2011 and May 2014, 101 consecutive biopsy-naive patients (mean age, 62 years ± 9.50), with increased prostate-specific antigen levels (> 4 ng/mL [> 4 μg/L]) or abnormal results from a digital rectal examination underwent multiparametric MR imaging. All patients subsequently underwent transrectal ultrasonography (US)–MR imaging fusion–guided biopsy of lesions suspected to be cancer that were identified at multiparametric MR imaging performed within 6 weeks after MR imaging. Inclusion criteria were having never undergone a biopsy and having undergone a multiparametric MR imaging examination and a subsequent transrectal US–MR imaging fusion–guided biopsy. The exclusion criterion was having undergone a nondiagnostic multiparametric MR imaging examination. The flowchart of the patient selection process is presented in Figure 1.

MR imaging protocol
All MR imaging studies were performed by using a combination of an endorectal coil (BPX-30; Medrad, Pittsburgh, Pa) tuned to 127.8 MHz and a 16-channel cardiac coil (SENSE; Philips Medical Systems, Best, the Netherlands) with a 3-T MR imager (Achieva; Philips Medical Systems), without prior bowel preparation. The endorectal coil was inserted with a semianesthetic gel (xylocaine, Lidocaine; Astra Zeneca, Wilmington, Del) while the patient was in the left lateral decubitus position. The balloon surrounding the coil was distended with 3 mol/L of perfluorocarbon (Fluorinert; 3M, St Paul, Minn) to a volume of approximately 45 mL. MR imaging parameters included T1-weighted imaging, triplanar (coronal, sagittal, and axial) T2-weighted imaging, diffusion weighted imaging.

Figure 1: Flowchart for selection of the patient population in the current study. mpMRI = multiparametric MR imaging, TRUS = transrectal US.
with a b value of 2000 sec/mm², apparent diffusion coefficient (ADC) mapping derived from a separate DWI MR imaging examination performed by applying five evenly spaced b values ranging from 0 to 750 sec/mm², and axial three-dimensional fast field-echo DCE imaging sequences. Axial DCE images were obtained before, during, and after a single dose of gadopentetate dimeglumine (Magnevist; Berlex, Wayne, NJ) administered at a dose of 0.1 mmol/kg of body weight through a peripheral vein at a rate 3 mL/sec by using a mechanical injector (Spectris MR injection System; Medrad, Pittsburgh, Pa). Each three-dimensional sequence was performed in 5.6 seconds. MR imaging pulse sequence parameters were defined in previous studies [7,8] (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T2 Weighted</th>
<th>DWI*</th>
<th>High b-value DWI†</th>
<th>DCE MR Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field of view (mm)</td>
<td>140 x 140</td>
<td>140 x 140</td>
<td>140 x 140</td>
<td>262 x 262</td>
</tr>
<tr>
<td>Acquisition matrix</td>
<td>304 x 234</td>
<td>112 x 109</td>
<td>76 x 78</td>
<td>188 x 96</td>
</tr>
<tr>
<td>Repetition time (msec)</td>
<td>4434/120</td>
<td>4986/54</td>
<td>6987 x 52</td>
<td>3.7/2.3</td>
</tr>
<tr>
<td>Echo time (msec)</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>8.5</td>
</tr>
<tr>
<td>Flip angle (degrees)</td>
<td>3.00</td>
<td>3.00</td>
<td>3.00</td>
<td>3.00</td>
</tr>
<tr>
<td>Section thickness (mm), no gaps</td>
<td>512 x 512</td>
<td>256 x 256</td>
<td>256 x 256</td>
<td>256 x 256</td>
</tr>
<tr>
<td>Image reconstruction matrix (pixels)</td>
<td>0.27 x 0.27 x 3.00</td>
<td>0.55 x 0.55 x 2.73</td>
<td>0.55 x 0.55 x 2.73</td>
<td>1.02 x 1.02 x 3.00</td>
</tr>
<tr>
<td>Reconstruction voxel imaging resolution (mm/pixel)</td>
<td>2.48</td>
<td>4.54</td>
<td>3.50</td>
<td>5.16</td>
</tr>
<tr>
<td>Time for acquisition (min:sec)</td>
<td>140 x 140</td>
<td>140 x 140</td>
<td>140 x 140</td>
<td>262 x 262</td>
</tr>
</tbody>
</table>

*For ADC map calculation. Five evenly-spaced b values (0–750 sec/mm²) were used. †b = 2000 sec/mm²

MR Imaging-Transrectal US Fusion Guided Biopsy

In a single session, patients with any lesions suspicious for prostate cancer at multiparametric MR imaging underwent a standard 12-core transrectal US–guided extended sextant biopsy independent of the multiparametric MR imaging results and fusion biopsy of multiparametric MR imaging target lesions performed by the same operator by using an office-based fusion platform (UroNav; InVivo Corp, Gainesville, Fla) [9]. Pre-biopsy T2-weighted MR images were segmented, registered, and fused with the real-time transrectal US images. Lesions suspicious for prostate cancer were displayed as targets and were sampled in the axial and the sagittal plane, resulting in two cores per target [10]. Needle trajectories were mapped with real-time electromagnetic tracking in the biopsy platform (Northern Digital, Ontario, Canada). Results of previous validation studies have indicated an accuracy of within 3 mm for this platform [11].
Histopathologic evaluation
All biopsy cores were immediately fixed in formalin and stained with hematoxylin and eosin, and a routine histopathologic evaluation was performed. Higher grade prostate cancer was defined as lesions showing a primary Gleason score pattern of 4 or higher. Pathologic specimens were reviewed by a single genitourinary pathologist (M.J.M., with more than 25 years of experience).

MR Image interpretation
In each patient, images of the lesions most suspicious for cancer (up to two) at multiparametric MR imaging were presented to five independent readers with varying levels of experience in multiparametric MR imaging of the prostate (reader 1, P.L.C., with 12 years of experience [approximately 4000 examinations]; reader 2, B.T., with 7 years of experience [approximately 3500 examinations]; reader 3, J.M., with 1 year of experience [approximately 500 examinations]; reader 4, S.S., with 1 year of experience [approximately 500 examinations]; reader 5, B.G.M., with 6 months of experience [approximately 250 examinations]). These five readers, all of whom were blinded to initial multiparametric MR imaging reports and resultant clinical-pathologic outcomes, scored the examinations. In each session, the lesions and four different pulse sequences (axial T2-weighted, ADC mapping with DWI, DWI performed with a b value of 2000 sec/mm², and DCE imaging) were shown to the readers, who independently scored the lesions according to the revised PI-RADS and the scoring system developed in-house and displayed on a commercially available workstation (DynaCAD software; Invivo, Orlando, Fla).

PI-RADS Scoring
According to the European Society of Urogenital Radiology guidelines, T2-weighted and DWI examinations were scored on a scale of 1–5 by using the PI-RADS system. For DCE images, a binary scale was used (0 = no focal early enhancement; 1 = presence of early focal enhancement). In addition, the overall score consisted of the score for the dominant sequence (T2-weighted for TZ lesions and DWI for PZ lesions) plus one point added to the overall score for DCE imaging results that were positive for cancer, but only if the addition of the one point converted the PI-RADS score from 3 to 4. (Table 2).

Scoring System Developed In-House
The lesions also were scored by using a previously validated in-house–developed multiparametric MR imaging scoring system [12–14]. The number of positive pulse sequences at multiparametric MR imaging for each lesion allowed determination of the final suspicion score as low, moderate, or high suspicion for prostate cancer (Table 3). In this scoring system, images from the three sequences (T2 weighted, ADC mapping with DWI, and DCE imaging) were rated as positive (score 0) or negative (score 1), and the final score was
Interobserver agreement and accuracy with the revised PI-RADS

Table 2: The Revised PI-RADS.

<table>
<thead>
<tr>
<th>Imaging Sequence and Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T2-weighted, PZ</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Uniform hyperintense signal intensity (normal)</td>
</tr>
<tr>
<td>2</td>
<td>Linear, wedge-shaped, or diffuse mild hypointensity, usually indistinct margin</td>
</tr>
<tr>
<td>3</td>
<td>Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity</td>
</tr>
<tr>
<td>4</td>
<td>Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and &lt;1.5 cm in greatest dimension</td>
</tr>
<tr>
<td>5</td>
<td>Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior</td>
</tr>
<tr>
<td><strong>T2-weighted, TZ</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Homogeneous intermediate signal intensity (normal)</td>
</tr>
<tr>
<td>2</td>
<td>Circumscribed hypointense or heterogeneous encapsulated nodule(s) (BPH)</td>
</tr>
<tr>
<td>3</td>
<td>Heterogeneous signal intensity with obscured margins</td>
</tr>
<tr>
<td>4</td>
<td>Non-circumscribed, homogeneous, moderately hypointense, and &lt;1.5 cm in greatest dimension</td>
</tr>
<tr>
<td>5</td>
<td>Same as 4, but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior</td>
</tr>
<tr>
<td><strong>DWI</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>No abnormality (i.e. normal) on ADC and high b-value DWI (≥b1400)</td>
</tr>
<tr>
<td>2</td>
<td>Indistinct hypointense on ADC</td>
</tr>
<tr>
<td>3</td>
<td>Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value DWI (≥ b1400)</td>
</tr>
<tr>
<td>4</td>
<td>Focal markedly hypointense on ADC and markedly hyperintense on high b-value DWI (≥ b1400); &lt;1.5cm on axial</td>
</tr>
<tr>
<td>5</td>
<td>Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior</td>
</tr>
<tr>
<td><strong>DCE</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>No early enhancement, or; diffuse enhancement not corresponding to a focal finding on T2 and/or DW or; focal enhancement corresponding to a lesion demonstrating features of BPH on T2WI.</td>
</tr>
<tr>
<td><strong>Positive</strong></td>
<td>Focal, and; earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues, and; corresponds to suspicious finding on T2W and/or DWI images</td>
</tr>
</tbody>
</table>

T2-weighted imaging and DWI were scored according to a five-point suspicion scale. DCE imaging results were scored as either negative or positive. The overall suspicion score consisted of the suspicion score for the dominant sequence (T2-weighted for TZ lesions and DWI for PZ lesions) and can be upgraded by one point with positive DCE imaging results when it increases the overall score substantially (ie, 3 to 4).

determined by using the matrix displayed in Table 3, from low and moderate likelihood to high likelihood in patients suspected of having of extracapsular extension. For analysis purposes, all lesions were subsequently grouped by location as either PZ or TZ lesions. Lesions with moderate or high suspicion for cancer were those that required biopsy, and lesions with low suspicion were those in which targeted biopsy was not required.
Statistical Analysis

Correlation among readers’ scores and pathologic results was estimated by using the Kendall $\tau$, with scores of the five readers averaged. The Kendall $\tau$ is a rank correlation coefficient that allows measurement of the similarity of the ordering of two random variables [15]. The values of the Kendall $\tau$ ranged from $-1$ to $1$, with $1$ corresponding to $100\%$ positive correlation, $-1$ corresponding to $100\%$ negative correlation, and $0$ corresponding to independence. To account for within-patient correlation of multiple lesions, a within-cluster resampling technique was used to obtain the estimate and standard error of the Kendall $\tau$ [16,17]. In each resampled data set consisting of one lesion randomly sampled with replacement from each patient, the Kendall $\tau$ and its standard error were calculated. The within-cluster resampling procedure was repeated 5000 times, each repeat generating a Kendall $\tau$ estimate and standard error. The final Kendall $\tau$ estimate was the average of these 5000 resampling-based estimates. The variance of the final Kendall $\tau$ estimate was the average of the resampling-based variances minus the variance of the resampling-based Kendall $\tau$ estimates. The Wald test was used to obtain the P value of the final Kendall $\tau$ estimate.

Generalized estimating equations with a logit link function and working independence correlation structure were used to estimate and compare the probability of cancer on the basis of reader scores for images from each imaging modality in different prostate zones. In each generalized estimating equation model, median reader score of the five readers and prostate zone were factors that allowed prediction, and pathologic scores
were the response variable that was dichotomized in two ways: cancer versus no cancer and low-risk cancer and benign lesions (Gleason score ≤ 3+4) versus clinically relevant cancer (Gleason score ≥ 4+3). The Wald test with robust variance estimates was used for inference with the assumption of a working independence model. Predicted probability of cancer at each score level was calculated from the estimated model.

With a median reader score greater than 3 considered as positive and less than or equal to 3 as negative at multiparametric MR imaging, sensitivity and specificity were calculated. Sensitivity was defined as the proportion of lesions positive for cancer, and specificity was defined as the proportion of lesions negative for cancer at multiparametric MR imaging. The κ statistic was used to estimate pairwise and overall per-lesion inter-reader agreement. Because reader scores of multiple lesions from the same patient were likely correlated, conventional standard errors of κ estimates, which require independent observations, are not valid. The bootstrap resampling procedure (number of bootstrap samples, 1000) was used to calculate the standard errors of the κ estimates, where the bootstrap sampling unit was the number of patients.

To assess performance with combined T2-weighted, DWI, and DCE imaging for prediction of cancer, the sum of the median reader scores of these sequences was used in the receiver operating characteristic (ROC) analysis for PZ and TZ prostate lesions separately. Statistical analysis was performed by using software (R version 3.1.0; R Foundation for Statistical Computing, Vienna, Austria [18]). Function “kappam.fleiss” in the interrater reliability package (irr package, R version 3.1.0; R Foundation) was used to calculate the multirater κ statistics, and function “geese” in the generalized estimating equation package (geepack, R version 3.1.0; R Foundation) was used to formulate generalized estimating equation models and obtain the generalized estimating equation estimates.

RESULTS

Lesion Characteristics

Seven patients were excluded from the analysis because of artifacts related to hip prosthesis. The final study population included 94 patients (Table 4). The total number of lesions sampled by means of transrectal US–MR imaging fusion–guided biopsy was 162. In 88 lesions (54%), biopsy results were positive for prostate cancer. Noncancerous lesions included 65 benign lesions and eight showing chronic inflammation (one prostatic intraepithelial neoplasia). The Gleason score distribution for cancerous lesions was as follows: 3+3 = 6 (n = 20), 3+4 = 7 (n = 34), 4+3 = 7 (n = 6), 4+4 = 8 (n = 17), 4+5 = 9 (n = 9), 5+4 = 9 (n = 1), and 5+5 = 10 (n = 1). Biopsy results revealed high-grade prostate cancer (Gleason score ≥ 4+3 = 7) in 33 (20%) lesions and lower grade prostate cancer (Gleason score ≤ 3+4 = 7) in 54 (33%) lesions.
Correlation of PI-RADS and In-house Scoring System with Pathologic Results

For each of the four multiparametric MR imaging sequences and the suspicion level, the correlation of pathologic results with PI-RADS and our in-house scoring system, respectively, was assessed by using the Kendall \( \tau \): T2-weighted imaging in the PZ (0.51, 0.17), T2-weighted imaging in the TZ (0.45, −0.11), DWI (0.42, 0.28), DCE MR imaging (0.23, 0.24), and suspicion (0.42, 0.49) (Table 5).

Table 5: Kendall \( \tau \) and P Values between Pathology Score and Mean In-House and PI-RADS Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>In-House System</th>
<th>PI-RADS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kendall ( \tau )</td>
<td>P Value</td>
</tr>
<tr>
<td>T2-weighted, PZ</td>
<td>0.17</td>
<td>0.0563</td>
</tr>
<tr>
<td>T2-weighted, TZ</td>
<td>-0.11</td>
<td>0.4560</td>
</tr>
<tr>
<td>DWI</td>
<td>0.28</td>
<td>0.0011</td>
</tr>
<tr>
<td>DCE MR imaging</td>
<td>0.24</td>
<td>0.0021</td>
</tr>
<tr>
<td>Overall score</td>
<td>0.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Extracapsular extension</td>
<td>0.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 4: Patient and Lesion Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>94</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62 (37 – 79)</td>
</tr>
<tr>
<td>No. of patients by cancer stage</td>
<td></td>
</tr>
<tr>
<td>cT1C</td>
<td>84</td>
</tr>
<tr>
<td>cT2A</td>
<td>8</td>
</tr>
<tr>
<td>cT2B</td>
<td>1</td>
</tr>
<tr>
<td>Prostate-specific antigen level (ng/mL)*</td>
<td>8.51 (0.74 – 51.13)</td>
</tr>
<tr>
<td>Prostate volume (mL)</td>
<td>47 (19-133)</td>
</tr>
<tr>
<td>Prostate-specific antigen density (ng/mL²) †</td>
<td>0.19 (0.02-1.68)</td>
</tr>
<tr>
<td>No. of lesions scored</td>
<td>162</td>
</tr>
<tr>
<td>Negative biopsy results</td>
<td>74</td>
</tr>
<tr>
<td>Positive biopsy results</td>
<td>88</td>
</tr>
<tr>
<td>No. of lesions in Gleason score range</td>
<td></td>
</tr>
<tr>
<td>≤ 3+4=7</td>
<td>54</td>
</tr>
<tr>
<td>≥ 4+3=7</td>
<td>34</td>
</tr>
</tbody>
</table>

Data in parentheses are the range. *To convert to Système International (SI) units (micrograms per liter), multiply by 1. †To convert to SI units (micrograms per liter squared), multiply by 1.
With the in-house scoring system, the correlation between reader score and pathologic scores was significant for DWI and DCE MR imaging (P < .05), but not significant for T2-weighted imaging. The correlation between the overall suspicion level and the pathologic score was significant (P < .0001). With the PI-RADS, the correlation between all scores and pathologic results was moderate and significant (P < .0001–.0024). These results are visually represented in Figure 2.

![Figure 2: Bar graph shows the Kendall τ for each scoring system. ADC = ADC mapping at DWI, T2W = T2-weighted imaging, * = significant value (P < .05).](image)

**PZ versus TZ Lesions**

Median reader score of each modality, pathologic results score, and location in the prostate are shown in Tables E1 and E2 (online). Because few lesions had low DWI reader scores and high pathologic scores, lower DWI reader scores were grouped in the order in which the corresponding predicted probability of cancer was estimable with the use of a generalized estimating equation model. None of the interaction between median reader scores and location of prostate cancer was significant in each generalized estimating equation model. When the PI-RADS was used to help detect cancer, the predicted probability of cancer was not significantly different between lesions in the PZ and those in the TZ. In comparison, when the PI-RADS was used to detect high-risk prostate cancer (Gleason score ≥ 4+3), the probability of detecting clinically significant prostate cancer in the PZ was significantly higher than that in the TZ with all three modalities, as is demonstrated in Table 6. The predicted probability of cancer determined as T2-weighted imaging PI-RADS scores of 2, 3, 4, and 5, respectively, was 0.17, 0.2, 0.67, and 0.95 in the PZ, and 0.13, 0.15, 0.6, and 0.93 in the TZ. When a threshold was applied to the median reader score at 3 (ie, median reader score ≤ 3 vs > 3), sensitivity and specificity, respectively, were 88% (60 of 68) and 71% (40 of 56) for the PZ and 85% (17 of 20) and 55% (10 of 18) for the TZ. ROC analysis showed that a total score for T2-weighted, DWI, and DCE MR imaging results achieved an area under the ROC curve of 0.86 and 0.87 for the PZ and the TZ, respectively.
Interobserver Agreement

For the in-house scoring system, more than 80% (119–124 of 162) of the lesions received positive readings throughout all readers and imaging modalities (Tables E2 and E3 [online]). The suspicion level was rated 2 in approximately two-thirds of the lesions (104–112 of 162), and extracapsular extension was negative in the majority of the lesions (118–128 of 162). For the PI-RADS scoring system, the distribution of scores depended on the pulse sequence. For example, T2-weighted imaging showed more lesions rated as grades 2 or 3 than did DWI. For each scoring system in each of the four multiparametric MR imaging sequences and for suspicion level, interreader agreement was assessed by using κ statistics. Pairwise κ values and standard errors are shown in Table E4 (online). Overall multireader κ values are listed in Table 7. These results are visually represented in Figure 3.

Table 6: Probability of Cancer by Reader Score and Zone *Data are for scores less than or equal to 4.

<table>
<thead>
<tr>
<th>Probability and Zone</th>
<th>PZ</th>
<th>TZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-weighted, PZ</td>
<td>0.17 0.2</td>
<td>0.13 0.15</td>
</tr>
<tr>
<td>T2-weighted, TZ</td>
<td>0.67 0.95</td>
<td>0.6 0.93</td>
</tr>
<tr>
<td>DWI</td>
<td>0.05 0.37</td>
<td>0.04 0.32</td>
</tr>
<tr>
<td>DCE MR imaging</td>
<td>0.67 0.17</td>
<td>0.62 0.14</td>
</tr>
<tr>
<td>Overall suspicion score</td>
<td>0.5175 0.05</td>
<td>0.5589 0.04</td>
</tr>
</tbody>
</table>

Table 7: Multireader κ Statistic and Standard Error for PI-RADS and In-House Scoring System

<table>
<thead>
<tr>
<th>Scoring System and Variable</th>
<th>κ score</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI-RADS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2-weighted, PZ</td>
<td>0.47</td>
<td>0.03</td>
</tr>
<tr>
<td>T2-weighted, TZ</td>
<td>0.37</td>
<td>0.06</td>
</tr>
<tr>
<td>DWI</td>
<td>0.40</td>
<td>0.03</td>
</tr>
<tr>
<td>DCE MR imaging</td>
<td>0.46</td>
<td>0.08</td>
</tr>
<tr>
<td>Overall suspicion score</td>
<td>0.46</td>
<td>0.03</td>
</tr>
<tr>
<td>In-house scoring system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2-weighted, PZ</td>
<td>0.20</td>
<td>0.05</td>
</tr>
<tr>
<td>T2-weighted, TZ</td>
<td>0.11</td>
<td>0.05</td>
</tr>
<tr>
<td>DWI</td>
<td>0.56</td>
<td>0.09</td>
</tr>
<tr>
<td>DCE MR imaging</td>
<td>0.39</td>
<td>0.08</td>
</tr>
<tr>
<td>Overall suspicion score</td>
<td>0.55</td>
<td>0.04</td>
</tr>
<tr>
<td>Extracapsular extension</td>
<td>0.69</td>
<td>0.05</td>
</tr>
</tbody>
</table>
DISCUSSION:

The findings of our study revealed that the new version of PI-RADS (version 2.0) has a moderate level of interobserver agreement for readers of varying experience. Similar levels of interobserver agreement were reported for the original PI-RADS. Rosenkrantz et al [19] showed that the interobserver reproducibility for the original PI-RADS was moderate (concordance correlation coefficient, 0.47) in readers of varying experience, which is similar to the results of our study. In another study, Rosenkrantz et al [20] reported a mean $\kappa$ of all possible combinations of three readers of 0.45. The authors of these studies applied a sector-based analysis and used radical prostatectomy as the reference standard. Schimmöller et al reported similar rates of interobserver agreement for the original PI-RADS ($\kappa = 0.55$ for T2-weighted, $\kappa = 0.64$ for DWI, and $\kappa = 0.65$ for DCE MR imaging) in three blinded readers of similar experience levels [21]. Authors of the study applied a lesion-based analysis with in-bore MR imaging–guided biopsy as a reference standard.

The revised version of PI-RADS used for T2-weighted imaging revealed a positive relationship between the probability of cancer and PI-RADS score in the PZ (score of 2, 0.17; score of 3, 0.2; score of 4, 0.67; and score of 5, 0.95) and in the TZ (score of 2, 0.13; score of 3, 0.15; score of 4, 0.6; and score of 5, 0.93). A threshold median reader score of 3 revealed sensitivity and specificity values of 88% and 71%, respectively, in the PZ and of 85% and 55%, respectively in the TZ for cancer detection. Several studies in which authors evaluated the original PI-RADS from 2012 showed higher accuracy in the PZ than in the TZ [20,22]. In our study, the results for the two zones were comparable. This might indicate better performance for detection of tumors in the TZ with the revised edition and generally increased awareness of anterior lesions in the TZ.

Authors of previous performance studies have relied on ROC curves. In our study, the total score of T2-weighted, DWI, and DCE MR imaging achieved an area under the ROC curve of 0.86 for the PZ and 0.87 for the TZ. Schimmöller et al [23] evaluated the original PI-RADS in 2014 in 566 lesions with confirmation at MR imaging in-bore biopsy as a refer-
ence standard. A combination of T2-weighted, DWI, and DCE MR imaging achieved an area under the ROC curve of 0.81. In another study of the same patient population, the authors [22] stated that the sensitivity and specificity for the detection of prostate cancer were 86.0% and 47.2%, respectively, when a cut-off PI-RADS summation value of 11 was used. This analysis is difficult to compare with the revised PI-RADS and its use of a five-point scale, and the comparison could have been influenced by the severity of disease in the study population. Baur et al [3] demonstrated an area under the ROC curve of 0.88 for T2-weighted, 0.93 for DWI, and 0.76 for DCE MR imaging for 113 lesions in 55 patients imaged with a 1.5-T imager, with MR imaging–guided biopsies as a reference standard [3]. The main message of this study was that DCE MR imaging did not add significant value for the diagnosis. In a study of 64 patients with 95 regions suspected to be cancer, Roethke et al [24] demonstrated an area under the ROC curve of 0.817 for T2-weighted imaging, 0.768 for DWI, and 0.758 for DCE imaging, with US/MR imaging–fusion guided biopsy as a reference standard. For all sequences combined, Portalez et al [25] showed an area under the ROC curve of 0.86 for the PI-RADS in 129 patients who were referred for repeat biopsies with fusion-guided biopsy as the reference standard. Junker et al [4] found an area under the ROC curve of 0.97 for all sequences combined in the PZ in 50 patients, with whole-mount prostatectomy as a reference standard. In the TZ, however, DCE MR imaging showed very low diagnostic accuracy (area under the ROC curve, 0.60). In a recent meta-analysis, Hamoen et al [26] included 14 studies (1785 patients), and the pooled data showed sensitivity of 0.78 (95% confidence interval: 0.70, 0.84) and specificity of 0.79 (95% confidence interval: 0.68, 0.86) for detection of prostate cancer, with negative predictive values ranging from 0.58 to 0.95. Sensitivity analysis revealed pooled sensitivity of 0.82 (95% confidence interval: 0.72, 0.89) and specificity of 0.82 (95% confidence interval: 0.67, 0.92) in studies with correct use of PI-RADS [26]. Thus, our results with PI-RADS version 2.0 are comparable to those of previous studies in which the original PI-RADS was used and suggest that there may be structural limits to the ability of PI-RADS or any scoring system based on MR imaging to allow detection of all prostate cancers with high specificity.

Our study had several limitations. First, the readers were trained with a three-point scoring system developed in-house. The initial test session with 20 cases showed very little agreement on PI-RADS scores, but when we added training sessions before the actual scoring session, we found that agreement improved dramatically (data not presented in this article). Therefore, the amount of training and familiarity with PI-RADS could have influenced the interreader variability. The data presented here represent the kind of variability one might expect early after the deployment of the second version of PI-RADS. We predict that interreader variability would decrease with increasing use. Another potential limitation is that the readers had different levels of experience. This might explain some of the variability seen. However, the variability we showed is com-
Interobserver agreement and accuracy with the revised PI-RADS

parable to that reported in other studies in which authors evaluated the previous version of PI-RADS. It is important that a broad range of experience be tested, because prostate MR imaging is likely to be used in both high- and low-patient volume settings. The hope is that PI-RADS will serve to equalize readings despite different levels of expertise. A third limitation is that only lesions suspected to be cancer were evaluated for this study. We only scored lesions that were previously determined to be sufficiently suspicious for cancer to warrant a fusion-guided biopsy according to parameters of the in-house scoring system used at the time of MR imaging. This was necessary because these were the only validated lesions. The in-house scoring system only allows identification of a lesion when there is a sufficient amount of suspicion to warrant biopsy (comparable to overall PI-RADS score ≥ 3) [12]. This also explains the relatively low number of lesions that were scored as PI-RADS 1 or PI-RADS 2 by the panel. Because only targeted biopsies were taken from the areas that were suspicious for cancer at multiparametric MR imaging and not from each of the 27 sectors in each prostate [27], we did not have any data from sectors that did not show lesions suspicious for cancer on MR images. Therefore, we could not draw conclusions about the true- and false-negative results on MR images or the present results for sensitivity, specificity, positive predictive value, and negative predictive value. However, PI-RADS mainly will be used for evaluation of multiparametric MR imaging for a lesion that is suspicious for cancer, so it is important to know how it performs in the exact setting in which it was tested. Another limitation was the definition of clinically relevant prostate cancer. We have accepted lesions with Gleason scores greater than or equal to 4+3 to be clinically relevant; however, there is currently no universally accepted consensus on this topic. Finally, the reference standard we used was MR imaging–transrectal US fusion–guided biopsy. Although fusion–guided biopsy is a very accurate technology to sample lesions in the prostate, it is not as accurate as the use of specimens at prostatectomy [28]. However, the requirement for surgical specimens had its own limitations, because it would have biased cases toward lesions moderately and highly suspected to be cancer and it would not have allowed testing of the characterized PI-RADS performance in a real-world population of patients undergoing biopsy. Therefore, we chose to work with a biopsy-naïve patient population with MR imaging–transrectal US fusion–guided biopsy results to study a diverse and representative patient population previously reported as a possible representative screening cohort [29].

In conclusion, PI-RADS is an important standardization tool for reporting multiparametric MR imaging results. However, the results of this study show that, like the first version of PI-RADS, the second version is only moderately reproducible. On average, it shows good correlation with histopathologic results and high sensitivity for clinically significant disease, but specificity is low. These data suggest that PI-RADS will continue to evolve as more experience is gained.
ADVANCES IN KNOWLEDGE:

• Scores derived from the use of the revised version of the Prostate Imaging Reporting and Data System (PI-RADS) are concordant with pathologic results for lesions in both the peripheral zone and the transitional zone of the prostate (Kendall $\tau$ for peripheral zone lesions, $0.51 \ [P < 0.0001]$ and for transitional zone lesions, $0.45 \ [P = 0.0008]$).
• None of the 12 lesions that were given a PI-RADS score of 2 were determined to show clinically relevant disease at transrectal US–MR imaging fusion–guided biopsy; in other words, no high grade lesions were missed.
• Moderate interreader agreement was shown (multireader $\kappa$ for overall PI-RADS score, 0.46), which is similar to the results of studies to assess the previous versions of PI-RADS.

IMPLICATIONS FOR PATIENT CARE:

• By implementing the new scoring system, clinicians can make better estimations of the risk of prostate cancer at multiparametric MR imaging.
REFERENCES:


Chapter 7

Multiparametric magnetic resonance imaging-transrectal ultrasound fusion–assisted biopsy for the diagnosis of local recurrence after radical prostatectomy

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ABSTRACT

Objective
Approximately 15% of patients who undergo radical prostatectomy (RP) for prostate cancer develop local recurrence, which is heralded by a rise in serum prostate-specific antigen (PSA) levels. Early detection and treatment of recurrence improves the outcome of salvage treatment. We investigated the ability of multiparametric magnetic resonance imaging (mpMRI)-transrectal ultrasound (TRUS) fusion-guided biopsy (FGB) combined with “cognitive biopsy” to confirm local recurrence of prostate cancer after RP.

Materials and methods
In this retrospective study conducted between January 2010 and December 2014, patients with rising PSA levels after RP who had no known evidence of distant metastases underwent mpMRI including T2-weighted (T2W) imaging, diffusion-weighted imaging, dynamic contrast-enhanced (DCE) MRI at 3 Tesla, and subsequent MRI-ultrasound fusion biopsy with cognitive assistance. The detection rate of locally recurrent disease was determined.

Results
A total of 10 patients (mean age = 67 y, mean PSA level = 3.44 ng/ml) met the inclusion criteria. Of the 10 patients, all had positive findings suspicious for local recurrence on mpMRI per entrance criterion. The most important features on mpMRI were early enhancement on DCE MR images and hypointensity on T2W images. The average lesion diameter on mpMRI was 1.12 cm (range: 0.40–2.20 cm). All suspicious lesions (16/16, 100%) were positive on T2W MR images, 14 (89%) showed positive features on apparent diffusion coefficient maps of diffusion-weighted images, and 16 (100%) were positive on DCE MR images. MRI-TRUS FGBs were positive in 10/16 lesions (62.5%) and 8/10 (80%) patients.

Conclusion
MRI-TRUS FGB with cognitive assistance is able to detect and diagnose locally recurrent lesions after RP, even at low PSA levels. This may facilitate early detection of recurrent disease and improve salvage treatment outcomes.

KEYWORDS
Prostate cancer, Biochemical recurrence, MRI, MRI-ultrasound fusion-guided biopsy
INTRODUCTION

Prostate cancer is the most common solid-organ malignancy in men, with an estimated 238,590 new diagnoses and 29,720 deaths in the United States of America in 2014 [1]. In 2007, there were 79,875 patients who underwent radical prostatectomy (RP) as a definitive treatment of prostate cancer in the USA [2]. Although RP provides long-term cancer control in most of the patients with localized prostate cancer [3], approximately 15% to 20% of patients have a rise in prostate-specific antigen (PSA) level, indicating recurrence of their disease after RP [4]. Early detection of disease recurrence after RP leading to early salvage therapy is associated with improved outcomes, whereas delayed diagnosis may limit the opportunity for salvage treatment [5]. A landmark study by Stephenson et al. [6] demonstrated a survival benefit for salvage radiation therapy when treatment was initiated when the PSA level was still less than 2 ng/ml. Others have confirmed these findings, suggesting improved outcomes with earlier treatments [7]. Furthermore, when the recurrent lesions can be localized, targeted dose escalation radiotherapy can be performed [8].

Over the last decade, the diagnostic accuracy of multiparametric magnetic resonance imaging (mpMRI) of the prostate has dramatically improved. Technology improvements and standardized acquisition and interpretation protocols have contributed to the increasing value of mpMRI [9]. However, most of the clinical research studies have been performed in preoperative patients. MRI-transrectal ultrasound (MRI-TRUS) fusion-guided biopsy (FGB) has been used to confirm the findings on mpMR images and is rapidly being adopted [10]. However, after surgery, the anatomic landmarks commonly used to register the MR and TRUS for fusion biopsy are absent, and it is thus more difficult to properly align and fuse the 2 data sets. Several studies have reported the value of mpMRI in the early detection of local recurrence after RP, but there is a paucity of data on the use of MRI-TRUS fusion biopsy in the setting of biochemical recurrence (BCR) [11-15]. In this study, we investigate the ability of MRI-TRUS fusion biopsy to confirm sites of local recurrence suspected by mpMRI.

MATERIALS AND METHODS

Study design and population
This retrospective single-institution study was approved by the local institution review board and was compliant with the Health Insurance Portability and Accountability Act: informed consent was obtained for each patient. The inclusion criteria included documented serum PSA level elevations (more than 0.2 ng/dl) after RP in the absence of known distant metastases, and an mpMRI examination of the prostatic fossa. The exclu-
sion criteria included insufficient preoperative medical history, prior or current history of androgen deprivation therapy, and the presence of metastatic disease in bones or lymph nodes on bone scan or computed tomography.

**Multiparametric MRI**

All MRI studies were performed using a combination of an endorectal coil (BPX-30; Medrad, Pittsburgh, PA) tuned to 127.8 MHz and a 16-channel cardiac coil (SENSE; Philips Medical Systems, Best, the Netherlands) with a 3-T magnet (Achieva; Philips Medical Systems, Best, the Netherlands), without prior bowel preparation. The endorectal coil was inserted using a semianesthetic gel (Xylocaine, Lidocaine; AstraZeneca, Wilmington, DE) while the patient was in the left lateral decubitus position. The balloon surrounding the coil was distended with 3 mol/l of perfluorocarbon (Fluorinert; 3M, St. Paul, MN) to a volume of approximately 45 ml, to reduce susceptibility artifacts induced by air in the coil’s balloon. The MRI protocol included triplanar T2-weighted (T2W) turbo spin-echo imaging, diffusion-weighted (DW) MRI, and axial 3-dimensional fast-field echo dynamic contrast-enhanced (DCE) MRI. Axial DCE images were obtained before, during, and after a single dose of gadopentetate dimeglumine (Magnevist; Berlex, Wayne, NJ), administered at a dose of 0.1 mmol/kg of body weight through a peripheral vein at a rate 3 ml/s using a mechanical injector (Spectris MR injection System; Medrad, Pittsburgh, PA). Sequence parameters were defined in previous studies [16-17].

**mpMRI evaluation**

mpMRI studies were evaluated by 2 radiologists (B.T. and P.L.C. with a cumulative experience of 8 and 15 years in prostate mpMRI, respectively), who were blinded to clinicopathologic information. Each mpMRI sequence was evaluated separately in a commercially available picture archiving and communication system (PACS) (V.11.3, Carestream Health, Inc., Rochester, NY). On T2W MR images and apparent diffusion coefficient (ADC) maps of DW MR images, the criteria for a suspicious lesion were presence of an isointense or hypointense focus at the urethral anastomosis within the prostatectomy fossa. For DCE MRI evaluation, the raw images were reviewed visually and the criterion for a suspicious lesion was the presence of an early enhancing focus within the prostatectomy fossa. A patient was called “negative for local recurrence” if no lesion was detected within the prostatectomy fossa, “low suspicion for local recurrence” in the presence of a lesion positive on T2W MR images or ADC maps alone, and “positive for local recurrence” in the presence of a lesion positive on T2W MR images or ADC maps and DCE MR images.
Fusion-guided biopsies

MRI-TRUS FGBs of target lesions were performed on a now commercially available platform that was developed in our institution (UroNav; Invivo Corp, Gainesville, FL) [18-20]. As the device became commercially available in May 2013, the first 5 patients were biopsied using the research version of the device (biopsied before May 2013). First, T2W MR images of the indicative lesion were segmented. The patient received prophylactic antibiotics prior and after biopsy. On the day of the biopsy, the prostatectomy fossa was scanned with TRUS, and MRI-TRUS fusion was attempted using visualized anatomic landmarks such as the bladder neck, vessels, and areas of calcification. Because such fusions are necessarily inexact without the prostate as a landmark, the actual biopsy was performed by identifying lesions on TRUS image that corresponded to the location of the lesion on the MR image. We termed this “cognitive assistance” to differentiate it from routine MRI-TRUS fusion biopsies that rely exclusively on the fusion image. The lesion identified on TRUS was segmented manually and the processed MR and TRUS images were registered to each other using the software fusion platform. Finally, lesions that were suspicious for recurrence were displayed as targets on real-time TRUS images and were sampled in the axial and the sagittal planes, resulting in 2 cores per target [21]. Needle trajectories were mapped with real-time electromagnetic tracking, which is part of the biopsy platform (Northern Digital Inc., Ontario, Canada).

RESULTS

The initial study population consisted of 39 patients for whom mpMRI was done between January 2010 and December 2014 (Table 1). All patients had a rising PSA level, which was more than the nadir. Of these 39 patients, 21 (54%) had positive findings on mpMRI. Among these 21 patients, 4 had metastatic disease and were treated with androgen deprivation therapy and 7 patients chose to undergo radiation therapy without biopsies. Thus, 10 patients consented to undergo MRI-TRUS FGBs, and they constitute our final patient population (Fig. 1). Patient characteristics are presented in Table 1. Their average age was 67 years (range: 61–75 y). The time interval between the RP and PSA recurrence averaged 107 months (range: 7–259 mo). Initial Gleason score varied between 3+2 and 4+5, and 4 patients (40%) had positive surgical margins after RP (Table 2).

All 10 patients had positive findings on mpMR images as part of study entry criteria. In total, 16 suspicious lesions were found. The most common features used for detection were early enhancement on DCE MR images, and a hypointense signal pattern on T2W MRI. A hypointense focal signal pattern on ADC maps was considered supportive evidence of recurrence. The average lesion diameter on mpMR images was 1.12 cm
(range: 0.40–2.20 cm). All 16 (100%) suspicious lesions were positive on T2W MRI (Fig. 1), 14 (89%) were positive on ADC maps and 16 (100%) were positive on DCE MR images. The targeted MRI-TRUS fusion biopsy with cognitive assistance revealed adenocarcinoma of prostatic origin in 10 of 16 biopsies (63%). Of the 16, 2 (12%) lesions proved to be healthy prostatic tissue. MRI-TRUS fusion biopsy showed fibromuscular tissue in 4 lesions (Fig. 2). On a per-patient basis, the cancer detection rate was 80% (8/10 patients) (Table 3).
Figure 1: Flowchart shows the initial enrollment and exclusion steps applied for the whole study population.

Figure 2: A 72-year-old man who presented after RP with a slowly progressing PSA recurrence (1.22 ng/ml at time of scan). There is a hypo-intense lesion visible at the 11-o’clock position at the level of the anastomosis on the T2W MR image (A). ADC map shows low signal intensity pattern in this region (B), and the lesion shows early focal contrast enhancement on DCE MRI (arrow) (C). Targeted TRUS-MRI fusion biopsy (D) confirmed recurrent prostate cancer.
## Table 2: Patient characteristics of the final study population, only biopsied patients

<table>
<thead>
<tr>
<th>Patient characteristics (N = 10)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y at PSA recurrence, mean (range)</td>
<td>67 (61–75)</td>
</tr>
<tr>
<td>Age, y at RP, mean (range)</td>
<td>58 (50–69)</td>
</tr>
<tr>
<td>T category at surgery, n (%)</td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>pT3a</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Gleason score at surgery, n (%)</td>
<td></td>
</tr>
<tr>
<td>3+2</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>3+3</td>
<td>2 (20%)</td>
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<tr>
<td>3+4</td>
<td>3 (30%)</td>
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<td>1 (10%)</td>
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<td>4+4</td>
<td>1 (10%)</td>
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<tr>
<td>4+5</td>
<td>2 (20%)</td>
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<tr>
<td>Surgical margins, n (%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Negative</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Preoperative PSA level in ng/ml, mean (range)</td>
<td>14.98 (2.70–46.50)</td>
</tr>
<tr>
<td>PSA level nadir in ng/ml, mean (range)</td>
<td>0.25 (&lt;0.01–1.35)</td>
</tr>
<tr>
<td>PSA at suspicion of recurrence in ng/ml, mean (range)</td>
<td>3.44 (0.14–21.74)</td>
</tr>
<tr>
<td>Time to PSA recurrence in months, mean (range)</td>
<td>107 (7–259)</td>
</tr>
</tbody>
</table>

## Table 3: Lesion Characteristics of the final study population

| Total positive findings on MRI, n (%) | 10 (100%) |
| Number of lesions per patient, mean (range) | 1.70 (1–3) |
| Total number of lesions, n | 16 |
| Lesion’s largest diameter in centimeters, mean (range) | 1.12 (0.40–2.20) |
| Total # of lesions positive on T2W MRI, n (%) | 16 (100%) |
| Total # of lesions positive on ADC maps, n (%) | 14 (89%) |
| Total # of lesions positive on DCE MRI, n (%) | 16 (100%) |
| Total # of lesions positive on T1W MRI, n (%) | 0 (0%) |
| Pathology on MRI-US fusion-guided biopsy | |
| Fibromuscular tissue, n (%) | 4 (25%) |
| Benign prostatic tissue, n (%) | 2 (13%) |
| Adenocarcinoma of prostatic origin, n (%) | 10 (63%) |
| Lesions positive on FGB in patients, PSA<1.00 | 3/8 |
| Lesions positive on FGB in patients, 1.00<PSA<2.00 | 4/4 |
| Lesions positive on FGB in patients, PSA>2.00 | 3/4 |
| Mean lesion diameter (range); positive lesions (cm) | 1.2 (0.4–2.2) |
| Mean lesion diameter (range); negative lesions (cm) | 0.9 (0.5–1.8) |
DISCUSSION

BCR after RP occurs in 15% to 20% of the patients [4], [22-23]. Salvage therapy is an important mode of therapy for these patients, as it improves patient survival [24-25]. A study by Stephenson et al. demonstrated that early detection and therapy of recurrent prostate cancer is associated with improved outcomes. In their analysis, there was no difference between the progression rates for patients with a recurrence PSA level of 1.0 ng/ml or less and those with a recurrence PSA level of 1.1 ng/ml through 2.0 ng/ml (P = 0.22). However, a PSA level more than 2.0 ng/ml was associated with a higher rate of progression (P<0.001) [6]. Therefore, the goal of this study was to test whether lesions detected by mpMRI could be confirmed histologically using combined MRI-TRUS FGB even at PSA levels less than 2 ng/ml, which was the case in 8 of our 10 patients.

In this study, 10 consecutive patients underwent mpMRI after referral for evaluation of rising PSA level after RP. Findings suspicious for recurrence included early enhancement on DCE MRI and focal hypo-intensity on T2W MRI. mpMRI combined with MRI-TRUS FGB demonstrated recurrent disease in 8 of 10 patients (80%) with PSA level in the range from 0.14 to 21.74 ng/ml. If we restrict the study patients to those with a PSA level less than 2 ng/ml, the biopsy technique demonstrated recurrent disease in 6 of 8 patients (75%) (mean PSA level = 0.90 ng/ml, range: 0.14–1.35 ng/ml). The prostatic fossa is notoriously difficult to biopsy, and these early results suggest that MRI-TRUS fusion guidance may aid in the localization of targets when compared with TRUS guidance alone.

Several studies have investigated the topic of MRI in the setting of local recurrence. Rischke et al. evaluated 33 patients with PSA level rise after RP who had response after salvage radiotherapy. All patients underwent prostate MRI before and after salvage radiation therapy. The authors used a cutoff value of PSA level (0.54 ng/ml) above which the lesion was always visible on MRI [13]. Verma et al. conducted a similar study in 90 patients with PSA level rise after RP. They found that 20% of these patients had positive MRI findings, of whom 80% had PSA values <1 ng/ml. Positive surgical margins at RP was a predictor of positive MRI findings [14]. Wassberg et al. [15] analyzed 51 patients with suspicious T2W MRI findings, and 33 (63%) of the biopsies were positive for recurrent prostate cancer. Another study with 22 patients demonstrated superior accuracy of mpMRI over F-18 Choline or C11 acetate positron emission tomography. MRI identified recurrent prostate cancer in 85% of the cases [26]. Thus, previous studies have documented the ability of MRI to detect recurrences, but subsequent validation has been made difficult by poor visualization of the prostatic fossa with TRUS alone.

In our study, a combination of DCE MRI and T2W MRI was the most helpful sequence in localizing suspicious foci for recurrence when compared with DW MRI. The key feature of DCE MRI for localizing the recurrent foci was early strong enhancement consistent with earlier studies [15], [27-28]. However, the high resolution T2W MRI was indispensable for
planning the MRI-TRUS FGB. Even though the final placement of the biopsy needle was under the control of the operator under direct TRUS visualization, the MRI-TRUS fusion was extremely helpful in guiding the operator to the correct region to be biopsied.

Detection rates of recurrent disease using US- or MRI-guided biopsies are reported to be low (range: 30%–66%), with a positive biopsy in less than 30% in patients with PSA levels <1 ng/ml [29-30]. The increased sensitivity (80%) of MRI-TRUS fusion is in part because the spatial accuracy of such biopsies is 2.4±1.2 mm [31], whereas the mean lesion size in our population was 8.4 mm (interquartile range: 5–9 mm). An additional implication of accurately localizing recurrences is that it enables targeted boost radiotherapy to confirmed lesions, which is thought to improve response [32]. In theory, recurrent lesions at the bladder neck should also be able to be biopsied and even treated using transurethral resection; however, no studies about this could be found.

This study has several limitations. First, the study size is limited and the results clearly must be validated in larger trials. It proved difficult to identify patients who had MRI-visible lesions who were willing to undergo biopsy, as the standard of care does not require biopsy. Additionally, the patients described here were highly selected for having a positive finding on mpMRI. However, these preliminary results may encourage physicians to study patients with BCR having PSA level<2.0 ng/ml with imaging and image FGB to deliver early precision radiotherapy to sites of local recurrence.

CONCLUSION

In conclusion, in the setting of BCR after RP, lesions detected by mpMRI can be biopsied using a combination of MRI-TRUS FGB and cognitive guidance even at PSA levels <2.0 ng/ml. This hybrid method using MRI-US fusion guidance and direct US targeting can be helpful to validate the MRI findings histopathologically even at low PSA levels. This approach may improve salvage treatment outcomes.
SUPPLEMENTARY MATERIALS

https://ars.els-cdn.com/content/image/1-s2.0-S107814391500263X-mmc1.mp4
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Part II

The role of Optical Coherence Tomography as a novel imaging modality for prostate tissue and detection of prostate cancer
Chapter 8

Prostate cancer diagnosis: the feasibility of needle-based optical coherence tomography

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ABSTRACT

Objective
To demonstrate the feasibility of needle-based optical coherence tomography (OCT) and functional analysis of OCT data along the full pullback trajectory of the OCT measurement in the prostate, correlated with pathology.

Methods
OCT images were recorded using a commercially available C7-XR™ OCT Intravascular Imaging System interfaced to a C7 Dragonfly™ intravascular 0.9mm diameter imaging probe. A computer program was constructed for automated image attenuation analysis. First, calibration of the OCT system for both the point spread function and the system roll-off was achieved by measurement of the OCT signal attenuation from an extremely weakly scattering medium (Intralipid® 0.0005 volume%). Second, the data were arranged in 31 radial wedges (pie slices) per circular segments consisting of 16 A-scans per wedge and 5 axial B-scans, resulting in an average A-scan per wedge. Third, the decay of the OCT signal is analyzed over 50 pixels (500 μm) in depth, starting from the first found maximum data point. Fourth, for visualization, the data were grouped with a corresponding color representing a specific μ_\text{oct} range according to their attenuation coefficient. Finally, the analyses were compared to histopathology. To ensure that each single use sterile imaging probe is comparable to the measurements of the other imaging probes, the probe-to-probe variations were analyzed by measuring attenuation coefficients of 0.03, 6.5, 11.4, 17, and 22.7 volume% Intralipid®. Experiments were repeated five times per probe for four probes.

Results
Inter- and intraprobe variation in the measured attenuation of Intralipid samples with scattering properties similar to that of the prostate was <8% of the mean values. Mean attenuation coefficients in the prostate were 3.8 mm\(^{-1}\) for parts of the tissue that were classified as benign (SD: 0.8 mm\(^{-1}\), minimum: 2.2 mm\(^{-1}\), maximum: 8.9 mm\(^{-1}\)) and 4.1 mm\(^{-1}\) for parts of tissue that were classified as malignant (SD: 1.2 mm\(^{-1}\), minimum: 2.5 mm\(^{-1}\), maximum: 9.0 mm\(^{-1}\)). In benign areas, the tissue looked homogeneous, whereas in malignant areas, small glandular structures were seen. However, not all areas in which a high attenuation coefficient became apparent corresponded to areas of prostate cancer. This paper describes the first in-tissue needle-based OCT imaging and three-dimensional optical attenuation analysis of prostate tissue that indicates a correlation with pathology. Fully automated attenuation coefficient analysis was performed at 1300 nm over the full pullback.
Conclusion
Correlation with pathology was achieved by co-registration of three-dimensional (3-D) OCT attenuation maps with 3-D pathology of the prostate. This may contribute to the current challenge of prostate imaging and the rising interest in focal therapy for reduction of side effects occurring with current therapies.

KEYWORDS:
prostate cancer, optical coherence tomography, diagnosis, imaging
INTRODUCTION:

Prostate cancer is the most prevalent cancer in the male population and the second most common cancer-related cause of death [1]. When elevated serum prostate specific antigen (PSA) concentration has raised suspicion, prostate biopsies are the gold standard to confirm the diagnosis of cancer. These biopsies are evaluated by a pathologist and the development of cancer is graded using the Gleason Score, which ranges from 1, unaggressive tumor (well-organized structure with low cellular density), to 5, aggressive tumor (irregular structures with high cellular density) [2].

The discovery of PSA made the incidence of prostate cancer increase drastically whereas cancer-related mortality remained unchanged [1,3]. Concerns have been raised about detection and overtreatment of these low-risk prostate cancers, since treatment-related side effects (erectile dysfunction and urinary incontinence) may impair quality of life significantly [4]. For these low- to intermediate-risk patients, focal therapy can be a favorable disease management option [5]. This form of therapy aims to eradicate known cancer sites, while leaving healthy tissue untouched, which has the potential benefit of diminishing side effects compared to radical treatments and, thus, maintaining quality of life [4]. However, for focal therapy, accurate identification, localization, demarcation, and grading of a lesion are essential. Imaging modalities such as magnetic resonance imaging (MRI) and transrectal ultrasound (TRUS) are insufficiently accurate to localize prostate tumors with a reported sensitivity of 0.87 and a specificity of 0.30 [6]. Another modality for prostate cancer localization is transperineal three-dimensional (3-D) prostate mapping biopsy. The prostate is sampled every 0.5 cm and the coordinates are correlated to tumor location. The limitations of mapping biopsies are the low volume of tissue sampled in a biopsy and, consequently, the large number of cores needed (average of 50 per prostate), resulting in a larger number of complications and physician-related delay of the results (pathologist has to evaluate all the biopsies), which prevent treatment from occurring in the same session as diagnosis [7,8]. The use of fusion technologies integrating MRI and TRUS to target the biopsy location has been shown to improve on these approaches [9]. Yet, targeted biopsies still rely largely on standard H&E pathology, which is analyzed at a later stage. If targeted biopsy is combined with a real-time technology which can visualize and analyze tissue structure and architecture similar to H&E histology, simultaneous diagnosis and treatment would be feasible.

Optical coherence tomography (OCT) has the potential to fulfill the premise of a fully digital targeted biopsy. OCT is an in vivo imaging modality, similar to ultrasonography, which allows real-time microscopic imaging and quantitative analysis of the backscattered light of an imaged sample. Using near-infrared light (1300 nm), OCT results in very detailed images with a resolution that can reach 10 μm, although the scattering limits the imaging depth to ~2 mm [10]. Technological advancements have led to novel
applications of OCT in urology [11-13], gastroenterology [14–16], gynecology [17,18], dermatology [19–21], cardiology [22–24], and neonatology [25]. The contrast in an OCT image is based on differences in light scattering between different cellular structures in a sample. The resulting exponential decay of the OCT signal with depth, which is parameterized by the attenuation coefficient \( \mu_{\text{oct}} \) (mm\(^{-1}\)), directly relates to the scattering properties of the tissue under study [26]. During carcinogenesis, a cell is subjected to cellular changes which alter the light scattering properties. Quantification of OCT images using \( \mu_{\text{oct}} \) measured from lesions in the ureter [12] kidney [11], vulva [18], oral tissue [27], and lymph node metastases [28] confirmed the ability of OCT to distinguish between tissue types based on \( \mu_{\text{oct}} \). We hypothesize that the attenuation coefficient also correlates with cellular properties of prostate tissue. To the best of our knowledge, this property was never demonstrated in the prostate before.

This study aims to demonstrate the feasibility of needle-based OCT and functional analysis of OCT data along the full pullback measurement trajectory of the OCT. This also includes validation of the OCT by system and probe calibration. We describe the first in-tissue needle-based OCT imaging and three-dimensional optical attenuation analysis of a single prostate after radical prostatectomy, which we compared with histopathological diagnosis. Our work aligns with stages 1 and 2a of the IDEAL framework of clinical technological innovations [29,30].

**MATERIALS AND METHODS**

**Optical Coherence Tomography Device and Visualization**

OCT images were recorded using a commercially available C7-XR™ OCT Intravascular Imaging System interfaced to a C7 Dragonfly™ Intravascular Rotating Imaging Probe (St. Jude Medical, St. Paul, Minnesota). The latter is a thin fiber optic probe with an outer diameter of 2.7 Fr (0.9 mm). During data acquisition, the swept-source OCT system produces cross-sectional images with a lateral resolution of 20 to 40 \( \mu \text{m} \) and a depth (axial) resolution of 15 \( \mu \text{m} \) in air and, hence, 11 \( \mu \text{m} \) in tissue (1024 data points). The automatic pullback system scans across a trajectory of 54 mm along the probe in ~5.4 s, producing a 541 frame dataset, which results in a 100 \( \mu \text{m} \) space between frames. This results in a total scanned cylindrical volume of 54 mm (length) by 10 mm (diameter). Imaging depth is limited by light scattering to ~2 mm. 3-D reconstruction was performed using the AMIRA™ (Visage Imaging GmbH, Berlin, Germany) software package.
Calibration and Three-Dimensional Attenuation Fitting

Signal attenuation is influenced by the technical properties of the OCT system itself, warranting careful calibration. The rotating imaging probes (like a lighthouse) for this system are provided in sterile packaging so that a priori calibration is not possible.

The attenuation coefficient ($\mu_{\text{oct}}$) was determined as described before [18,26]. Briefly, the decay of light intensity with depth ($\text{mm}^{-1}$) is quantified by fitting the OCT data to a single exponential decay using:

$$i(z) \propto e^{-2z \mu_{\text{oct}}} + y_0$$

where $2z$ is the axial round-trip path length of the light in the sample and $\mu_{\text{oct}}$ is the attenuation coefficient; $y_0$ is a term accounting for the fraction of noise offset. The square root accounts for the fact that the detector current $i(z)$ is proportional to the field returning from the sample, rather than intensity [26]. Prior to fitting, the signal is corrected for system-induced attenuation, i.e., reduction in amplitude with increasing distance to the focal point (quantified through the confocal point spread function [31] and reduction in amplitude with increasing distance from the zero-delay point, the so-called sensitivity roll-off due to finite spectral line width of the swept source and finite integration time of the detector [32]).

The ability of the St. Jude OCT system to measure correct values of $\mu_{\text{oct}}$ was validated by measuring $\mu_{\text{oct}}$ for increasing concentrations of a scattering medium (Intralipid®) as our group described previously [33,34]. The OCT system induced signal attenuation (due to the combined effect of the confocal point spread function and the sensitivity roll-off, see below) was calibrated on a highly diluted Intralipid sample (0.0005 volume%). After correction for water absorption ($\sim 0.2 \text{ mm}^{-1}$), an attenuation of 1.1 mm$^{-1}$ remained, which is subtracted from subsequently measured $\mu_{\text{oct}}$ values. Validation of $\mu_{\text{oct}}$ measurements was performed by determining the attenuation coefficient from Intralipid dilutions with increasing scattering coefficient. To ensure that each single use sterile imaging probe is comparable to the measurements of the other imaging probes, the probe-to-probe variations were analyzed by measuring attenuation coefficients of 0.03, 6.5, 11.4, 17, and 22.7 volume% Intralipid®. Experiments were repeated five times per probe for four probes.

In previous studies, we concluded that attenuation coefficients in tissue can reliably be determined on depth segments down to 50 μm length (provided 50 to 100 A-scans can be averaged to suppress signal variation due to speckle) [35]. Recently, algorithms have been presented that allow determination of the attenuation coefficient down to the pixel level [36]. Since our goal is to localize tumor tissue along the trajectory of the biopsy needle, we devised the procedure outlined below to reduce the amount of data.

Visual inspection of the OCT images reveals that the data appear largely homogeneous along the pullback, so that fitting regions can be set at 50 data points in the automated analysis. To practically implement the attenuation analysis on a full 3-D pullback dataset acquired with the St. Jude OCT console, a custom-made plugin was
developed for ImageJ [37]. The $\mu_{\text{oct}}$ analysis is performed on the raw data (Fig. 1). First, to optimize the fitting procedure, the data were arranged in 31 discrete radial wedges (pie-slices) per circular segment. Each wedge consists of 16 radial A-scans per wedge and 5 axial B-scans [Fig. 1(b)]. The resulting average wedge is further smoothed using a Savitsky-Golay filter with a width of 21 data points [Fig. 1(c)] [38]. Second, the first 90 data points in an A-scan were removed since they contain only inner reflections of the probe itself [Fig. 1(d)]. Third, the decay of the OCT signal is analyzed starting from the first maximum data point until 50 points (500 μm) in depth, using Eq. (1) [Fig. 1(e)]. Fourth, subtraction of the $\mu_{\text{oct}}$ of the calibration measurement (1.1 mm$^{-1}$) from the signal decay yields the attenuation coefficient. Finally, the OCT data were visually inspected for extremely high or low scattering structures to account for extraordinary high or low attenuation coefficients created by structures like calcifications, cysts or air gaps between tissue and probe. These values were excluded from the correlation analysis with pathology. For visualization, the data were grouped with a corresponding color representing a specific $\mu_{\text{oct}}$ range according to their attenuation coefficient; $\mu_{\text{oct}} = 0$ to 5.5 mm$^{-1} = \log$ java hue, 0.65 to 1.00, $\mu_{\text{oct}} > 5.5$ mm$^{-1}$ and <0.5 = gray (Fig. 2).

**Measurement of Prostate Tissue**

Directly after radical resection, the prostate was transported to the pathology department for ex vivo measurements. First, a silicon catheter was placed to indicate the urethra. Six intravenous (IV) catheters [Terumo Surflo® 18 G×2(1/2)] were introduced in the prostate, two in the transitional zone and four in the peripheral zone. The needle was removed from the catheter and the OCT probe was inserted in the IV catheter. During measurements, the IV catheter was retracted to ensure direct contact of the C7 Dragonfly™ OCT imaging probe with prostate tissue. Measurements (OCT pullbacks) started at the apex and extended to the base of the prostate. After data collection, the catheters were reintroduced over the OCT imaging probe and left behind in the tissue to mark the imaging trajectory for correlation with the pathological diagnosis (Fig. 3).

**Correlation of 3-D OCT Data with Prostate Histopathology**

Following OCT measurements, an independent pathologist diagnosed the histological slides according to our institute’s standard protocol. The prostate was placed in formalin over night for fixation with the IV catheters in place. On day 2, the pathologist colored the two prostate sides to indicate left and right and dissected the prostate into slices of 3 to 5 mm (lamellation). From these slices, a thin layer was skived for microscopic analysis. The contours of the OCT measurement trajectories, as well as areas of malignant tissue, were marked on the slides. All individual microscopic slides were reconstructed into a 3-D pathology representation showing the prostate contour, benign tissue, tumor, and OCT probe trajectories using AMIRA™. The 3-D OCT pullbacks and corresponding
Figure 1: (a) Raw optical coherence tomography (OCT) data consist of 1024 radially directed A-scans per B-scan and 541 B-scans in the z direction, covering 541*100 μm=54.1 mm. (b) 16 A-scans and 5 B-scans were averaged to smoothen the data, resulting in 31 radial averaged A-scans and 108 B-scans over the 54.1 mm length. (c) Savitzky-Golay filter was applied to smooth the A-lines. (d) The first 90 data points were removed from each averaged A-scan to remove scattering properties from the probe itself. (e) Attenuation analysis was performed over first 50 points after the maximum of the resulting curve (red part).
Figure 2: The raw data were plotted (upper part). With the help of a customized Image J plug-in, the attenuation coefficient was analyzed (middle part). Each range of attenuation coefficients was given a color for interpretation corresponding to the scale bar on the left side (lower part).

Figure 3: Ex vivo OCT measurement directly after radical prostatectomy. (a) Performance of the measurement with the 0.9 mm C7 Dragonfly™ OCT imaging probe positioned in the tissue. Measurement pullbacks start at the apex (left on the picture) and end at the base of the prostate (right in the picture). (b) Marking the trajectory by replacing the intravenous (IV) catheters in the tissue after measurements for optimal correlation with whole mount histopathology.
attenuation maps were manually co-registered, which allows for visual correlation of pathology and OCT data. Additionally, an overlay of quantitative attenuation plots and pathology was created.

**RESULTS**

The calibration measurements in various Intralipid concentrations are depicted in Fig. 4, demonstrating a nonlinear increase of attenuation coefficient with increasing concentration. These values and nonlinear behavior, which is due to dependent and multiple scattering, are in concordance with our earlier published results [33,34]. As shown in Fig. 5 and Table 1, the smallest difference in $\mu_{\text{oct}}$ per probe is 0.03 mm$^{-1}$; the largest difference in $\mu_{\text{oct}}$ per probe is 0.33 mm$^{-1}$. The smallest difference in $\mu_{\text{oct}}$ between probes is 0.15 mm$^{-1}$; the largest difference in $\mu_{\text{oct}}$ between probes is 0.65 mm$^{-1}$. For Intralipid concentrations within the scattering range of prostate tissue (3–6 mm$^{-1}$) two times the standard deviation of the measurements, an indication of the precision (reproducibility) of our measurement technique, was <8% of the mean of the measured values.

Analysis of the OCT data obtained in the prostate resulted in mean attenuation coefficients of 3.8 mm$^{-1}$ for parts of the tissue that were classified as benign (SD: 0.8 mm$^{-1}$, minimum: 2.2 mm$^{-1}$, maximum: 8.9 mm$^{-1}$) and 4.1 mm$^{-1}$ for parts of tissue that were classified as malignant (SD: 1.2 mm$^{-1}$, minimum: 2.5 mm$^{-1}$, maximum: 9.0 mm$^{-1}$).

![Figure 4](image-url)

**Figure 4:** Attenuation measurements were validated by measurement of $\mu_{\text{OCT}}$ of samples with increasing concentrations of Intralipid®. The boxplots represent mean and range for all probes combined (see also Table 1).
Figure 6(a) shows a 3-D representation of the OCT measurement with visualization of three separate B-scans. In Fig. 6(b), which was characterized as malignant tissue on pathology, glandular appearing structures can be observed. In Fig. 6(c), which was characterized as benign tissue on pathology, homogeneous prostate tissue can be seen. In Fig. 6(d), a cyst filled with clear fluid is shown, which the automated analysis recognizes as a high attenuation coefficient. The ring around the B-scans visually represents the attenuation coefficient (the same color scale is used as in Fig. 2). It is clear that the attenuation coefficient differs in prostate tissue.

Figure 7 shows a prostate after histopathological evaluation. After fixation in formalin, the prostate was painted orange on the left side and blue on the right side. Subsequently, the prostate was sliced from base (slice 1) to apex (slice 8), and all slices were positioned with the same side up. The OCT measurement trajectories, indicated by the IV catheters, are very well visible. Four H&E stained microscopy slides per prostate slice were obtained and the pathologist indicated areas of tumor on these slides, as marked in red. These microscopic slides were overlaid on the overview picture of the prostate slices. Using AMIRA™, we reconstructed the prostate contour and lesion contours by stacking the slices in 3-D [Fig. 8(a)]. By plotting the St. Jude OCT measurements [Fig. 8(c)] and attenuation maps [Fig. 8(d)] in these reconstructed contours by using the holes of the IV catheters as a guide, we could estimate the distance between the slices (average slice thickness). Also, we were able to estimate which part of the OCT measurements went through tumor and which parts went through benign tissue. Finally, the information on co-registration was used to determine which B-scans corresponded to the sampled...
areas in the prostate slices. The attenuation information from these matched B-scans was also plotted in the picture of the prostate slices (Fig. 7, 1 to 8). Not all areas in which a high attenuation coefficient became apparent corresponded to areas of prostate cancer.

**DISCUSSION**

We demonstrate a method that allows for 3-D quantitative analysis of OCT optical attenuation coefficient datasets that may indicate a correlation with tissue disease status.

*Figure 6: Structural properties of prostate tissue. (A) Three-dimensional (3-D) representation of an OCT measurement of prostate tissue with a visualization of three separate B-scans. (B) B-scan from malignant area (Gleason 3+4) of the prostate. Glandular appearing structures are observed in these malignant areas (arrow). Optical attenuation coefficients in this area are high, indicated by the red ring around the raw data (visualizing the output of the automated attenuation analysis). (C) B-scan from a benign region of the prostate. In these benign areas, homogeneous tissue was seen, resulting in a low attenuation coefficient, indicated by the blue ring (visualizing the output of the automated attenuation analysis). (D) B-scan from an area in which a cyst was seen. In these irregular areas, attenuation coefficient matching is not always accurate, resulting in a high variation of attenuation coefficients, indicated by the multiple colors on the ring (visualizing the output of the automated attenuation analysis). The scale bar is 5 mm.*
This study is the first to show the feasibility of quantitative needle-based OCT in the prostate. This study is the first step toward real-time objective diagnosis of prostate cancer, a largely emphasized challenge in urology.

Full clinical translation of OCT should build on three fundamental pillars. First, qualitative properties should be objectified with quantitative information, which can be spatial measurements from images (e.g., layer thicknesses), attenuation coefficients such as in our study, or more complex statistics related to tissue organization. A major challenge is relating measured optical properties to gold standard pathology diagnosis. This gap cannot be bridged without fundamental studies—far beyond the scope of our present contribution—that include both advanced OCT signal modeling and leveraging the potential of quantification of digital pathology.

Second, the technology should be compatible with existing procedures and protocols. We presently use the clinically proven OCT equipment C7-XR™ OCT Intravascular Imaging System interfaced to a C7 Dragonfly™ Intravascular Imaging Probe (St. Jude Medical, St. Paul, Minnesota). Since the sterile probes are unpackaged just before measurements, prior calibration of the probes is not possible. We, therefore, devised an efficient, cost-effective procedure based on an easily obtained Intralipid™ suspension. Moreover, this study shows that intra- and interprobe variation is minimal, which suggests high data fidelity even if post hoc calibration is not possible (for example, because blood has entered the imaging catheter). However, the study shows that post measurement...
calibration of the probes improves measurement precision, since there is some small variation between the probes.

Third, the future of prostate cancer will be image-guided targeted diagnosis, likely by a combination of imaging technologies [39]. Using TRUS, a location estimation of the OCT probe can be obtained. In addition to this, OCT visualizes the position of a lesion along the optical biopsy axis. It has been shown that when MRI data were fused with data from a conventional TRUS, the sensitivity increased drastically. More biopsies were
Prostate cancer diagnosis: the feasibility of needle-based optical coherence tomography

Figure 9: Schematic representation of histopathology matching challenges. Each blue block (numbered 1 to 8) represents a slice of prostate. The bold red lines on each left side of a blue block represent the pathology slide (part of the prostate that is actually visualized under the microscope). The striped bar in the middle represents an OCT scan, and each stripe represents a B-scan. The letters on the left side represent the possible scenarios. A, slice of prostate that looks benign but actually is half tumor (false negative); B, prostate slice that looks malignant and is malignant (true positive); C, prostate slice that looks malignant but is half benign (false positive); and D, prostate slice that looks negative and is negative (true negative). It is clear that because of the matching issues, the difference between benign and malignant attenuation coefficients becomes smaller.

Table 1: Mean optical attenuation coefficients per probe with range (visual representation in figures 1 and 2). Note that per probe the smallest and largest range in $\mu_{\text{oct}}$ are 0.06 mm$^{-1}$ and 0.33 mm$^{-1}$, respectively. Between probes the smallest and largest difference in measured $\mu_{\text{oct}}$ are 0.15 mm$^{-1}$ and 0.65 mm$^{-1}$, respectively.

<table>
<thead>
<tr>
<th>Volume Concentration</th>
<th>Probe 1</th>
<th>Probe 2</th>
<th>Probe 3</th>
<th>Probe 4</th>
<th>All probes combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03%</td>
<td>0.35 (0.32-0.39)</td>
<td>0.38 (0.33-0.42)</td>
<td>0.45 (0.42-0.48)</td>
<td>0.41 (0.37-0.45)</td>
<td>0.40 (± 0.05)</td>
</tr>
<tr>
<td>6.50%</td>
<td>3.45 (3.35-3.53)</td>
<td>3.54 (3.50-3.60)</td>
<td>3.74 (3.68-3.78)</td>
<td>3.73 (3.60-3.85)</td>
<td>3.62 (± 0.14)</td>
</tr>
<tr>
<td>11.40%</td>
<td>4.95 (4.92-4.98)</td>
<td>5.05 (5.02-5.09)</td>
<td>5.05 (5.00-5.09)</td>
<td>5.14 (5.11-5.21)</td>
<td>5.05 (± 0.07)</td>
</tr>
<tr>
<td>17%</td>
<td>5.52 (5.47-5.60)</td>
<td>5.59 (5.52-5.68)</td>
<td>5.82 (5.81-5.83)</td>
<td>5.97 (5.91-6.13)</td>
<td>5.72 (± 0.19)</td>
</tr>
<tr>
<td>22.70%</td>
<td>5.85 (5.73-6.05)</td>
<td>5.78 (5.76-5.80)</td>
<td>6.11 (6.01-6.20)</td>
<td>6.19 (6.12-6.23)</td>
<td>5.98 (± 0.19)</td>
</tr>
</tbody>
</table>
found positive in the fused group and more malignant tissue was found per biopsy [40] even accomplishing results similar to transperineal 3-D prostate mapping biopsy [41]. Our hypothesis is that integrating OCT in the combined results of MRI/TRUS fusion will further improve the diagnostic accuracy. Moreover, results will become objective and real time. For the diagnosis of kidney tumors, similar developments are ongoing. Projects are running to test the ability of OCT as a means of optical biopsy for kidney cancer (NCT02073110, Ref. [42]) using the same OCT device as is used in our study. The few studies performed regarding OCT in the prostate focus on the qualitative interpretation of optical findings to identify surgical margins and neurovascular bundles [43–46]. One manuscript described a difference between malignant and benign prostate tissue structures visualized with OCT; however, these results were not quantitatively analyzed [47].

When the OCT technology further improves (smaller, higher-resolution, faster machines) and analysis software evolves (e.g., structure recognition, automatic learning, etc.), the technology will most likely become faster, more objective and more accurate.

OCT is a new diagnostic modality in the prostate. We acknowledge the limitations that this study entails. First, the St. Jude system evaluates tissue every 0.1 mm, whereas whole mount pathology assesses the tissue in theory every 4 mm. Due to free hand slicing, this slice thickness varies in practice between 3 and 5 mm, creating ~20 OCT images uncertainty in the first slice. This matching-uncertainty is of non-negligible proportion, since every prostate slice has this variable slice thickness of 3 to 5 mm. Furthermore, we assumed in this study that the slice thickness is constant throughout the prostate slice. However, it is very well possible that a slice might be slightly wedge shaped in reality. Also, when a tumor is not present throughout the whole slice, it can cause matching issues (Fig. 9). All these aspects create uncertainty in the 3-D OCT histopathology matching and have to be overcome for further validation studies. Solving this issue is currently in progress by using a customized tool for dedicated pathology matching and slicing. Second, the St. Jude imaging probe does not have a marker that indicates angular probe position in tissue, so a method should be designed to register this. Further studies are in progress that provide larger numbers of patients and address the slicing and pathology-matching issues described above. Finally, in ex vivo measurements, blood flow and tissue perfusion are not present. In vivo measurements are needed to determine whether or not the results are reproducible.

CONCLUSION

We demonstrated the feasibility of needle-based 3-D quantitative 1300 nm OCT in prostate tissue as a first step toward objective and real-time digital diagnosis of prostate cancer. Fully automated attenuation coefficient analysis was performed over the full pull-
back. Optimal correlation with pathology was achieved by co-registration of 3-D OCT attenuation maps with 3-D pathology of the prostate. This approach may contribute to the current challenge of prostate imaging and the rising interest in focal therapy for reduction of side effects occurring with current therapies. However, in further research, the challenges of exact histopathology correlation as well as μ\text{oct} analysis of different cell types of the prostate need to be addressed.
REFERENCES

Prostate cancer diagnosis: the feasibility of needle-based optical coherence tomography


Chapter 9

Prostate cancer diagnosis by optical coherence tomography: first results from a needle based optical platform for tissue sampling

BG Muller, DM de Bruin, MJ Brandt, W van den Bos, SH van Huystee, DJ Faber, D Savci, PJ Zondervan, TM de Reijke, MP Laguna-Pes, TG van Leeuwen, JJMCH de la Rosette

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ABSTRACT

The diagnostic accuracy of Optical Coherence Tomography (OCT) based optical attenuation coefficient analysis is assessed for the detection of prostate cancer.

Needle-based OCT-measurements were performed on the prostate specimens. Attenuation coefficients were determined by an earlier described in-house developed software package.

The mean attenuation coefficients (benign OCT data; malignant OCT data; p-value Mann-Whitney U test) were: (3.56 mm$^{-1}$; 3.85 mm$^{-1}$; p < 0.0001) for all patients combined. The area under the ROC curve was 0.64. In order to circumvent the effect of histopathology mismatching, we performed a sub-analysis on only OCT data in which tumor was visible in two subsequent histopathological prostate slices. This analysis could be performed in 3 patients. The mean attenuation coefficients (benign OCT data; malignant OCT data; p-value Mann-Whitney U test) were: (3.23 mm$^{-1}$; 4.11 mm$^{-1}$; p < 0.0001) for all patients grouped together. The area under the ROC curve was 0.89.

Functional OCT of the prostate has shown to differentiate between cancer and healthy prostate tissue. The optical attenuation coefficient in malignant tissue was significantly higher in malignant tissue compared to benign prostate tissue. Further studies are required to validate these initial results in a larger group of patients with a more tailored histopathology matching protocol.
INTRODUCTION

During the course of the last decades, localized low-risk prostate tumors are detected earlier, in line with the rising awareness and new and improved imaging modalities [1]. However, current treatment protocols aim at systemic or radical procedures, with considerable side effects such as erectile dysfunction and/or incontinence [1]. With regard to these low-risk tumors, concerns have been raised about diagnosis and over-treatment of these low-risk prostate cancers. Hence, the concept of focal therapy is emerging as a recommendable approach and is positioned between radical therapy and expectant management in order to maintain treatment efficacy while minimizing morbidity [2-4].

For the success of focal therapy, adequate disease characterization, such as grading and mapping of the significant cancer foci in the prostate are of great importance. Optimal diagnostic requirements would theoretically provide 3D mapping and visualization of the tumor, along with visualization of the biologic characteristics of all cancer foci in the prostate, regardless of size or grade. This is not provided by currently imaging methodology and biopsy protocols [5,6].

Optical Coherence Tomography (OCT)

OCT is a technique that allows for minimal invasive imaging of structures in biological tissues. The principle is similar to ultrasonography, except that light waves provide the back-scattered information, rather than acoustic waves. Using near infrared light (1300 nm), a detailed image can be produced with a penetration of approximately 1–2 mm and resolutions up to 10 µm [7], as is shown in Figure 1. As the light penetrates the tissue, the optical properties of tissue, such as scattering and absorption, limit the imaging depth. In other words, the optical attenuation coefficient, which defines the decay of OCT signal with depth, can be used to differentiate between different tissues. Recent studies indicate that by using Lambert-Beer’s law of exponential attenuation [8], quantitative measurement of the attenuation coefficient by OCT can aid in the discrimination of neoplastic and cancerous tissue over normal tissue [9-13].

Within urology, most research has been done to assess the potential of...
OCT to accurately diagnose bladder cancer [14-16]. In the kidney, OCT was successful in discriminating between benign and malignant renal tissue [9]. In the prostate, OCT has been used to identify neurovascular bundles and assessment of surgical margins after robotic radical prostatectomy [17]. However, until now, the interpretation of OCT images of the prostate is solely based on the qualitative image interpretation, without further quantitative analysis of the OCT signal. The attenuation coefficient is expected to provide valuable clinical information because it quantitatively determines disease related changes of the tissue. The methods for full 3D attenuation analysis of prostate tissue were described in previous work [18]. The aim of this study is to assess the feasibility of OCT to discriminate between malignant and benign tissue within the prostate, using the attenuation coefficient. We hypothesize that the optical attenuation coefficient is higher in prostate tumor areas than in unaffected areas. The project aligns with stage 2a of the IDEAL guidelines for surgical innovation [19, 20].

MATERIALS AND METHODS

We performed a prospective ex-vivo pilot study on 6 prostates directly after radical prostatectomy. The institutional review board waived the necessity for informed consent, since the measurements were performed on resected ex-vivo material.

Inclusion criteria
Patients diagnosed with prostate cancer and scheduled for a radical prostatectomy were eligible for the study.

OCT acquisition
OCT images were recorded using a commercially available C7-XR™ Intravascular Imaging System interfaced to a C7 Dragonfly™ Intravascular Imaging Probe (St. Jude Medical, St. Paul, Minnesota, USA). This rotating (like a lighthouse) fiber-optic OCT system with an outer probe diameter of 2.7 Fr (0.9 mm) produces cross-sectional images with an axial resolution of 10 µm in tissue. The automatic pullback system scans across a trajectory of 54 mm along the probe in 5.4 seconds, producing a 540-frame dataset (image (B-scan) every 0.1 mm). This results in a total scanned cylindrical volume of 54 mm (length) by 10 mm (diameter) with a scattering limited imaging depth of approximately 2.5 mm.

Prostate handling
Directly after radical resection, the fresh prostate was transported to the pathology department for ex-vivo OCT-measurements. Four or six intravascular (IV)-catheters (Terumo Surflo® 18G × 2½) were placed on specific locations in the prostate. Two IV-catheters
were positioned in the transition zone and two or four in the peripheral zone (Figure 2A). Each IV-catheter was given a number according to the scheme in Figure 2B on the right side. The needle was removed from the IV-catheter and the C7 Dragonfly™ OCT probe was introduced in the IV-catheter. The IV catheter was retracted over the OCT imaging probe, to ensure probe contact with tissue. Measurements (OCT “pullbacks”) started at the apex and extended to the base of the prostate (Figure 2C). After data collection, the IV-catheters were reinserted over the OCT imaging probe to mark the imaging trajectory for optimal correlation with the pathological diagnosis (Figure 2D). The prostates were sliced perpendicular to the IV catheters, so that the histopathological slides were in the same plane as the OCT B-scans.

![Figure 2: (A) IV-Catheter: After insertion in the prostatectomy specimen, the needle was extracted and the OCT probe was introduced in the plastic catheter. This IV-catheter was retracted over the probe (*) before the measurement was performed. After the OCT measurement, the IV-catheter was reintroduced over the OCT probe to mark the trajectory. (B) OCT Measurement Scheme: Each catheter was inserted in the prostate specimen according to this scheme. 2 catheters were introduced into the transition zone (TZ) and 2 or 4 catheters were introduced into the peripheral zone (PZ). OCT measurements “pullbacks” were made from apex to base. (C) Ex-vivo OCT measurement directly after radical prostatectomy with the 0.9 mm imaging probe, the retracted IV-catheter is visible on the right. (D) Marking the trajectory with IV-catheters for optimal correlation with whole mount histopathology.](image-url)
OCT image visualization

Using the 3D visualization software package AMIRA™ (Visage Imaging GmbH, Berlin, Germany), a 3D reconstruction of the OCT data was made. Using this reconstruction as shown in Figure 3.1, we determined which parts of the measurement represent prostatic tissue and which parts represent air. The part of the pull-back maneuver that did not pass through prostatic tissue was excluded.

Extracting quantitative information; Attenuation coefficient

Briefly, the decrease of light intensity [mm$^{-1}$] is quantified by fitting OCT data to a single exponential decay model, after imperatively accounting for system specific calibrations [18, 21, 22].

Prior to attenuation analysis, the data was corrected for OCT system dependent signal roll-off, including the confocal point spread function [8, 22]. After this correction, based on a calibration measurement on samples with accurately known optical properties, we used Beer’s law to describe the OCT signal as: $I(z) = \sqrt{[e^{-2\mu_{\text{oct}}z}]} + y_0$, where $2z$ is the round-trip
path length of the light in the sample, $\mu_{\text{oct}} \, [\text{mm}^{-1}]$ is the attenuation coefficient and $y_0$ is a term accounting for the fraction of noise offset. The square root accounts for the fact that the detector current $i(z)$ is proportional to the field returning from the sample, rather than intensity.

The residual of the fit is defined as the difference between the attenuation fit values and the actual OCT data values. A large residual value indicates a poor fit of the attenuation model and in this case the attenuation coefficient is unreliable. These large residual values can be caused by e.g. calcifications or cysts. Areas with a residual value > 9 pixels were therefore excluded from the analysis. Finally, the regions were color coded according to the measured attenuation coefficients. For $\mu_{\text{oct}}$ between 0–5.5 mm$^{-1}$, the color scale was set to 0.65–1.00 using the HSB color space programmed in Java. For $\mu_{\text{oct}}$ > 5.5 mm$^{-1}$ and <0.5 mm$^{-1}$, the color was set to grey. The whole process is illustrated in Figure 3 and more extensively explained in earlier work [18].

**Histopathological evaluation**

Following OCT evaluation, an independent uro-pathologist performed the histopathological examination. The prostate was placed in formalin over night for fixation. Subsequently, the right and left sides of the prostate were color coded (Figure 4A) and the prostate was sliced into slices of 3–5 millimeters (Figure 4B). From each of these slices, a thin layer (slide) was cut for microscopic analysis. The pathologist indicated malignant areas on these microscopy slides. Subsequently, the microscopic slides were correlated with the macroscopic pictures of the prostate slices (Figure 4C) by the use of in-house developed software. The contours of the four to six OCT measurement channels as well as malignant tissue were marked. Afterwards, the pathology results were reconstructed in 3D (Figure 4D).

Co-localization of OCT data with histopathology was achieved by dividing the total number of OCT B-scans of a full pull-back over the number of histopathology slices. This results in a group of OCT B-scans per histopathology slice that represent the approximate histopathology location. If a histology slice showed malignancy at the OCT image location, the whole group of OCT B-scans was deemed malignant. If no malignancy was present in the histology, the whole group of OCT B-scans was deemed benign. An average attenuation coefficient was calculated per B-scan. Finally, the resulting mean $\mu_{\text{oct}}$ values in benign areas were compared to mean $\mu_{\text{oct}}$ values in malignant areas [18].

**Statistical analysis**

The difference in mean attenuation coefficients between healthy and malignant prostate tissue across all patients, was tested using a one-tailed Mann-Whitney U test ($p < 0.05$). Receiver Operating Characteristic (ROC) curve analysis was performed on OCT data of all patients grouped together. This ROC curve evaluates the diagnostic performance
Figure 4: 3D histopathology correlation: The prostate was fixated in formalin overnight and colored (A). The prostate was sliced and a picture of every slice was taken (B). The pathologist marked the contours of the tumors on each histology slide, and the slides were overlaid on each picture of the large prostate slice, using a custom-made computer program (C). Using the same software, the prostate was reconstructed in 3D (D).
Prostate cancer diagnosis by optical coherence tomography: first results

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at OR (years)</td>
<td>Mean: 65 (range: 52-75)</td>
</tr>
<tr>
<td>PSA at OR (ng/mL)</td>
<td>Mean: 5.1 (range: 3.2 – 7.8)</td>
</tr>
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<td>Biopsies</td>
<td>Gleason</td>
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<td>(3+3=6)</td>
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<tr>
<td>(3+4=7)</td>
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<td>(3+5=8)</td>
<td>n = 1</td>
</tr>
<tr>
<td>(4+4=8)</td>
<td>n = 1</td>
</tr>
<tr>
<td>(4+5=9)</td>
<td>n = 1</td>
</tr>
<tr>
<td>Number of cores positive</td>
<td>Mean: 6.5 (Range 1 - 12)</td>
</tr>
<tr>
<td>Radical Specimens</td>
<td>Gleason</td>
</tr>
<tr>
<td>(3+3=6)</td>
<td>n = 2</td>
</tr>
<tr>
<td>(3+4=7)</td>
<td>n = 2</td>
</tr>
<tr>
<td>(3+5=8)</td>
<td>n = 1</td>
</tr>
<tr>
<td>(5+4=9)</td>
<td>n = 1</td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
<td>n= 0 out of 6</td>
</tr>
<tr>
<td>Extracapsular extension</td>
<td>n= 4 out of 6</td>
</tr>
<tr>
<td>Pelvic Lymph Node Dissection</td>
<td>n= 3 out of 6</td>
</tr>
<tr>
<td>Lymph nodes involved</td>
<td>n= 0 out of 3</td>
</tr>
<tr>
<td>Resection margins positive</td>
<td>n= 1 out of 6</td>
</tr>
</tbody>
</table>

of a test by plotting the fraction of true-positives out of the positives versus the fraction of false-positives out of the negatives for different threshold values. The area under the curve measures a form of test accuracy.

All statistical analyses were performed in Graphpad Prism 6 computer software.

RESULTS

6 patients were included in the study (see Table 1). Mean age was 65 years (range 52–75), mean PSA was 5.10 ng/mL (range: 3.2–7.8), two patients had Gleason Score (GS) 6 (3 + 3) on histopathology of the resected prostate, two had GS 7 (3 + 4), one had GS 8 (3 + 5) and one had GS 9 (5 + 4). None of the six had seminal vesicle invasion, four of the six had extracapsular extension, in three of six patients a pelvic lymph node dissection was performed of which none showed lymphatic invasion. Five out of six prostates had negative resection margins on histopathology.
Figure 5: Attenuation coefficients for benign and malignant areas: Left side) The first 6 graphs represent the attenuation coefficients per patient. The pair of boxplots located at the right represents the data of all patients grouped together. Boxplots represent medians and interquartile ranges. The means are indicated by the square in the middle of each boxplot. An asterisk (*) means that there is a significant difference between malignant and benign attenuation coefficients. Right side) Receiver Operator Characteristics (ROC) curve analysis for all patients grouped together resulted in an area under the curve of 0.64.

Figure 6: Schematic representation of histopathology matching challenges: Each blue block (numbered 1–8) represents a slice of prostate. The bold red lines on each left side of a blue block represent the pathology slide (the parts of the prostate that are actually visualized under the microscope). The striped bar in the middle represents an OCT scan and each stripe represents a B-scan. The letters on the left side represent the possible scenarios. A) slice of prostate that looks benign, but actually is half tumor (false negative). B) prostate slice that looks malignant and is malignant (true positive). C) prostate slice that looks malignant but is half benign (false positive), and (D) prostate slice that looks negative and is negative (true negative). It is clear that because of the matching issues, the difference between benign and malignant attenuation coefficients becomes smaller. This image is not scaled to size.
**Histology vs. attenuation coefficient**

Data was analyzed per patient. The mean attenuation coefficients for benign and malignant areas for these 6 patients are depicted in Figure 5 (left). The mean number of B-scans analyzed per group (sample size) was 376 per patient for benign data and 164 per patient for malignant data.

The mean attenuation coefficients (benign OCT data; malignant OCT data; p-value Mann-Whitney U test) were: (3.40 mm$^{-1}$; 3.50 mm$^{-1}$; $p = 0.044$) for patient 1, (3.67 mm$^{-1}$; 3.97 mm$^{-1}$; $p < 0.0001$) for patient 2, (3.72 mm$^{-1}$; 3.93 mm$^{-1}$; $p < 0.0001$) for patient 3, (3.40 mm$^{-1}$; 3.64 mm$^{-1}$; $p = 0.0001$) for patient 4, (3.56 mm$^{-1}$; 3.52 mm$^{-1}$; $p = 0.2365$) for patient 5, (3.62 mm$^{-1}$; 4.12 mm$^{-1}$; $p < 0.0001$) for patient 6, and (3.56 mm$^{-1}$; 3.85 mm$^{-1}$; $p < 0.0001$) for all patients combined. A one-tailed Mann-Whitney U test showed a significant difference in mean attenuation coefficient for all patients except patient 5 ($p = 0.2365$). ROC analysis has been performed on this data, resulting in an area under the ROC curve of 0.64 ($p < 0.0001$) (Figure 5).

However, these results can be challenged by a mismatch of the histopathology compared to the OCT measurements. Each prostate slice is only evaluated at the surface. When a tumor is located only in half of the slice, the other half of the OCT data is wrongly attributed (see Figure 6).

For this reason we did a sub-analysis in which we only evaluated OCT data that was clearly prostate cancer in two subsequent prostate slices (scenario B in Figure 6). Assuming that the tissue in between the two pathology slices is prostate cancer, this sub-analysis would identify more reliable differences in the attenuation coefficient of benign versus malignant prostate tissue. In three patients, cancer could be found which was both in the OCT measurement trajectory and in two subsequent prostate slices. Per patient, around 60 malignant B-Scans were compared to around 60 benign B-Scans. Results are shown in Figure [7]. The mean attenuation coefficients (benign OCT data; malignant OCT data; p-value Mann-Whitney U test) were: (2.94 mm$^{-1}$; 4.36 mm$^{-1}$; $p < 0.0001$) in patient 1, (3.60 mm$^{-1}$; 4.02 mm$^{-1}$; $p < 0.0001$) for patient 2, (3.28 mm$^{-1}$, 3.91 mm$^{-1}$, $p < 0.0001$) in patient 4, and (3.23 mm$^{-1}$; 4.11 mm$^{-1}$; $p < 0.0001$) for all patients grouped together.

A Mann-Whitney U test showed significant differences in attenuation coefficient between benign and malignant tissue in all groups. ROC analysis has been performed on this subset of data, resulting in an area under the ROC curve of 0.89 ($p < 0.0001$) (Figure 7).
DISCUSSION

We showed that needle-based functional shows a significant difference in optical attenuation coefficient between benign and malignant prostate tissue. Our findings thus contribute to the current challenge of prostate imaging and the rising interest in focal therapy for reduction of side effects occurring with radical treatment methods for prostate cancer [23].

OCT applied for the detection of prostate cancer is relatively new. The few studies performed regarding OCT in the prostate focused on identification of the neurovascular bundles during surgery [24-26], or cancer (positive margin) detection by qualitative image analysis [27]. D'Amico et al. described structural differences in prostate tissue measured with a swept-source OCT device [28]. One of the main advantages of OCT over conventional diagnostic technologies, next to the fact that the technology provides instant real-time diagnosis, is that it is objective, by quantitative analysis of the data. Current methods of histopathology are time-consuming and sensitive to subjectivity of the pathologist. By performing quantitative analysis of OCT data, we expect to avoid these diagnostic boundaries as there are in conventional pathology, such as delay in diagnosis and subjectivity. As a comparison, computer aided diagnosis (CAD) systems have shown to increase speed and accuracy in finding prostate cancer on MRI images in less experienced readers [29]. Studies have been executed ex-vivo and in-vivo to assess the potential of OCT to discriminate between malignant and benign tumors and healthy

Figure 7: Attenuation coefficients for only benign and malignant areas in two subsequent prostate slices: Left side) The first 3 pairs of boxplots represent the attenuation coefficients per patient for benign and malignant areas. The pair of boxplots located at the right represents the data of all patients grouped together. Boxplots represent medians and interquartile ranges. The means are indicated by the square in the middle of each boxplot. Left side) Receiver Operator Characteristics (ROC) curve analysis for all three patients grouped together resulted in an area under the curve of 0.89.
tissue using the optical attenuation coefficient: e.g. bladder [30], kidney [9], ureter [10], vulva [13] and esophagus [31]. They all show a significantly higher optical attenuation coefficient in tumorous tissue as compared to healthy tissue.

Another major advantage of OCT is that the technology evolved to a needle-based platform, enabling microscopic resolution 3D optical biopsies of tissue. These ultra-thin high resolution needle-based imaging platforms have already proven their efficacy in the lymph nodes [32], lung [33], breast [34] and skeletal muscle [35]. It is expected that in the future, technology will become faster, and resolutions will become higher (to the micrometer level), resulting in even higher diagnostic accuracy. This can ultimately lead to template saturation OCT of the prostate, resulting in instant, objective prostate cancer diagnosis and staging. Within this study all analyses are performed off-line, but when the software is fully developed the analyses can be performed on site. This will eventually even be amplified by fast available computer systems. For now, the time for the analyses to run is a few seconds. Moreover, in line with recent developments in minimally invasive treatment options for prostate cancer, same day treatment will be feasible when diagnosis is accurate and fast. Expectations are that quantitative analysis of OCT data will aid in swift diagnosis and therefore focal treatment of prostate cancer [36].

The following limitations, however, have to be addressed in future research. The standard pathology protocol is not sufficient to validate a micrometer-level technology as OCT is. As described earlier, free hand slicing leads to variable slice thickness and mismatch between histopathology and OCT data. The St Jude system evaluates tissue every 0.1 mm whereas whole mount pathology assesses the tissue in theory every 4 mm. Also, when a tumor is not present throughout the whole slice, it will inevitably lead to matching issues, falsely leading to a small difference in attenuation coefficient between tumor and healthy tissue (Figure 6). A sub-analysis of data, in which only cancer and unaffected tissue was taken into consideration when it was present in two subsequent slices (scenario B in Figure 6), rendered a much larger difference in attenuation coefficients. Also, free hand slicing leads to a variation in slice thickness of about 1–2 mm between slices, creating about 10–20 OCT B-scans uncertainty in the first slice. This “matching-uncertainty” is of non-negligible proportion, since every prostate slice has this variation in slice-thickness. Furthermore, we assumed that slice-thickness is constant throughout the prostate-slice, while in reality prostate slices could also be wedge-shaped. Currently, a system for prostate slicing is being developed, which ensures one to one matching of the OCT measurement trajectories to histopathology with an inaccuracy of 0.1 mm to overcome these issues.

A limitation is the small number of B-scans that went through malignant areas compared to the large number of B-scans that went through benign areas. Ideally we should have similar sample sizes among each group.
Besides prostate cancer, there can be several other tissue structures (benign glands, stroma, cystic atrophy) that potentially can influence the optical attenuation coefficient. By exact pathology correlation, we aim to investigate the influence of these structures on automated attenuation analysis. Finally, in ex-vivo measurements, blood flow and tissue perfusion are not present. In-vivo measurements are needed to render if the same results are reproducible. The study is in line with stage 2a of the IDEAL guidelines for surgical innovation [19, 20]. The data from this study can and should be used to get an indication of how many patients are needed exactly to calculate diagnostic accuracy. We believe that OCT is not a technology to find a lesion, but rather to get local information about the tissue. Therefore, we propose to avoid the use of OCT as a stand-alone technology, but rather integrate it in other technologies as MRI or Contrast Enhanced Ultrasound. When OCT alone turns out not to be sufficiently reliable for local grading of a suspected lesion, it can be combined with e.g. tissue spectroscopy to increase accuracy. The results warrant further studies in the next stage of IDEAL (2b: exploration) in a larger group of patients.

CONCLUSION

Functional needle based OCT of the prostate demonstrates a significant difference in optical attenuation coefficient between healthy and malignant prostate tissue. The optical attenuation coefficient was significantly higher in malignant tissue compared to benign prostate tissue. Further studies are required to validate these initial results in a larger group of patients with a more tailored histopathology matching protocol.

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CONFLICTS OF INTEREST

There we no conflicts of interest reported for this manuscript.
REFERENCES:


Chapter 10

Customized tool for validation of optical coherence tomography in differentiation of prostate cancer

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ABSTRACT

Objective:
To design and demonstrate a customized tool to generate histologic sections of the prostate that directly correlate with needle-based optical coherence tomography pullback measurements.

Materials and Methods:
A customized tool was created to hold the prostatectomy specimens during optical coherence tomography measurements and formalin fixation. Using the tool, the prostate could be sliced into slices of 4 mm thickness through the optical coherence tomography measurement trajectory. In this way, whole-mount pathology slides were produced in exactly the same location as the optical coherence tomography measurements were performed. Full 3-dimensional optical coherence tomography pullbacks were fused with the histopathology slides using the 3-dimensional imaging software AMIRA, and images were compared.

Results:
A radical prostatectomy was performed in a patient (age: 68 years, prostate-specific antigen: 6.0 ng/mL) with Gleason score 3 + 4 = 7 in 2/5 biopsy cores on the left side (15%) and Gleason score 3 + 4 = 7 in 1/5 biopsy cores on the right side (5%). Histopathology after radical prostatectomy showed an anterior located pT2cN0 adenocarcinoma (Gleason score 3 + 4 = 7). Histopathological prostate slides were produced using the customized tool for optical coherence tomography measurements, fixation, and slicing of the prostate specimens. These slides correlated exactly with the optical coherence tomography images. Various structures, for example, Gleason 3 + 4 prostate cancer, stroma, healthy glands, and cystic atrophy with septae, could be identified both on optical coherence tomography and on the histopathological prostate slides.

Conclusion:
We successfully designed and applied a customized tool to process radical prostatectomy specimens to improve the coregistration of whole mount histology sections to fresh tissue optical coherence tomography pullback measurements. This technique will be crucial in validating the results of optical coherence tomography imaging studies with histology and can easily be applied in other solid tissues as well, for example, lung, kidney, breast, and liver. This will help improve the efficacy of optical coherence tomography in cancer detection and staging in solid organs.
KEYWORDS

optical coherence tomography; prostate; needle-based; validation; histopathology

ABBREVIATIONS

3D 3-dimensional
IV intravascular
MRI magnetic resonance imaging
OCT optical coherence tomography
PSA prostate-specific antigen
US ultrasound
INTRODUCTION

Prostate cancer is the second most common cancer in men (after skin cancer) and the second most common cause of cancer-related death (after lung cancer). In 2014, it was estimated that 233,000 new cases developed, and approximately 29,480 deaths occurred in the United States [1]. During the past 2 decades, a steady increase in the detection of prostate cancer has occurred largely due to the increased use of prostate-specific antigen (PSA) screening. This has led to an increased use of systematic transrectal ultrasound (US)-guided biopsy in which the prostate is sampled in a standardized stereotypical fashion, regardless of the tumor location, which results in a high rate of false-negative findings [2]. Advanced imaging modalities have the potential to address this issue by allowing more accurate tumor localization, which would in turn enable image-guided targeted biopsies [3,4] and facilitate optimal treatment planning. These advanced imaging modalities will prove especially useful with the emergence of novel and potentially less morbid targeted therapies [5].

Optical coherence tomography (OCT) produces high-resolution images of tissue. The principle of this optical technology is analogous to B-mode ultrasonography, except that light is being used instead of sound. Huang et al described the first application of OCT (in the retina and the coronary artery) in 1991 [6]. The contrast in the OCT images is based on differences in the back-scattering properties of the tissue, which are projected by gray-scale levels. With resolutions of 5 to 10 μm and an imaging depth of around 2 mm, depending on the light source used [7,8], images comparable to histopathology can be created. In the prostate, OCT has been used for a variety of purposes. During laparoscopic radical prostatectomy, OCT has proven to be successful in identifying the neurovascular bundles, which could enhance surgical precision during nerve-sparing surgery [9]. Furthermore, Doppler OCT, a technology to assess blood flow in microvasculature, was proven to be effective in the rat prostate for real-time microvascular monitoring during photodynamic therapy for prostate cancer [10]. Optical coherence tomography was also used for the assessment of surgical margins of the specimens after robotic radical prostatectomy. Sensitivity, specificity, positive predictive value, and negative predictive value were 70%, 84%, 33%, and 96%, respectively [11]. D’Amico et al also showed differentiation of different structures in the prostate on OCT [12].

Recent technological developments have led to needle-based OCT imaging of tissue [13]. Thin fiber optic helical scanning OCT probes are built into needles, which allow the introduction of the OCT probe into solid tissue such as the prostate [14]. The resulting images can be analyzed on visible qualitative tissue structures [15] or more quantitatively on light scattering parameters [16] and/or measured size of visible structures [17], which can be compared to histopathology of tissue [18]. The detection of prostate cancer with OCT would enable a digital biopsy of the prostate with instant results, resulting in
the possibility of cancer diagnosis and treatment in the same session. In the prostate, OCT was successfully used in rats by Rais-Bahrami et al [19] and Aron et al [9] during laparoscopic radical prostatectomy to identify the cavernous nerves. Yet, one-to-one correlation of OCT images with gold-standard histopathology images is essential for validation of the technology and requires very precise colocalization [18].

The correlation between imaging modalities and histopathology is challenging. Several studies reported on a similar challenge in validation of multiparametric magnetic resonance imaging (MRI) for prostate cancer [20-22]. Especially in studies evaluating OCT images, one-to-one histology correlation is extra important because of the high resolution at micrometer level. This proof-of-concept study demonstrates the feasibility and use of a customized device to generate histological sections of the prostate that directly correlate with OCT pullback measurements on a millimeter level. Exemplary coregistration results between OCT and histopathology of the prostate are given.

MATERIALS AND METHODS

The OCT system used in the study is the commercially available C7-XR intravascular imaging system interfaced to a C7 Dragonfly intravascular imaging probe (St Jude Medical, St Paul, Minnesota). The system is originally designed for intravascular (IV) OCT and operates a probe with a diameter of only 0.9 mm, which fits through a small 17-G needle. It is therefore possible to perform OCT measurements in solid tissue as the prostate. The C7-XR Intravascular Imaging System takes 5.4 seconds to acquire a 3-dimensional (3D)-OCT helical motorized pullback image of 540 B-scans over a trajectory of 54 mm (length) with a pullback speed of 10 mm/s (Figure 1). The radius or imaging depth is limited by scattering to approximately 2 mm.

Directly after radical prostatectomy, a silicon tube was passed through the urethra for orientation purposes. Base (left) and apex (right) as well as ventral and dorsal side were identified. The prostate was measured, weighed, and inked ventral right side (red), ventral left side (yellow), dorsal right side (green), and dorsal left side (blue). After inking, the fresh prostate was anchored in a grid-based customized tool with 4 anchoring needles in the center of the grid (Figure 2). Six IV catheters (Intranule, 105 × 1.3 × 1.7 mm, 16 G; Vygon, Ecouen, France) were introduced from the left side to the right side of the prostate. The grid-based customized mold was used to ensure a parallel IV catheter position (Figure 2). The inner needles were removed from the IV catheters, and the OCT imaging probe was introduced into the IV catheter while flushing with water (to prevent the formation of air bubbles). The IV catheters were transparent, therefore, the OCT pullback measurements could be performed while the IV catheters were still in place. After the OCT measurements were finished, long needles were placed through
the measurement trajectories in order to keep the IV catheters parallel while the prostate was fixed in formalin.

Subsequently, the prostate was fixed in formalin for 48 hours. After fixation, the prostate was sliced of exactly 4 mm thickness using our in-house-developed customized tool for pathology validation. One of the sides from our grid-based measurement and fixation tool was detached, and the grid was fitted in a guided cutting tool. Small rails ensured that the knife was positioned exactly in front of the IV catheters (measurement trajectories). Knife guiders that fold around the knife were introduced through the other side of the grid and inserted in the IV catheters to guide the knife exactly through the measurement trajectories (Figure 3). Slices that did not contain measurement trajectories were cut without guidance. After slicing, a high-resolution overview picture was made according to protocol (Figure 4). From the slices with measurement trajectories, whole-

Figure 1: St Jude C7-XR intravascular optical coherence tomography (OCT) system. A, Schematic detail of the probe tip. The OCT imaging probe (on 3-dimensional [3D] schematic illustration and as a cross section of the tip of the probe) was 0.9 mm in diameter and fitted through an intravenous catheter. The probe functions as a lighthouse, it shines light sideways, and makes pullbacks of 54 mm in 5.4 seconds. B, By the imaging console, the OCT pullback was controlled. C, C7 Dragonfly intravascular imaging probe, which was compatible to the C7-XR intravascular imaging console depicted in B. D, Detail of the C7 Dragonfly probe tip.
Figure 2: Customized grid for optical coherence tomography (OCT) measurements and fixation in formalin. A, Fresh prostate stained for orientation (®) and fixed in a grid (□) on both sides for parallel OCT measurements. Ventral right side (red), ventral left side (yellow), dorsal right side (green), dorsal left side (blue). A silicon tube was inserted through the urethra for orientation purposes. B, Transparent intravenous (IV) catheters were inserted from left to right, parallel to each other, with the help of the grids on either side of the prostate (same coordinate in as out). C, The OCT imaging probe (OCT) was inserted through the transparent IV catheters. Pullback measurements were made from the right to the left side. D, Enlargement of the positioning grid on either side of the prostate. The prostate was fixed in the grid with 4 fixation needles located in the center indicated by Δ. After the OCT measurements, the prostate was fixed in formalin for 48 hours in the grid.

Mount histology slides were made in order to see the entire measurement trajectory (Figure 4).

The histopathology slides were evaluated by a single urogenital pathologist with 10 years of experience (L.R.) who was blinded to the OCT measurements. Alongside the measurement trajectories, the structures were described and correlated with the OCT measurements.

Using the imaging software AMIRA (version 5.5; FEI Visualization Sciences Group, Mérignac Cédex, France), we determined which part of the OCT measurement trajec-
ries passed through the prostate. Subsequently, we fused the OCT data with the histopathology in a 3D computer environment. In this way, we were able to exactly correlate the OCT B-scan with the location on histopathology.

RESULTS

A radical prostatectomy was performed in a patient (age: 68 years, PSA: 6.0 ng/mL) with Gleason score $3 + 4 = 7$ in 2/5 biopsy cores on the left side (15%) and $3 + 4 = 7$ in 1/5 biopsy cores on the right side (5%). Histopathology after radical prostatectomy showed an anterior located pT2cNx adenocarcinoma Gleason $3 + 4 = 7$. 

Figure 3: Customized cutting tool for the exact correlation with histopathology. A, First, one of the sides was removed from the grid, and the grid was placed in the customized cutting tool. The inner needles were removed from the first 2 intravenous (IV) catheters. Underneath the grid, there are rails that position the measurement trajectories in front of the knife ($\bigcirc$). From the other side, knife guiders were introduced in the grid (•) that fold around the knife and enter the IV catheter. They were locked in their position by turning the locking bar ($\ast$). The prostate is indicated by ©. Ventral right side (red), ventral left side (yellow), dorsal right side (green), dorsal left side (blue). B, The prostate was sliced by pushing the whole grid toward the locking bar, forcing the knife to slice through the measurement trajectories. C, After slicing, it was clearly visible that the measurement trajectories are exactly sliced through the center. The forceps hold one side of the IV catheter, which is sliced exactly in 2 halves.
Using 3D imaging software AMIRA, the 3D-OCT measurement volumes were fused with the histopathology slice (Figure 5). Subsequently, we defined the number of B-scans that went through prostate tissue and divided that through the number of millimeters trajectory on histopathology. In this way, we could calculate the number of B-scans per millimeter and exactly locate the measurement site with an accuracy of 0.1 mm. We could identify various structures in the histopathology, which we also observed in the OCT measurements, which confirmed an accurate matching. Some examples are depicted in Figure 6. Alongside the measurement trajectory, the following structures were recognizable: (1) prostate cancer Gleason 3 + 4. In the OCT image, no structural informa-
tion could be obtained (homogeneous aspect of tissue). However, it was clear that the light did not penetrate as far into the tissue as in other measurement locations (higher attenuation of light). The increased scattering is presumably due to the high nuclear density in that area, combined with the lowered amount of cytoplasm in these cells (lower nucleus–cytoplasm ratio), as observed in histopathology. (2) Some cystic atrophy with septae was seen alongside the OCT measurement trajectory. On the OCT B-scans, structures are clearly recognizable (Figure 6B, arrows), and light penetration is relatively deep (low attenuation). (3) Stroma was visible in the OCT B-scan as a homogeneous scattering medium in which light penetrates relatively deep (low attenuation). This is presumably because of the low nuclear density in the stroma, which could also be seen on histopathology. (4) Healthy glands were also located alongside the OCT imaging trajectory. In the OCT B-scans, the glands were recognizable (Figure 6D, arrows) and the light penetrates more deeply into the tissue (lower attenuation). (5) Cystic atrophy with large cysts was clearly seen on the OCT B-scans. They perfectly align with the shape of the cysts seen in the same area on histopathology (Figure 6E, arrows).

Figure 5: Three-dimensional (3D) fusing of optical coherence tomography (OCT) volume with histopathology slide (slice 5, Figure 4). Using 3D imaging software AMIRA, entire 3D OCT volumes were fused with the histopathology slide. For each measurement, one plane (slice of 3D volume) in the X–Z direction was visualized as well as 5 B-scans (X–Y direction). The letters correspond to the B-Scans in Figure 6.
Figure 6: Five B-scans from the fused histopathology slide. A, Area of Gleason 4 prostate cancer. In the optical coherence tomography (OCT) B-scan, this is seen as a homogenous tissue with low penetration depth. In the histopathology slides, nuclear density is seen. B, Cystic atrophy with septae. The cysts are clearly seen on the OCT images (arrows), the septae can be seen on both OCT images and histopathology (#). C, Stroma. In the OCT B-scan, this is seen as a homogenous area with high penetration depth. D, Healthy glands. The glands can be seen on the OCT B-scans as a heterogeneous area (indicated by the arrows). E, Cystic atrophy without septae. The arrows indicate some of the cysts. It is well seen that the cysts have the same shape as the areas on histopathology. NB: The letters of the B-scans correspond to the letters in Figure 5.
As can be seen in Figure 6, the structures seen on OCT correlate well with the structures on histopathology. The imaging trajectories on OCT measured 41.5 and 39.5 mm, whereas they measured 39.5 and 41.0 mm, respectively, in the whole-mount histopathology slides.

**DISCUSSION**

Matching of data obtained from a high-resolution imaging techniques as OCT to histopathology is prone to fail because of slight misalignments and misorientations between the images. In order to improve the coregistration of whole-mount histology sections to fresh tissue OCT pullback measurements, we successfully designed and applied a customized tool to process radical prostatectomy specimens. A major limitation of conventional needle biopsies is that the tissue is only visualized in 2 dimensions, whereas important structures for determining cancer and invasiveness of the disease are more clearly seen in 3 dimensions. What is true in radiology is expected in pathology: 3D imaging will give an immense increase in the information content, which is expected to increase sensitivity and specificity of early cancer diagnostic technologies [23]. Standard pathology protocols, however, are insufficiently accurate for the validation of a micrometer resolution needle-based technology as OCT.

For the validation of other novel diagnostic modalities, one-to-one histopathology matching is essential but presents itself with a challenge. Turkbey et al designed a custom-made 3D printed mold for the validation of multiparametric MRI for prostate cancer diagnosis. These molds, based on the 3D MRI images, allowed cutting the specimens in exactly the same plane as the MRI scans [22,24,25]. This method can be used for deeply penetrating imaging technologies (as MRI and US) but are less suitable for superficial (less deeply penetrating) imaging technologies as OCT. Hariri et al designed a method to compare OCT images with histopathology in the ex vivo setting to validate OCT in bronchial tissue [26]. The method worked in the ex vivo setting by cutting the bronchi open and placing ink markers on the tissue where in between the OCT measurements were performed. A similar technique had been used in cardiology [27,28] for the visualization of high-risk plaques. Wagstaff et al used an approach where they acquired a core biopsy of in vivo renal tissue over the same trajectory as a biopsy was harvested [29], an approach that is challenged by the high percentage of nondiagnostic specimens that occurs in renal biopsy protocols [30].

The customized tool for OCT measurements and histopathology matching does have some limitations we have to address. There is a small difference in the length of trajectory between the OCT measurements and the histopathology slide, which can be explained by the formalin fixation-related shrinkage of the prostate. A study by Jonmarker et al
described an average linear shrinkage of 4.5%, corresponding to a volume correction factor of 1.15 [31]. Another study found a linear shrinkage of 4.3% and a net volumetric shrinkage of 12.4%, resulting in a correction factor for tissue shrinkage of 1.14 [32]. In our sample, we found a linear shrinkage of 4.8% and 5.3%. Moreover, in large prostates, when fixed in formalin for 48 hours, the differences in fixation can be present between the outer and inner parts of the tissue block, which may cause nonuniform shrinkage and therefore minor (<1 mm) mismatch in images and histopathology.

The axial rotation of the imaging probe in the tissue is estimated based on the location of the urethra (if visible) and steepness of the borders of the prostate. Although this method is reasonably accurate, an inaccuracy of approximately 10° in probe rotation may exist. In future studies, a marker can ensure axial probe rotation in tissue before measurements.

One of the main advantages of OCT over conventional diagnostic technologies, next to the fact that the technology provides instant real-time diagnosis, is that it is objective, by quantitative analysis of the data. Current methods of histopathology are time consuming and sensitive to subjectivity of the pathologist. By performing quantitative analysis of OCT data, we expect to avoid these diagnostic boundaries as there are in conventional pathology, as delay in diagnosis and subjectivity. We believe that OCT is not a technology to find a lesion but rather to get local information about the tissue. Therefore, we propose to integrate OCT in other technologies as MRI or contrast-enhanced US. When OCT has been validated as a reliable artificial biopsy. Diagnosis and treatment of prostate cancer can be performed on the same day, in a minimally invasive manner.

To our knowledge, we are the first to describe a one-to-one method for full specimen histopathology matching with needle-based OCT in solid tissue. By demonstrating examples of B-scans and identifying structures on OCT that could also be seen on histopathology, we showed that matching is nearly perfect. Besides prostates, the technology can also be applied in other solid tissues, for example, lung, kidney, breast, and liver. The technology presented is an important step in order to validate a high-resolution imaging technique as OCT. When OCT has proven to be valid in the ex vivo setting, the next step will be to validate the technology in vivo.

CONCLUSION

We successfully designed and applied a customized tool to process radical prostatectomy specimens to improve the coregistration of whole-mount histology sections to fresh tissue OCT pullback measurements. This technique is crucial in validating the results of OCT imaging studies with histology and can easily be applied in other solid tissues as well, for example, lung, kidney, breast, and liver. This method will help improve the ef-
fficacy of OCT in cancer detection and staging in solid organs. Future work will focus on a technique to validate OCT in the prostate using this method in a larger group of patients.

DECLARATION OF CONFLICTING INTERESTS

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SUPPLEMENTAL MATERIAL

The online supplemental video is available at <https://journals.sagepub.com/doi/suppl/10.1177/1533034615626614/suppl_file/OCT_prostate_customized_tool_filmpje_met_logo's.mp4>.
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Chapter 11

Needle based optical coherence tomography for the detection of prostate cancer: a visual and quantitative analysis in 20 patients

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ABSTRACT

Objectives
To define diagnostic accuracy of needle-based OCT for prostate cancer detection by visual and quantitative analysis.

Materials and Methods
106 3D OCT data sets were acquired in twenty prostates after radical prostatectomy and precisely matched with pathology. OCT images were grouped per histological category. Two reviewers performed blind assessments of the OCT images. Sensitivity and specificity for malignancy detection were calculated. Quantitative analyses by automated optical attenuation coefficient calculation were performed.

Results
OCT can reliably differentiate between fat, cystic- and regular atrophy and benign glands. The overall sensitivity and specificity for malignancy detection was 79% and 88% for reviewer 1 and 88% and 81% for reviewer 2, respectively. Quantitative analysis for differentiation between stroma and malignancy showed a significant difference (4.6 mm\(^{-1}\) vs. 5.0 mm\(^{-1}\) Mann-Whitney U test \(p<0.0001\)). A Krushkal-Wallis test showed a significant difference in median attenuation coefficient between stroma, inflammation, Gleason 3 and Gleason 4 (4.6 mm\(^{-1}\), 4.1 mm\(^{-1}\), 5.9 mm\(^{-1}\), 5.0 mm\(^{-1}\) respectively). However, attenuation coefficient varied per patient and a related-samples Wilcoxon signed rank test showed no significant difference per patient (\(p=0.17\)).

Conclusion
This study confirmed the one to one correlation of histopathology and OCT. Precise matching showed that most histological tissues categories in the prostate could be distinguished by their unique pattern in OCT images. In addition, the optical attenuation coefficient can play a role in the differentiation between stroma and malignancy, however a per patient analysis of the optical attenuation coefficient did not show a significant difference.
ABBREVIATIONS

A-scan = Amplitude scan, this is reflected signal along a single axis
B-scan = Cross sectional image, existing of two axes. For this research, it exists of 500 A-scans formed into a circle and beholds all data of a single OCT probe rotation.
IV catheter = Intravenous catheter
MRI = Magnetic resonance imaging
OCT = Optical coherence tomography
PIRADS = Prostate imaging reporting and data system
TRUS = Transrectal ultrasound
NPV = Negative predictive value
PPV = Positive predictive value
ROC = Receiver operating characteristic
ROI(s) = Region(s) of interest
INTRODUCTION

Prostate cancer consisted 26% of the new cancer diagnoses in 2015, and it was the second most common cause of cancer related death in the USA [1]. PSA screening led to an increase in the diagnosis of low- and intermediate risk prostate cancer [2]. Focal therapy is emerging as an attractive treatment option for these patients, since it only treats the cancerous part of the prostate, while leaving the remaining part unharmed. Focal therapy has significantly less side effects when compared to radical treatment [3-9]. However, accurate imaging on a microscopic level is crucial for case selection and the application of focal therapy.

Imaging technologies that are currently investigated for prostate cancer include multiparametric MRI (mpMRI) and transrectal ultrasound (TRUS) [10]. These technologies provide information on a macroscopic level with voxel sizes of ~1mm³ on MRI and pixel sizes of ~ 0.2mm x 0.2mm on TRUS. Standard histopathology provides diagnostic information on prostate cancer on a microscopic level. This process however, is time consuming, is moderately reproducible between observers and it produces artefacts on subsequent radiological images [11, 12]. An imaging modality that provides reproducible instant information on a microscopic level and that can be used intra-operatively and in the outpatient department would make the process of diagnosis, treatment and monitoring faster (automated image processing) and more accurate (less open for interpretation error).

OCT is a high-resolution imaging method in which contrast is based on differences between light scattering of tissue structures [13]. Although the imaging depth is limited to approximately 2mm, OCT has an important advantage over standard histopathology, because OCT can, either non or minimally invasively, be applied in vivo, using scan heads or probes in conjunction with balloons, catheters or needles. Recent developments in needle-based OCT enable minimally invasive puncturing of tissue and therefore in-tissue imaging [14, 15]. Furthermore, the OCT signal can be quantitatively analyzed, thereby providing tissue specific parameters such as the optical attenuation coefficient [14, 16]. The optical attenuation coefficient can function as a measure for tissue density. In previous studies, one to one matching of the OCT images with histology remained challenging [14, 16], while precise histopathology correlation is essential to draw well-founded conclusions from the measured OCT data and to understand which tissue types in the prostate can be distinguished by OCT. Therefore, a customized prostate measurement and slicing device was developed which facilitates the necessary one to one correlation of OCT images of fresh prostate tissue with histology. It has been demonstrated that OCT is able to characterize tissue structures as seen on histopathology [17-19]. Additionally, the tissue density is expected to translate into a different attenuation coefficient when compared with benign tissue. The objectives of the present study are to identify
unique structural characteristics in needle-based OCT images, which by pathology are proven benign or malignant prostatic tissues, based on visual parameters and/or quantitative analyses by means of the optical attenuation coefficients. We hypothesize that the obtained structural characteristics and quantitative parameters can be translated into a diagnostic accuracy that approaches biopsy levels. The study is performed according to the IDEAL guidelines for the validation of medical devices [20], and according to the STARD criteria for diagnostic studies [21].

METHODS

A prospective observational ex-vivo study was performed in 20 prostates immediately after radical prostatectomy. The hospital’s ethical board waived the need for evaluation.

Participants

Patients at least 18 years of age, diagnosed with prostate cancer and scheduled for radical prostatectomy were eligible for inclusion in this study. Potentially eligible patients were identified at the outpatient clinic of the urology department at the VU University Medical Center in Amsterdam between August and November 2014. Inclusion was on a consecutive basis.

**Flowdiagram 1: Automated Quantitative analysis. The process is described in detail in the appendix**
Test methods

Optical coherence tomography measurements were recorded using a commercially available C7-XR™ Imaging System interfaced to a C7 Dragonfly™ Imaging Probe (St. Jude Medical, St. Paul, Minnesota, USA) (figure 1). The system uses a wavelength of 1300 nm with a bandwidth of 55 nm, with a scan rate of 100 frames/sec (500 A-lines/frame) [22, 23]. The Imaging probe was inserted into a transparent intravascular (IV)-needle catheter (Terumo Surflo® 18G x 2½) allowing tissue puncturing. A detailed description of the device, its adaption for prostate imaging, and the measurement protocol were provided in a previous paper [14]. Briefly, the rotating fiber-optic probe with an outer diameter of 2.7 Fr (0.9mm) produces cross-sectional images with an axial resolution of 10 - 15 µm and lateral resolution of 20 – 40 µm [24]. A 360 degree probe rotation provides 504 A-scans of ~5 mm. The 504 A-scans were converted into one cross-sectional image or B-scan.

Figure 1: The St. Jude OCT system
A. C7-XR™ OCT console. B. The C7 Dragonfly OCT imaging probe connected to the OCT driver containing the optical fiber and focusing optics and electronic components for measurements. C. Schematic detail of the OCT probe: the light is deflected perpendicular to the probe’s axis into the tissue while the probe rotates and is pulled back, resulting in a cylindrically scanned OCT volume of the tissue surrounding the probe.
Needle based optical coherence tomography for the detection of prostate cancer: 20 patients

In the cylindrical configuration, the B-scan is thus presented with a diameter of 10mm in diameter. The automatic pullback system scans over a trajectory of 54mm in ~5.4s, producing a 540-frame/B-scan dataset, resulting in a cylindrical scan of the prostate tissue of 54 mm x 10 mm, with an imaging depth of 2 mm limited by scattering [14].

Ex-vivo OCT measurements were performed in fresh tissue at the pathology department directly following radical resection. Four (in a small prostate) or six (in a large prostate) intravascular (IV)-catheters were placed in the prostate using the customized tool as described in previous work [25]. After removal of the insertion needle the C7 Dragonfly™ OCT probe was inserted into the in-situ transparent IV catheter and OCT measurements of the prostate tissue were acquired.

Histopathological evaluation
The prostate was sliced after 48 hours formaldehyde fixation. For slicing, the knife was guided through the OCT imaging trajectory (figure 2) [25]. Whole mount histopathological slides were produced and stained with hematoxylin and eosin according to the standard VUMC pathology protocol. The histological diagnosis was made by an expert uro-pathologist who was informed about biopsy and clinically relevant findings but blinded for the OCT results. Afterwards, all whole mount slides were digitized. The pathologist performed the marking and annotation of histological structures in the digitized whole mount slides using annotation software designed by our department. Nine histopathological tissue categories were annotated: cystic atrophy, regular atrophy, benign glands, stroma, inflammation, fat and malignancy Gleason pattern 3, Gleason pattern 4 and Gleason pattern 5.

Data analysis
Measurement of the histopathological OCT trajectory length was performed using the pathology annotation software after digital scale calibration to correct for prostate shrinkage after fixation. A starting point was defined at the border of the prostate. Total trajectory length and all distances from the beginning of the trajectory to marked histological structures were measured. This procedure was performed for the histological structures on both sides of the trajectory (ventral (painted red and yellow) and dorsal (painted blue and green)). The OCT scan creates a 360-degree view of the tissue. Histopathology was 2D and thus contained only information in one plane. Rotational matching was ensured by overlapping identical structures seen in histopathology and OCT, as is indicated by the arrows in figure 3. The urethra and outer shape of the prostate provided a rough estimation of orientation. Cysts were used for final precise orientation.

The B-scan locations were matched to the distances measured in the histological slides. Based on this information, a virtual overlay of the OCT scan over the histology was made. In this way, the histological classification of every single B-scan was deduced.
Figure 2: Customized prostate measurement and slicing tool

A) First, the prostate is fixed between two grids, ensuring parallel IV catheter insertion for measurements. 4 stabilizing needles in the middle ensure that the prostate does not move during slicing (red arrow in B).

B) OCT measurements are performed. Afterwards, the prostate is fixated for 48h in formalin.

C) The prostate is placed in the slicing device, with knife guiders surrounding the knife, ensuring that the prostate is sliced perfectly through the OCT imaging trajectory (D and E). The procedure is extensively described in earlier work [25].
Needle based optical coherence tomography for the detection of prostate cancer: 20 patients

Figure 3: Correlation of histology and OCT
A) Digitized H&E stained whole mount slide of the prostate. The two (horizontal) trajectories from the OCT measurements are clearly visible. The pathologist annotates the tissue types in different colors. The black arrow indicates an atrophic cyst. B) An OCT B-scan at the level of the atrophic cyst from figure A. The blue arrow shows the same atrophic cyst. The blue-yellow line corresponds with the longitudinal cross-section of the cylindrical dataset depicted in figure C. C) A longitudinal cross-section of the OCT scan, also used for final rotational correlation with histology. The blue arrow indicates the atrophic cyst, seen in A and B. D) 3D visualization of OCT images matched one-to-one with histopathology.
Qualitative data analysis

For each of the nine histological categories, locations were selected where opposing sites (ventral and dorsal to the imaging trajectory) were classified in the same category; we refer to these regions as the regions of interest (ROIs). On these locations, we assume that all tissue surrounding the catheter channel has the same histological characteristics. The corresponding OCT B-scans were saved to a database. Subsequently, 110 B-scans across the histological categories were selected by RK, randomized, and offered to two reviewers (BM and AS) blinded for the biopsy histology assessment and further clinical information. Prior to analysis, the two reviewers received a short training based on example images and a short qualitative description of the OCT images. Both reviewers independently assigned the B-scans to one of the nine histological categories for comparison to the histological classification.

Quantitative data analysis

Quantification of the optical attenuation coefficient was performed using custom-written code (Matlab 7.11.0 R2010b, The Mathworks Inc., Natick, MA, USA). The optical attenuation coefficients from the ROIs were obtained by processing the data according to steps described in Flowdiagram 1. The region of interest (ROI), is divided into fit regions (FR) with the following dimensions: (31*6 A-lines). Each separate A-line in a FR was laterally averaged, and attenuation coefficient ($\mu_{\text{OCT}}$) was fitted according to the method in appendix 1 yielding 1 $\mu_{\text{OCT}}$ per fit region, which correspond to a specific location in the histopathology. These values were used for analysis.

The process is described in detail in Appendix 1 and illustrated in figure 4. We used our experience from previous work to design the program [14, 16, 26].

In order to improve the data quality, a margin of error was included for the OCT–histopathology correlation process. Five B-scans, covering 0.5 mm in scan length, at the beginning and end of each ROI were deleted. The remaining ROIs had to contain at least six B-scans for final inclusion. The attenuation coefficients of these regions were stored in a database based on the histologic classification. The determined values for stroma, inflammation, and all malignancy categories were grouped per patient. In case of missing data of whole mount slides or OCT scans, the specific OCT scan/histology combination was excluded from the analysis.

Statistics

The results of the visually reviewed OCT B-scan were compared to the whole mount histopathology slides. Additionally, answers were grouped based on similar histological classification. Finally, all scores were grouped for benign and malignant histology. Sensitivity, specificity, false negative and false positive calculations were performed manually using a 2x2 table. The inter-observer agreement expressed in kappa was calculated.
Needle based optical coherence tomography for the detection of prostate cancer: 20 patients

Kappa (k) < 0 was defined as ‘poor agreement’, 0 to 0.20 ‘slight agreement’, 0.21 to 0.4 ‘fair agreement’, 0.41 to 0.60 ‘moderate agreement’, 0.61 to 0.8 ‘substantial agreement’, and above 0.81 ‘almost perfect agreement’.

Optical attenuation coefficients of malignancy Gleason patterns 3, 4 and 5 were grouped. With a Kolmogorov-Smirnov test, that data was tested for a normal distribution. A Mann-Whitney U test was performed for comparison of the attenuation coefficient of stroma and malignancy, using MedCalc v 15.8. A Kruskal Wallis test was performed to compare attenuation coefficients of stroma, inflammation, Gleason 3 and Gleason 4 individually. A p-value of ≤0.05 stated significance. Additionally, receiver operating characteristic (ROC) curve analyses were performed. The area under the curve (AUC) was calculated to determine test accuracy.

Figure 4: (A) First, tissue types were assigned by the pathologist, (B) Regions were selected with the same histopathology on both sides of the imaging trajectory, 5 B-scans on both sides of the ROI were taken as a safety margin and not included in the analysis. The B-scans in this region (dotted yellow line and example in (C) were further analyzed as described in the appendix (D). The fit starts 20 pixels after reaching tissue surface, the fitlength is 226 pixels. An average of the final 100 pixels was used as a measurement of the noise.

for every category.
RESULTS

Patient characteristics

Patient characteristics are described in table 1: Twenty consecutive patients were included. On these 20 prostates, 106 3D-OCT measurements were performed. The mean age was 65 years with a mean PSA of 11.5 ng/ml at the time of surgery. All patients except one underwent prostate biopsies with Gleason scores ranging from 3+3 to 4+4. One patient was included based on benign prostate hyperplasia trans-urethral resection results. Histologic specimen examination provided Gleason scores ranging from 3+4 to 4+5 and one benign specimen. Seminal vesicle invasion, extracapsular invasion, pelvic lymph node involvement and positive resection margins were present in two, six, one and five patients, respectively.

<table>
<thead>
<tr>
<th>Patients</th>
<th>n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation (years)</td>
<td>mean: 64.5 (range: 55 - 76)</td>
</tr>
<tr>
<td>PSA at operation (ng/ml)</td>
<td>mean: 11.5 (range: 2.9 -36)*</td>
</tr>
<tr>
<td>Biopsies (Gleason)</td>
<td>3+3 n=5</td>
</tr>
<tr>
<td></td>
<td>3+4 n=11</td>
</tr>
<tr>
<td></td>
<td>4+3 n=2</td>
</tr>
<tr>
<td></td>
<td>4+4 n=1</td>
</tr>
<tr>
<td>Total number of cores</td>
<td>mean: 9.6 (range: 6 - 15)</td>
</tr>
<tr>
<td>Number of cores positive</td>
<td>mean: 4 (range: 1 - 7)**</td>
</tr>
<tr>
<td>Specimen (Gleason)</td>
<td>0+0 n=1</td>
</tr>
<tr>
<td></td>
<td>3+4 n=7</td>
</tr>
<tr>
<td></td>
<td>4+3 n=11</td>
</tr>
<tr>
<td></td>
<td>4+5 n=1</td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
<td>n=2</td>
</tr>
<tr>
<td>Extracapsular invasion</td>
<td>n=6</td>
</tr>
<tr>
<td>Pelvic lymph node dissection</td>
<td>n=7</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>n=1</td>
</tr>
<tr>
<td>Resection margins positive</td>
<td>n=5</td>
</tr>
</tbody>
</table>

OCT and histology correlation

A total number of 52 whole mount histopathological slides were available. The OCT trajectories were visible in 50 slides. Malignancy was visible in 19 histology slides in 13 prostates. Twenty-one slides were damaged during production, resulting in areas with data loss. Matching of OCT scans with histology was achieved with high precision in 36 slides. The urethra and outer boundaries of the prostate contributed to the first rotational orientation. Mainly cysts but also other landmarks such as the urethra provided data for precise rotational orientation as can be seen in Fig. 3. Rotational inaccuracy was estimated at 10 deg.
Qualitative description of B-scans

The earlier selected representative OCT B-scans that were grouped per histopathological tissue type were reviewed for identification of unique marks on OCT. Figure 5 shows a representative B-scan per category. Review of the B-scans showed that part of the histopathology was well identifiable by OCT based on unique characteristics. Cystic atrophy (figure 5.1) was visually identified by cavities (>0.5mm), divided by septae. The content of the cavities appears opaque due to back-scattered light. Regular atrophy (figure 5.2) has smaller (0.1 – 0.3mm), dark, more grouped cavities than those found in cystic atrophy. Benign glands (figure 5.3) have even smaller, mostly grouped cavities (≤0.1mm). The cavities could be dark or opaque. Fat (figure 5.4) had a honeycomb structure, consisting of a unique pattern of bright stripes, alternated by dark dots.

The remaining histopathological classifications were more difficult to distinguish by OCT. Malignancy Gleason pattern 3 and 4 (figure 5.5 and 5.6) present as homogeneous tissue structures. High signal surrounding the probe and low signal in depth represented a low signal penetration (<1mm), probably due to a high cell density. Stroma (figure 5.7), similarly to malignant tissue, appeared homogeneous, but with an increased signal depth (≥ 1mm). Parallel ellipsoidal shaped lines on both sides of the probe were unique for stroma and probably caused by fibrotic tissue, yet this was not seen in all stromal B-scans. Inflammation (figure 5.8) had a homogeneous pattern with high cell density and signal penetration of approximately 1mm, with vague outer boundaries.

Figure 5: Histological tissue characteristics seen in OCT. The inner part of the OCT probe and the IV catheter in the middle are made black.
Qualitative blind assessment of B-Scans

Blind assessment of OCT B-scans was done by two reviewers (see table 2). The percentages represent the number of B-scans correctly scored by the reviewer. Grouping scores for categories with similar histology and intended treatment improved the results. Combining benign glands, cystic atrophy and regular atrophy resulted in scores of 100% and 88.9%. Combination of stroma and inflammation resulted in scores of 56% and 59%. Malignancy Gleason patterns 3, 4 and 5 resulted in correct scores of 79% and 88%. In particular, stroma and inflammation were most often misidentified, totaling n=17 and n=17 out of 41 for reviewer 1 and 2, respectively. Grouping malignant and benign scores gave an overall sensitivity and specificity for malignancy detection of 79% and 88% for reviewer 1 and 88% and 81% for reviewer 2, respectively. Negative predictive values were high (94% and 96% for reviewer 1 and 2 respectively). Positive predictive values were relatively low (66% and 57% for reviewer 1 and 2 respectively).

The inter-observer agreement on OCT images was calculated and resulted in moderate agreement between observers (weighted kappa of 0.50 for overall test values).

When test results were combined into similar groups with similar histology and intended treatment, benign cystic structures (benign/cystic and regular glands), benign stromal structures (stroma/inflammation), and malignant structures (Gleason pattern 3/4/5), there was substantial agreement between observers (Kappa of 0.64). When the

<table>
<thead>
<tr>
<th>Table 2: Results of visual OCT B-scan scoring.</th>
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<tbody>
<tr>
<td><strong>Scores:</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Benign glands</strong></td>
</tr>
<tr>
<td>15/16  94 %  11/16  69 %</td>
</tr>
<tr>
<td><strong>Cystic atrophy</strong></td>
</tr>
<tr>
<td>8/9   89 %  7/9   78 %</td>
</tr>
<tr>
<td><strong>Regular atrophy</strong></td>
</tr>
<tr>
<td>8/11  72 %  4/11  36 %</td>
</tr>
<tr>
<td><strong>Stroma</strong></td>
</tr>
<tr>
<td>16/31  52 %  13/31  42 %</td>
</tr>
<tr>
<td><strong>Gleason pattern 3</strong></td>
</tr>
<tr>
<td>2/5   40 %  3/5   60 %</td>
</tr>
<tr>
<td><strong>Gleason pattern 4</strong></td>
</tr>
<tr>
<td>9/19  47 %  6/19  32 %</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
</tr>
<tr>
<td>1/10  10 %  4/10  40 %</td>
</tr>
<tr>
<td><strong>Fat</strong></td>
</tr>
<tr>
<td>9/9   100 %  9/9   100 %</td>
</tr>
<tr>
<td><strong>Grouped scores:</strong></td>
</tr>
<tr>
<td><strong>Benign, cystic, regular</strong></td>
</tr>
<tr>
<td>36/36  100 %  32/36  89 %</td>
</tr>
<tr>
<td><strong>Stroma, inflammation</strong></td>
</tr>
<tr>
<td>23/41  56 %  24/41  59 %</td>
</tr>
<tr>
<td><strong>Malignancy 3,4,5</strong></td>
</tr>
<tr>
<td>19/24  79 %  21/24  88 %</td>
</tr>
<tr>
<td><strong>Malignancy detection (Gl 3/4/5):</strong></td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
</tr>
<tr>
<td>79 %  88 %</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
</tr>
<tr>
<td>88 %  81 %</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
</tr>
<tr>
<td>93 %  96 %</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
</tr>
<tr>
<td>65 %  57 %</td>
</tr>
</tbody>
</table>
results were grouped in two groups: benign structures (Stroma and Inflammation) and malignant structures (Gleason pattern 3/4/5), there was moderate agreement between observers (kappa of 0.57).

**Quantitative analysis – attenuation coefficient**

Automated attenuation coefficient calculations were performed for additional differentiation between stroma and malignancy. Twelve patients were included; eight patients could not be included in the analysis, as the tumor or inflammation was not scanned by OCT.

We noticed that the attenuation coefficient (malignant and benign) differed per patient. The attenuation coefficient was higher for malignancy than for stroma (5.0 mm\(^{-1}\) versus 4.6 mm\(^{-1}\)). This yields for most patients except four (table 3, figure 8). Data was tested for a normal distribution with a Kolmogorov-Smirnov test and normality was rejected in both benign and malignant data (p<0.0001). A Mann-Whitney U test showed a significant difference in attenuation coefficient (p<0.0001). Additional analyses with an ROC curve

**Table 3:** Overview of the mean attenuation (mm\(^{-1}\)) coefficient per histological category per patient. Only patients with malignant OCT data were included in the analysis. (standard deviation) [number of b-scan excluded/total number of b-scans (percentage of b-scans excluded)]

<table>
<thead>
<tr>
<th></th>
<th>AC stroma (mm(^{-1}))</th>
<th>AC inflammation (mm(^{-1}))</th>
<th>AC Gleason 3 (mm(^{-1}))</th>
<th>AC Gleason 4 (mm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.9 (1.0) [30/95 (32%)]</td>
<td>4.5 (0.8) [26/80 (33%)]</td>
<td>-</td>
<td>6.5 (1.1) [1/32 (3%)]</td>
</tr>
<tr>
<td>2</td>
<td>4.5 (0.8) [256/672 (38%)]</td>
<td>-</td>
<td>4.8 (0.8) [35/80 (44%)]</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>5.00 (0.9) [307/672 (46%)]</td>
<td>4.8 (0.6) [13/32 (41%)]</td>
<td>-</td>
<td>4.9 (0.7) [184/1136 (16%)]</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>4.6 (1.5) [57/128 (45%)]</td>
<td>-</td>
<td>-</td>
<td>6.1 (1.4) [2/48 (4%)]</td>
</tr>
<tr>
<td>7</td>
<td>4.6 (0.9) [78/208 (38%)]</td>
<td>-</td>
<td>-</td>
<td>4.6 (0.6) [89/384 (23%)]</td>
</tr>
<tr>
<td>8</td>
<td>4.5 (0.9) [256/672 (38%)]</td>
<td>4.5 (1.4) [8/16 (50%)]</td>
<td>-</td>
<td>5.6 (1.0) [2/16 (13%)]</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>4.8 (0.8) [98/400 (25%)]</td>
<td>-</td>
<td>-</td>
<td>4.6 (0.6) [15/48 (31%)]</td>
</tr>
<tr>
<td>11</td>
<td>4.8 (1.1) [55/96 (57%)]</td>
<td>-</td>
<td>-</td>
<td>5.2 (0.8) [37/128 (29%)]</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>4.3 (0.8) [93/144 (65%)]</td>
<td>-</td>
<td>6.1 (0.7) [1/48 (2%)]</td>
<td>6.1 (0.4) [4/16 (25%)]</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>4.6 (0.7) [48/112 (43%)]</td>
<td>-</td>
<td>-</td>
<td>4.9 (0.9) [182/640 (28%)]</td>
</tr>
<tr>
<td>18</td>
<td>6.4 (2.1) [61/128 (48%)]</td>
<td>-</td>
<td>-</td>
<td>5.4 (1.0) [68/2240 (31%)]</td>
</tr>
<tr>
<td>19</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>4.4 (0.8) [39/80 (49%)]</td>
<td>-</td>
<td>-</td>
<td>4.3 (0.8) [25/48 (52%)]</td>
</tr>
<tr>
<td>Mean</td>
<td>4.4 (0.9)</td>
<td>4.7 (1.0)</td>
<td>5.5 (1.0)</td>
<td>5.1 (0.9)</td>
</tr>
</tbody>
</table>
as accuracy measurement of the attenuation coefficient in discrimination of malignancy and stroma showed an area under the curve of 0.62. For a threshold value of 4.6 mm\(^{-1}\), the test has a sensitivity of 68% and a specificity of 49% (figure 6). Separate categories were analyzed with a Kruskal Wallis test (figure 7), which showed a significant difference in median attenuation coefficient between stroma, inflammation, Gleason 3 and Gleason 4 (4.6 mm\(^{-1}\), 4.1 mm\(^{-1}\), 5.9 mm\(^{-1}\), 5.0 mm\(^{-1}\) respectively) (p<0.05). Since attenuation coefficient strongly differed per patient, we also decided to perform a paired samples Wilcoxon signed rank test. The dot-and-line diagram is shown in figure 9. The paired samples T-test does not show a significant difference in optical attenuation coefficient between benign and malignant tissues in the prostate per individual patient p=0.17.
This study demonstrates that needle-based OCT can identify unique tissue patterns in benign and malignant prostatic tissue and is even able to distinguish benign tissue from malignant prostate (p<0.05). Visually, all types of prostatic tissue were identifiable on OCT, although malignancy, stroma and inflammation present as similar patterns and therefore it was more challenging to differentiate between those categories. Additional computed OCT analysis by means of the attenuation coefficient did contribute to discrimination of benign from malignant tissue in the prostate. However, when analyzed on a per patient basis, there was no significant difference in optical attenuation coefficient.
The unique aspect of this study is the one to one correlation of OCT and histopathology in prostate cancer. In previous work, the correlation of histopathology and OCT scans was a serious drawback [10, 14]. For this reason, a customized tool for OCT measurement and prostate slicing was developed. The feasibility of precise correlation of histopathology and OCT of the device was described in earlier work [25]. Using this method, we performed a single blind qualitative and quantitative accuracy study of OCT in a larger cohort of 20 patients ex-vivo.

Limitations on data matching
The correlation of 3D OCT scans and 2D histopathology was based on two assumptions. First, OCT probe rotation in the prostate tissue was approximated by corresponding structures seen in OCT and histology. The estimated rotational inaccuracy is 10 degrees, which we consider a small inaccuracy. Second, when both sides of the trajectory contained identical histological structures, it was assumed that all tissue surrounding the OCT probe was from the same histological category. Although this seems plausible, histopathology showed a large heterogeneity in prostatic tissue, therefore it might be possible that some areas contain tissue from another category. In order to minimize measurement errors, we identified five B-scans on both sides of the ROIs as the margin of error and excluded them from data analysis.

Because the OCT-probe only samples part of the tissue, we missed the tumor in 8 patients. For this reason, we did not include this OCT data in the visual assessment and we were not able to analyze the attenuation coefficient on malignancy in these patients.

Limitations in visual assessment
For visual assessment, the observers were affiliated with OCT but were not formally trained for detection of prostate cancer. Therefore, it is plausible that their assessment scores can be improved by OCT assessment training. This training could consist of an explanation of the unique tissue characteristics followed by an extended test of prostatic B-scans. This method has been successfully executed before in other imaging studies, e.g. using MRI to visualize prostate cancer, training significantly increased diagnostic accuracy [27, 28].

Limitations in quantitative assessment using the optical attenuation coefficient
It was remarkable that the optical attenuation coefficient for one category (for example Gleason 4) could differ within a patient with μOCT values ranging 1-2 mm⁻¹. This intra-patient variation might be because prostate tissue is heterogenous and is therefore challenging for the pathologist to delineate an area as benign or malignant. Moreover, the pathologist analyzes the whole mount prostatic histology slide using a 40 X microscope.
and delineates this using software on a digital lower resolution image of the same slide, a process prone to errors. We partially corrected for this by removing 5 B scans from each side of each ROI as described earlier. Yet, it is also known from histological studies that healthy prostate tissue differs between patients and therefore tumor tissue might differ between patients as well [29]. Furthermore, a fair amount of fits (approximately 30%) was excluded from the analysis because the calculated fit did not exactly match the measured data. Most likely, these specific regions of the prostate are too heterogeneous for a correct fit, e.g. cysts, but they might still have a clinical significance. Technology such as automated texture analysis and pattern recognition, could contribute to solve this problem and could increase the performance of OCT for prostate cancer detection [30]. Furthermore, when more data is available, convolutional neural networks could be trained to perform the analyses on the OCT data, as it now starting in conventional histopathology [31].

**Perspective to other work in the field**

Ex-vivo application of OCT on the human prostate was first described in the year 2000. 2D cross sectional OCT scans were generated of specimens after radical prostatectomy [32]. It was claimed that OCT could distinguish malignant from benign prostate tissue on the basis of architectural differences in the tissue. OCT has also been described for prostatic nerve identification in order to spare them during radical prostatectomy experiments [33, 34]. In 2009 Dangle et al. evaluated surgical margins, seminal vesicle invasion and capsular invasion with OCT ex-vivo in prostates after radical prostatectomy. They found that OCT overestimated the amount of margin involvement, but the NPV was high. For surgical margins on OCT sensitivity, specificity, PPV and NPV was 70%, 84%, 33%, and 96%, respectively [35]. Recently, a study by Lopater et al described the initial application of Full Field OCT for the detection of prostate cancer in prostate biopsies. This ex-vivo OCT imaging method approaches the resolution of traditional histological slides with a resolution of about one micrometer. The images were scored solely by architectural structures and solely in the 2D setting, sensitivity, specificity, PPV and NPV values were 63%, 74%, 55.5% and 80% respectively [36]. In our study, sensitivity (79% and 88%) and specificity (88% and 81%) for malignancy detection were higher than in these previous studies. PPVs (66% and 57%) and NPVs (94% and 96%) were higher or comparable to these previous studies. Although PPVs were higher than previous studies, they were still considerably lower than the NPVs. This indicates that OCT, as it is investigated here, can be a good test to exclude disease in the prostate. The advantage of the St Jude C7-XR™ Intravascular Imaging System is that it is commercially available and applicable in a sterile environment. Consequently, the application of this OCT system in the outpatient clinic or even in a surgery setting is relatively easy. The small probe diameter even allows for in vivo insertion in the prostate. Images are acquired in 3D, which increases the amount
of information substantially when compared to 2D histopathology. Needle based OCT lacks the spatial resolution to function as a stand-alone diagnostic modality in prostate cancer. However, it can make the process of conventional histopathology faster and possibly more accurate. Since OCT results are quantifiable, it can reduce interrater variability, which is high for conventional histopathology [37].

CONCLUSION

This study validates one to one correlation of histopathology and OCT by using the uniquely designed prostate slicing device in a cohort of 20 patients. Correlation showed that most histological tissues have a unique pattern and therefore could be visually identified on OCT, such as cysts, lines, view in depth or signal intensity. The abilities of OCT for prostate cancer identification were explored and qualitative visual analysis confirmed the hypothesized high cell density of malignant tissue. In addition, the optical attenuation coefficient contributes to the differentiation between stroma and malignancy, although a per-patient analysis did not show a significant difference. These findings may serve as a basis for an in-vivo study combining OCT and prostate biopsy histopathology; allowing comparison of both tests and exploring the clinical potential of OCT in digital pathology of the prostate.

DISCLOSURES/ CONFLICT OF INTEREST

None of the authors declares any conflict of interest

ACKNOWLEDGEMENTS

This study was funded by an unrestricted research grant from the Cure for Cancer Foundation.
APPENDIX: FITTING THE OPTICAL ATTENUATION COEFFICIENT

Quantification of the optical attenuation coefficient was performed using custom-written code (Matlab 7.11.0 R2010b, The Mathworks Inc., Natick, MA, USA). Methods were derived from our previous work [14, 16, 26]. First, OCT amplitude data was loaded into the software. Isolation of tissue-related data from the original data set was achieved by a succession of image processing steps applied to all B-Scans. First, low SNR regions were excluded by applying a pixel value threshold on the amplitude data. Next, to remove the catheter from the B-Scans, an algorithm utilizing region connectivity as well as a priori knowledge about the catheter-tissue geometry was implemented. Following this, a 5 x 5 Gaussian low pass filter was applied to the catheter-free images; this step served to improve performance of the ensuing edge detection using the Sobel method. The thus detected tissue edge was then smoothed further by carrying out local regression using weighted linear least-squares (assigning lower weight to outliers and zero weight to data outside six mean absolute deviations) and a 2nd degree polynomial model. OCT amplitude data of the prostate tissue was isolated from the original B-Scan by selecting all data below this smoothed edge. Finally, this data was straightened and then divided into fit regions (FRs) with the following dimensions: 31 x 6 x 226 pixels in the fast axis, slow axis and depth (located 20 pixels below the tissue edge), respectively. These individual FRs were then laterally averaged, yielding a single average A-line for each FR. Subsequently, a FR-specific attenuation coefficient (μOCT) was determined by non-linear least squares fitting the following formula to this average A-line: 

\[ \langle A(z) \rangle = t(z) \cdot h(z) \cdot A \cdot \exp(-\mu_{OCT}(z-z_0)) + \text{noise}. \]

\( \langle A(z) \rangle \) is the averaged OCT amplitude in depth, \( z \) is the position in depth, \( z_0 \) is the position of the tissue boundary, \( A \) and \( \mu_{OCT} \) are free running parameters (amplitude and attenuation coefficient, respectively). The fit always starts 20 pixels below the tissue surface to ensure the absence of tissue edge reflection. The noise is defined as the average of the last 100 pixels of the data. The system dependent parameter \( t(z) \) (describing the confocal point spread function) is defined as:

\[ t(z) = \frac{1}{\sqrt{\left( \frac{z-z_f}{znZ_{R0}} \right)^2 + 1}}, \]

where \( z_f \) is the position of the focus in depth, \( Z_{R0} \) is the Rayleigh length, and \( n \) is the refractive index of the medium. The sensitivity roll-off \( h(z) \) is defined as:

\[ h(z) = \text{sinc} \left( \frac{\pi}{2} \cdot \frac{z}{z_{\text{max}}} \right) \cdot \exp \left( -\frac{n^2 \cdot s^2}{16 \cdot 1n(2) \cdot \left( \frac{z}{z_{\text{max}}} \right)^2} \right). \]

Here, \( z_{\text{max}} \) is the maximal imaging depth of the OCT system and \( s \) is the ratio between the spectral resolution to the sampling interval. The contribution of the confocal point spread function and the sensitivity roll-off were determined by fitting the equation for \( \langle A(z) \rangle \) to the OCT amplitude of a sample with a low concentration of Intralipid (0.003%) using 4 different catheters, for
which negligible scattering is assumed, and \( Z_{r0} \) and \( s \) were the free running parameters [38, 39]. The median values for \( Z_{r0} \) and \( s \) are 0.73 mm and 1.4 respectively which corresponds to reported values [40, 41]. After fitting, all fits were judged by an experienced observer and non-matching fits (e.g. because of a cyst in the data) were excluded from the analysis. In this way, only accurate representations of the optical attenuation coefficient were included in the analysis. Finally, all obtained attenuation coefficient values were multiplied by 1.4 (refractive index for tissue) yielding values per mm [42].
REFERENCES:

Part III

Discussion and summary
Chapter 12

General discussion and future perspectives
General discussion and future perspectives

FIRST AIM OF THE THESIS

Curative treatment of prostate cancer is currently performed through radical prostatectomy +/- lymphadenectomy or radiation (external beam or brachytherapy) in combination with short, or long-term androgen deprivation therapy. These treatment modalities do have major side effects, such as loss of erectile function or incontinence and thus can have a significant impact on quality of life in prostate cancer patients. Focal therapy can offer an alternative minimal invasive treatment option in patients with low-risk and especially intermediate-risk prostate cancer. It aims to achieve oncological control and reduction of anxiety (of living with a cancer) on the one hand, without the side effects of radical treatment on the other hand and preserving functional outcome. The first aim of this thesis was to advance the development and standardization of imaging and treatment protocols for focal therapy and prostate cancer imaging for focal therapy planning, guidance and follow-up (chapters 2 - 7).

Current concerns about focal therapy

Focal therapy in organs aiming to prevent morbidity of side effects of radical treatment is not a new concept. The best example in which it is already applied for a long time is breast cancer. Three decades ago, imaging of breast tumors had significant limitations and was unreliable for organ-preserving surgical treatments. Scoring protocols for breast x-ray imaging and, at a later stage, for breast MRI were developed through formal attempts to establish agreement among experts on areas of uncertainty [1-3]. These attempts resulted in reduced inter-observer variability and improved the positive predictive value of pathology from breast biopsies, which paved the way for lumpectomy (focal therapy of the breast). With the development of the BI-RADS (Breast Imaging - Reporting and Data System), together with other advancements, breast cancer imaging improved allowing breast preserving treatment of breast cancer [4, 5]. Nowadays, focal therapy is the most prevalent treatment for breast cancer, with an oncological survival rate similar to that obtained with radical treatment, but with drastically improved quality of life for breast cancer patients [6]. Focal therapy is also an upcoming treatment strategy in urological organs, such as kidney and testis. An example of this is the introduction of the partial nephrectomy for smaller kidney tumors, but also a variety of other focal therapies have been introduced for patients who are considered unfit to undergo surgery such as cryoaablation or radiofrequency ablation of kidney tumors [7].

Focal therapy is also an appealing treatment strategy for men with localized prostate cancer. However, there are certainly some important concerns with regard to focal therapy of the prostate that need further investigation:

• How to deal with multifocality of prostate cancer? There are theories that only the largest tumor with the highest Gleason score in the prostate (“index lesion”) will me-
tastasize. However, recent studies show that other “less significant” tumors still have to be actively monitored to prevent upgrading and becoming clinically significant [8, 9] (not addressed in this thesis).

- Prostate imaging needs to be optimized for focal treatment planning, guidance and follow-up (chapters 2, 3, 4, 6).
- So far, there is no standardization of follow-up after focal therapy of the prostate. There are some issues that make this a difficult subject. PSA, for example, will rise, instead of decline in the first few days after focal therapy. Contrary to radical prostatectomy, PSA will not reach undetectable levels. It rather reaches a nadir after several months, comparable to radiotherapy (external or brachytherapy). This makes PSA unreliable as a marker for follow-up after focal therapy. MpMRI is currently the most suitable imaging modality for follow-up after focal therapy. However, there is no consensus on interpretation and optimal prostate imaging following focal therapy. What does the ablated lesion look like and how does it change over the course of time? And even more important, what does a recurrence look like? Also PI-RADS is not standardized for follow-up after focal therapy (chapters 5 and 7).
- Focal therapy has only been proven effective mostly in low-risk prostate cancer [10]. However, it was already known that active treatment has no survival benefit over the active surveillance in low-risk patients [11-13]. It is, therefore, especially important that focal therapy is investigated in the intermediate-risk groups (ISUP 2 and 3) to proof its efficacy (not addressed in this thesis).
- Only small size exploratory studies have been conducted in prostate focal therapy. It is essential that future studies are performed in a standardized way in order to be able to compare data on a larger scale in the future.

Prostate imaging

Chapter 2 is a narrative review of imaging modalities for patient selection, treatment guidance and follow-up after focal therapy. We concluded that state-of-the-art imaging in all phases of focal therapy is essential for treatment safety. Enhanced transrectal ultrasound (TRUS) imaging and mpMRI of the prostate are the most widely investigated technologies. In chapter 3 and chapter 4 we concluded that mpMRI is the optimal approach to achieve the objectives needed for patient selection and follow-up in focal therapy. However, mpMRI has to be made on a high-quality machine and using the correct protocols (3T with or without endorectal coil or 1.5 with endorectal coil) and judged by an experienced (uro-)radiologist. Structured and standardized reporting of prostate mpMRI is essential. However, when mpMRI outcome is compared to Gleason score, the technology was not accurate enough to consistently determine tumor aggressiveness. Template guided saturation biopsies to select patients for focal therapy can be discarded if a high quality mpMRI is available, however, suspicious lesions should
always be confirmed by (targeted) biopsy. In this rapidly developing field, most research is based on expert opinion and reported only from centers of excellence. We concluded that, therefore, large standardized studies are essential. Several years after publication of these chapters, the results of the PROMIS trial, the PRECISION trial and 4M trial are being implemented in clinical practice [14-16]. For example, following the EAU guidelines, a prostate mpMRI as a first investigation should be made when prostate cancer is suspected, followed by a targeted prostate biopsy, since 2019. It is also now recommended to use PI-RADS v.2.0 as a guideline for mpMRI acquisition and interpretation, and finally, to use pre-biopsy mpMRI data as staging information. These changes will have an impact on patient selection and inclusion in focal therapy protocols.

**PI-RADS V.2.0**

In 2015, The PI-RADS v.2.0, an improved version of PI-RADS v.1.0, was developed to simplify and further facilitate standardization of prostate mpMRI. In chapter 6 we concluded that the new version of PI-RADS (v.2.0) has a moderate inter-observer agreement for readers of varying experience. Similar levels of inter-observer agreement were reported for the original PI-RADS v.1.0. Accuracy for tumors in the peripheral zone was comparable to the accuracy of tumors in the transition zone. DCE MR imaging did not contribute to the diagnosis. PI-RADS is an important standardization tool for reporting mpMRI results. However, the results of this study showed that, like the first version of PI-RADS, the second version is only moderately reproducible among readers. On average, it shows a good correlation with histopathologic results and high sensitivity for clinically significant disease, but specificity is low. Our data suggest that PI-RADS will evolve as more experience is gained. Other studies regarding PI-RADS v.1.0 showed similar levels of agreement. However, we expect the agreement to increase with training of uro-radiologists. During the work on this thesis, an adapted version of PIRADS v.2.0 was published in 2019, PIRADS v.2.1. It is the anticipation of the consensus group that inter-reader variability numbers will improve and mpMRI interpretation will be simplified with this latest version [17].

**Follow-up after focal therapy and detection of recurrences**

In the implementation process of focal therapy as a standard of care, standardization of patient follow-up is necessary as well. In chapter 5, the results of a Delphi based consensus meeting on follow-up are discussed. A specific roadmap was provided for the middle- and long-term follow-up of currently available focal therapies. Until now, there is little evidence of how follow-up after focal therapy should be performed. Several consensus projects and studies about this topic have been performed since and are summarized by Tay et al. [18]. However, the implementation and standardized follow-up is still lacking.
In chapter 7, we showed that mpMRI with an endorectal coil at 3 Tesla – transrectal ultrasound fusion guided biopsy was able to identify local recurrence at low serum PSA levels in patients with rising PSA following radical prostatectomy. Our results suggest that mpMRI can detect recurrent lesions after radical prostatectomy, even at low PSA levels. The study showed that the TRUS/MRI fusion device is very accurate, and that it can even target very small lesions to obtain an accurate biopsy. These results can help improve salvage treatment outcomes. However, a critical note is that with the development of PSMA PET [19, 20] and nano-MRI [21], a recurrence can be detected even earlier at lower PSA levels (<0.2 ng/mL). These technological advancements in imaging are currently intensively studied. The general concept nowadays is that salvage treatment should start as early as possible, the use of histology is not required before treatment [22, 23]. Outside of this thesis, we investigated changes in the prostate after focal therapy. A teaching abstract on this topic was submitted to the RSNA annual meeting in 2014 and received a certificate of merit. Figure 1 is a figure from this abstract. It shows a Gleason 3+4 lesion in the prostate before and one year after focal laser ablation. First, lesions tend to swell (first 1-3 months), and after a while the ablated lesion resolves, which is shown as a dent in the prostate capsule, where the lesion used to be.

**Figure 1:** 75-year old man with a serum PSA of 7.33ng/ml with Gleason 3+4 cancer in the left mid-base anterior transitional zone (arrows in the baseline mpMRI) (top row). MRI guided focal laser therapy was performed for this lesion. One year follow up mpMRI shows no evidence of residual-recurrent cancer in the treated area. Moreover, the treated lesion appears a defect area in the left mid anterior transitional zone (bottom row). Biopsy of this treated region was benign.
SECOND AIM OF THE THESIS

Optical Coherence Tomography is an optical technology that provides minimal invasive and microscopic imaging of structures in biological tissues. It acquires 3D digital images in high (almost cellular) resolution. The digital images can be quantified objectively in several ways that can aid in diagnosis of diseases. It has the potential to better identify patients qualifying for focal therapy. The second aim of this thesis was to explore Optical Coherence Tomography as a novel imaging modality for prostate tissue and detection of prostate cancer (chapters 8 - 11).

Pitfalls of conventional pathology are time investment, labor intensity and there is substantial inter-rater variability. A technology such as needle-based OCT has the potential to make diagnosis faster, less labor intensive, more accurate, cheaper, and create a possibility of combining diagnosis and focal treatment in one session (e.g. when we use a fiber-based probe for OCT diagnosis and later the same fiber based probe for focal laser ablation of the prostate). We were the first to apply needle-based OCT in prostate tissue. Furthermore, we were the first to quantify our results (in a simple way) by means of the optical attenuation coefficient. In order to do so we had to solve the following issues:

- For quantitative analyses, a customized computer program had to be designed to perform automated analyses of the optical attenuation coefficient. (chapter 8)
- The OCT system had to be calibrated and tested in prostate tissue. (chapter 8 and 9)
- The problem of very precise histopathology matching had to be solved in order to perform adequate histopathology matching and accurately correlate OCT images to histopathology. (chapter 10)
- The technology has to be validated qualitatively and quantitatively in a large number of prostate cancer OCT measurements. (chapter 11)

Calibration of the OCT system

Chapter 8 demonstrates the feasibility of needle-based 3D quantitative 1300 nm OCT in prostate tissue as a first step towards objective and real-time digital diagnosis of prostate cancer. In this chapter, the in-house designed automated analysis software was explained, as well as the method of calibration of the OCT system and analysis software. Fully automated attenuation coefficient analysis was performed over the full OCT pullback. The method of tissue measurement and analysis was tested and shown in one prostate.

Pilot study

Functional needle based OCT of the prostate demonstrates a significant difference in the optical attenuation coefficient between healthy and malignant prostate tissue. This was shown in chapter 9, where the optical attenuation coefficient was significantly higher in malignant tissue compared to benign prostate tissue. Further studies are required to
validate these initial results in a larger group of patients with a more tailored histopathol-
ygy matching protocol.

Precise histopathology matching
Matching OCT one-to-one with histology was described in chapter 10. By successfully
designing and applying a customized tool to process radical prostatectomy specimens,
the co-registration of whole mount histology sections to fresh tissue OCT pullback mea-
surements was achieved. The methodology described in this work is crucial for validation
of the results of OCT imaging studies with histology and can easily be applied in other
solid tissues as well, for example, lung, kidney, breast and liver. Our method will help
improve the efficacy of OCT in cancer detection and staging in solid organs.

Validation of the technology in 20 patients
In chapter 11 we validated the one to one correlation of histopathology and OCT. This
was done by using the uniquely designed prostate slicing device from chapter 10 in a
cohort of 20 patients. Correlation showed that most histological tissues have a unique
pattern and could, therefore, be visually identified on OCT, such as fat, stroma, atrophy
and cysts. The abilities of OCT for prostate cancer identification were explored and
qualitative visual analysis confirmed the hypothesized high cell density of malignant tis-
sue. The optical attenuation coefficient contributes to the differentiation between stroma
and malignancy. However, a per-patient analysis did not show a significant difference
between benign (stroma) and malignant (Gleason grade 3 and Gleason grade 4) tissue).
These findings served as a basis for an in-vivo study combining OCT and prostate biopsy
histopathology; allowing comparison of both tests and exploring the clinical potential of
OCT in digital pathology of the prostate. In 2019 we published the first OCT measure-
ments of the prostate in-vivo [24]. There were no adverse events. A biopsy was taken
from the same site as the OCT images and showed similar results as in the ex-vivo setting
(figure 2).

FUTURE PERSPECTIVES

Future perspectives on prostate MRI
During the years of work on this thesis, the quality of mpMRI and with that the detection
rates of prostate cancer improved drastically [25]. Not only imaging protocols and equip-
ment improved in quality, also radiologists developed standardized protocols of mpMRI
reading and reading became more accurate and reproducible. Smart technologies
like mpMRI –TRUS fusion improved diagnosis of prostate cancer and made it less time
consuming compared to for example transperineal mapping biopsies or MRI guided biopsies [26].

Because of these improvements in imaging technologies, focal therapy could be an increasingly more attractive option for patient with intermediate-risk prostate cancer. Advances in imaging with biological markers may be able to take the leap necessary to visualize lesions that can be treated with focal therapy. An example is prostate-specific membrane antigen (PSMA). Nowadays PSMA-PET CT scans are used for staging only, but one can imagine a role in the primary detection of the index lesion. A recent (however retrospective) study showed that 68-Ga PSMA PET/CT reflects radical prostatectomy histopathology better, compared to mpMRI considering multifocal and bilateral disease [27, 28]. We can only imagine the levels of accuracy when PSMA-PET MRI will be investigated.
In theory, PSMA based technology for primary localization of prostate cancer can be promising. However, it is just at the exploratory stage, with little scientific evidence yet. There is still little known about follow-up imaging after focal therapy of the prostate. Since PSA is not a good indicator following focal therapy, follow-up has to be (at least partially) image-based and should be aimed at finding recurrent lesions. However, there is no substantial evidence about follow up after focal treatment and how the prostate looks at different time intervals after treatment using different ablation techniques. It is difficult to develop a standardized scoring system for this, since different ablative energies cause different lesions in the prostate.

Focal therapy in prostate cancer remains controversial for several reasons. The guideline committee of prostate cancer of the EAU gave a critical note last year on focal therapy. The difficulty of detecting all cancerous areas in the prostate is the main issue. Moreover, clinical effectiveness in the intermediate-risk group is not proven, only in low-risk patients. Patients should, therefore, only be treated within the context of a clinical trial with predefined criteria. The ESUT position, however, is more positive. “Focal therapy is a new option in the armamentarium of prostate cancer. Technological improvements and the development of novel energy sources should make it possible to treat lesions with even greater precision, while limiting the risk of side effects. In the future, we should probably be able to effectively expand the indications of this technique to include more aggressive tumors.”

New prospective studies of focal therapy on intermediate-risk patients are now starting to be published and randomized trials are initiated. Just recently, Guillaumier et al. published a multicenter 5 years follow-up study on HIFU in 505 patients. For the whole patient cohort, metastasis-free, cancer specific and overall survival at 5 years were 98%, 100% and 99%, respectively. We are awaiting the results of more prospective trials and suspect the results of focal therapy will improve while implementing the improvements in prostate cancer imaging.

Future perspectives of OCT in prostate tissue

In this thesis we demonstrated that needle based OCT with automated imaging analysis is feasible in the prostate. Calculation of the optical attenuation coefficient is one way of automated image analysis, but a wide variety of methods is possible. In recent years, major advancements in image analysis software have been achieved. Maybe the best example of image analysis is the facial recognition software nowadays on most mobile phones and laptops and the image analysis software that is used in self-driving cars. Software can almost immediately recognize a face and find the matching name of that person on the internet or in a database. The software is so accurate that a human face can be used as a password for a mobile device. Software packages (computer aided diagnosis or CAD) for analysis of histopathology slides and optical biopsy technologies
such as OCT are currently being developed [34, 35]. In literature, we see a trend towards
the development and use of neural networks, in which computers can be fed a known
training set of i.e. digital pathology and learn to see whether a new sample is either
benign or malignant [36]. As Gleason grading is quite complex, inter-rater variability
between pathologists is considerable. Studies between experienced pathologists in
grades grading Gleason grade is at the highest “moderate” with a kappa value of only 0.39
[37]. Therefore it is expected that automated image analysis can improve the diagnosis
of prostate cancer by making it more objective.

However promising, CAD systems and deep learning based neural network are not yet
ready for widespread clinical application. One of the main issues that has to be tackled,
is the enormous amount of digital data that has to be stored and analyzed, which is a
computationally challenging issue. Today, storage and analysis is expensive and very
time consuming, but rapid increase in data storage capacities, computational power and
smart digital learning code will undoubtedly solve these problems in the near future [38].

Most OCT devices are easy to use in a clinical setting. The advantage of the St Jude
C7-XR®™ Intravascular OCT Imaging System is that it is commercially available and ap-
licable in a sterile environment. Consequently, the application of this OCT system in the
outpatient clinic or even in a surgical setting is relatively easy. The small probe diameter
allows for in-vivo insertion into the prostate through a needle [24]. Images are acquired
in 3D, which increases the amount of information substantially when compared to 2D
histopathology. Unfortunately, today’s needle based OCT lacks the spatial resolution to
function as a stand-alone diagnostic modality in prostate cancer. This was one of the pit-
falls in chapter 11. However, in March 2019, Gardecki et al. described the development
of a micro-OCT system that has a spatial resolution of one µm and can be implemented
into a needle to enable optical biopsy of the prostate [39]. With the required spatial
resolution, OCT can make the process of conventional histopathology faster and possi-
bly more accurate.

Another way to increase the accuracy of OCT, is to combine it with other optical imaging
technologies. Recently, the first results were published on using ex-vivo Optical Coher-
ence Elastography (OCE) for the detection of prostate cancer. With this technology, also
the stiffness of the tissue can be evaluated qualitatively and quantitatively in 3D, with
micrometer resolution [40]. OCT technology will evolve over time using smaller probes
and systems with better resolution [39] combined with automated software tools like
elastography, attenuation polarization and speckle analysis [41] and automated pattern
recognition integrated [42]. It could be combined with other optical technologies such as
spectroscopy [43]. In this way, information about the tissue’s metabolic properties, which
is impossible with conventional histology will be possible to obtain. Therefore, multipa-
rametric OCT might eventually reach similar or perhaps even better results compared to
conventional histology. The technology has the potential to be faster, less invasive, more
objective, and even more accurate than conventional histopathology. It can provide real time, high resolution dynamic information on living tissue. Furthermore, because the OCT images provide 3D data instead of the conventional 2D histopathology, more spatial information is offered. Finally, the information obtained by an OCT platform will be quantifiable and, therefore, less vulnerable for interpretation errors. These factors will reduce the high inter-observer variability that is associated with conventional histopathology.

Finally, further developments could result in a dual modality one-step diagnosis and focal treatment system for intermediate-risk prostate cancer. Multiparametric OCT can help to accurately localize prostate cancer lesions and guide focal treatment directly into the diseased part of the prostate. An example is Focal Laser Ablation, a well-known form of focal therapy [44]. We can imagine a system in which laser treatment is delivered through the same fiber-based probe as the diagnostic fiber, in a one–needle-dual-fiber system.
REFERENCES


General discussion and future perspectives


Chapter 13

Summary & Nederlandse samenvatting
SUMMARY

Prostate Cancer is among the leading causes of cancer-related death in men. Side effects of radical treatments (erectile dysfunction and urinary incontinence) have a clear impact on the quality of patients’ lives. In selected patients, focal therapy can be applied. With this concept, treatment is directed only at the tumorous part of the prostate, leaving the remaining prostate unharmed, and, therefore, reducing the side effects of radical treatments. Focal therapy is a relatively new, experimental form of treatment for a highly selected group of patients. Accurate localization of the target lesion in the prostate gland and planning of treatment before starting focal therapy is of paramount importance.

The most widely investigated and promising imaging technology for the prostate is multiparametric MRI (mpMRI). As with any new form of diagnosis or treatment, it is essential to develop guidelines and/or standard operating procedures: Guidelines for the detection of localized prostate cancer, but also for patient selection, treatment guidance, and patient follow-up in focal therapy. Only with uniform high-quality data acquisition, valuable data can be generated to support or reject the use of new forms of treatment or imaging.

The suspicion of prostate cancer by rise in prostate specific antigen (PSA), on prostate imaging or digital rectal examination must always be confirmed by prostate biopsies. A relatively new imaging technology in the field of oncology is Optical Coherence Tomography (OCT). Using back-scattered light, it can produce high-resolution images of tissue at even cellular levels (optical biopsy).

The objectives of this thesis were, first, to advance the development and standardization of imaging and treatment protocols for focal therapy and prostate cancer imaging for focal therapy planning, guidance and follow-up (chapters 2 - 7), and second, to explore the role of OCT as a novel imaging modality for prostate tissue and detection of prostate cancer and thus improving patient selection for focal therapy (chapters 8 - 11).

As an introduction to this thesis, we assessed the current state of imaging technologies for prostate cancer. Chapter 2 provides a summary of novelties in mpMRI and ultrasound imaging technologies for patient selection for focal therapy, treatment guidance and follow-up in 2012. It underlines that standardization of conduct in imaging for focal therapy in prostate cancer is essential for development of uniform data and guidelines.

The process of standardized data and guideline formation starts with expert opinion. Chapter 3 describes a Delphi consensus project among radiologists, urologists and basic researchers from Europe and North America. The goal was to identify the optimal requirements for performing mpMRI, and the current status of optimally performed mpMRI to (i) determine focality of prostate cancer (e.g. localizing small target lesions of ≥0.5 mL), (ii) to monitor and assess the outcome of focal ablation therapies, and (iii) to identify the diagnostic advantages of new mpMRI methods. Consensus was reached
on most key subjects: The panel concluded that mpMRI is the optimum approach to achieve the selection objectives needed for focal therapy, if made on a high-quality machine (3T with/without endorectal coil or 1.5T with endorectal coil) and judged by an experienced radiologist. State of the art mpMRI is capable of localizing small tumors for focal therapy. However, structured and standardized reporting of prostate mpMRI is of vital importance. The panel finally concluded that template-guided saturation biopsies are no longer necessary when a high-quality state of the art mpMRI is available; however, suspicious lesions should always be confirmed by (targeted) biopsy.

Advancing on the knowledge obtained in chapter 3, we performed a larger and more structured consensus project in chapter 4. The goal of the project was to define the role of mpMRI for treatment planning, guidance and follow-up in focal therapy for prostate cancer. An online questionnaire was circulated according to the Delphi method. A face-to-face consensus meeting followed three rounds of questions that were sent to a 48-participant expert panel consisting of urologists, radiologists and engineers. Consensus was reached in 41% of all key subjects. Patients selected for focal therapy should have biopsy-proven prostate cancer. Biopsies should ideally be performed after mpMRI of the prostate. Standardization of imaging protocols is essential and mpMRIs should be read by an experienced radiologist. In the follow-up after focal therapy, mpMRI should be performed after 6 months, followed by a yearly mpMRI. mpMRI findings should be confirmed by targeted biopsies before re-treatment.

Since focal therapy of prostate cancer is a new concept, little is known about patient follow-up after treatment. Standardization of follow-up is imperative for the creation of uniformly comparable data in clinical trials. Therefore, we conducted a structured consensus project in chapter 5 on this topic. This project was also conducted according to the Delphi method. The topics discussed were: (1) general, (2) biopsies, (3) PSA, (4) digital rectal examination, (5) imaging, (6) quality of life (QoL) and (7) registration and pooling of data. The project was concluded with a face-to-face meeting in which the following conclusions were formulated: The follow-up duration after focal therapy should be a minimum of 5 years. The following modalities should be included in assessing post-treatment outcomes: mpMRI and biopsies, assessment of erectile function, QoL, urinary symptoms and incontinence. A systematic 12-core transrectal ultrasound (TRUS) biopsy combined with 4–6 targeted biopsy cores of the treated area and any suspicious lesion(s) should be performed after 1 year, and thereafter only when there is suspicion on imaging. The ideal way to perform targeted biopsies is to use TRUS–MRI fusion technology. PSA should be performed for research purposes, in the first year every 3 months, and after the first year every 6 months. mpMRI is the optimal imaging modality for follow-up after focal therapy. It should be performed at 6 months and at 1 year following treatment; after the first year post-treatment, it should be performed every year until 5 years following treatment. All data should ideally be pooled in a common global database.
In 2016, the Prostate Imaging Reporting and Data System (PI-RADS) steering committee published PI-RADS v.2.0 guidelines for the conduct and interpretation of prostate mpMRIs. In Chapter 6, we assessed the accuracy and inter-observer variability of this new PI-RADS v.2.0 in a biopsy naive population. 101 patients with elevated prostate-specific antigen levels underwent mpMRI of the prostate and subsequent TRUS–MRI fusion–guided biopsy. Suspicious lesions detected at mpMRI were scored by five readers who were blinded to pathologic results by using to the newly revised PI-RADS v.2.0. Results for 87 (54%) lesions were positive for prostate cancer. Scores derived from the use of the revised version of PI-RADS are concordant with pathologic results for lesions in both the peripheral zone and the transitional zone of the prostate (Kendall $\tau$ for peripheral zone lesions, 0.51 [P < 0.0001] and for transitional zone lesions, 0.45 [P = 0.0008]). None of the 12 lesions that were given a PI-RADS score of 2 showed clinically relevant disease at transrectal US–MR imaging fusion–guided biopsy; in other words, no high-grade lesions were missed. Moderate interreader agreement was shown for this PI-RADS v.2.0 (multireader $\kappa$ for overall PI-RADS score, 0.46), which is similar to the results of studies to assess the previous versions of PI-RADS.

Following radical treatment, patients may develop a local recurrence of their prostate cancer. Early detection and treatment of recurrence improves the outcome of salvage treatment. Chapter 7 investigates the use of mpMRI/TRUS fusion guided biopsy to detect recurrent prostate cancer after radical prostatectomy at an early stage. Patients with rising PSA levels after radical prostatectomy who had no known evidence of distant metastases underwent mpMRI at 3 Tesla, and subsequent MRI-TRUS fusion biopsy with cognitive assistance. The average lesion diameter on mpMRI was 1.12 cm (range: 0.40–2.20 cm). All suspicious lesions (16/16, 100%) were positive on T2W MR images, 14 (89%) showed positive features on apparent diffusion coefficient maps of diffusion-weighted images, and 16 (100%) were positive on DCE MR images. MRI-TRUS FGBs were positive in 10/16 lesions (62.5%) and 8/10 (80%) patients. We concluded that MRI-TRUS fusion guided biopsy with cognitive assistance is able to detect and diagnose locally recurrent lesions after RP, even at low PSA levels. This may facilitate early detection of recurrent disease and improve salvage treatment outcomes.

The second part of the thesis explores the potential of OCT as a novel imaging modality for the imaging of prostate tissue. In order to ensure accurate measurements, the system needed to be calibrated. Chapter 8 describes calibration measurements of the OCT system. A customized computer program was designed to automatically analyze and quantify OCT pullbacks. Explorative measurements were performed in 1 prostate. In benign areas, the tissue visually appeared homogeneous, whereas in malignant areas, small glandular structures were observed. The results were quantified by measuring the optical attenuation coefficient. Not all areas in that showed a high attenuation coefficient, corresponded to areas of prostate cancer.
With a calibrated OCT system, the optical properties of prostate tissue were further explored. In **chapter 9**, the diagnostic accuracy of the optical attenuation coefficient for the detection of prostate cancer was assessed in 6 prostates. The mean attenuation coefficients (benign OCT data; malignant OCT data; p-value) were: (3.56 mm\(^{-1}\); 3.85 mm\(^{-1}\); p < 0.0001) for all patients combined. The area under the receiver operating characteristic (ROC) curve was 0.64. In order to circumvent the effect of histopathology mismatching, a sub-analysis was performed on only OCT data in which tumor was visible in two subsequent histopathological prostate slices. This analysis could be performed in only 3 patients. The mean attenuation coefficients (benign OCT data; malignant OCT data; p-value) were: (3.23 mm\(^{-1}\); 4.11 mm\(^{-1}\); p < 0.0001) for all patients grouped together. The area under the ROC curve was 0.89.

This challenge of histopathology matching was solved in **chapter 10** by the development of a customized device that matches OCT data to histopathology. Using the tool, the prostate could be sliced into slices of 4 mm thickness through the optical coherence tomography measurement trajectory. In this way, whole-mount pathology slides were produced in exactly the same location as the optical coherence tomography measurements were performed. Full 3-dimensional optical coherence tomography pullbacks were fused with the histopathology slides using the 3-dimensional imaging software AMIRA, and images were compared. Various structures, for example, Gleason 3 + 4 prostate cancer, stroma, healthy glands, and cystic atrophy with septae could be identified both on OCT and on the histopathological prostate slides, indicating precise matching of histopathology.

In **chapter 11**, the results of 106 OCT datasets measured in 20 patients with the customized tool for pathology matching were analyzed, quantitatively as well as qualitatively. OCT can reliably differentiate between fat, cystic- and regular atrophy and benign glands. The overall sensitivity and specificity for malignancy detection was 79% and 88% for reviewer 1 and 88% and 81% for reviewer 2, respectively. Quantitative analysis for differentiation between stroma and malignancy showed a significant difference (4.6 mm\(^{-1}\) vs. 5.0 mm\(^{-1}\) p<0.0001). There was a significant difference in median attenuation coefficient between stroma, inflammation, Gleason grade 3 and Gleason grade 4 (4.6 mm\(^{-1}\), 4.1 mm\(^{-1}\), 5.9 mm\(^{-1}\), 5.0 mm\(^{-1}\) respectively). However, attenuation coefficient varied per patient and no significant difference was seen in a per patient analysis (p=0.17). It is expected that with improvement in resolution of the current OCT systems, the accuracy of prostate cancer detection will go up.

**Chapter 12** provides concluding remarks on the thesis. It contains a critical discussion and considers future perspectives.
Prostaatcarcinoom is een van de meest voorkomende maligniteiten bij mannen. De bijwerkingen van conventionele prostaatkankerbehandelingen (erectiele dysfunctie en incontinentie) hebben duidelijke gevolgen voor de kwaliteit van leven van patiënten. Bij geselecteerde patiënten kan focale therapie van de prostaat worden toegepast. Bij deze behandeling wordt alleen de prostaatkanker behandeld en blijft de rest van de prostaat onaangedaan. Met deze focale therapie kunnen bijwerkingen van conventionele therapieën aanzienlijk gereduceerd worden. Focale therapie is een nieuwe vorm van therapie die niet bij alle patiënten kan worden toegepast. Het is namelijk van groot belang dat de gebieden met prostaatkanker in de prostaat heel precies in beeld kunnen worden gebracht.

De huidige meest accurate manier om deze gebieden in de prostaat in beeld te brengen in multi-parametrische MRI (mpMRI). Zoals bij elke nieuwe vorm van diagnose of therapie is het van belang dat er goede richtlijnen bestaan voor het gebruik van deze technologieën. We duiden hiermee op richtlijnen voor de detectie van gelokaliseerd prostaatcarcinoom, maar ook op richtlijnen voor patiënten selectie, sturing van de behandeling en follow-up na focale therapie voor gelokaliseerd prostaatcarcinoom. Alleen wanneer data op een uniforme manier verkregen wordt, kan er substantieel bewijs worden verkregen om nieuwe vormen van therapie en beeldvorming te ondersteunen of te verwerpen.

De klinische verdenking op prostaatkanker, bijvoorbeeld door een stijging van het prostaat specifiek antigeen (PSA), of door een afwijking op beeldvorming van de prostaat of een afwijkend rectaal toucher, moet altijd bevestigd worden met een biopt. Een andere nieuwe beeldvormende techniek binnen de oncologie is Optische Coherentie Tomografie (OCT). Gebruikmakend van terugverstrooid licht kunnen hoog resolutie beelden van weefsel worden verkregen (optisch biopt).

Het doel van dit proefschrift is tweeledig: 1) de ontwikkeling en standaardisatie bewerkstelligen van protocollen voor beeldvorming en focale behandeling van prostaatcarcinoom (hoofdstuk 2-7). 2) het onderzoeken van OCT als een nieuwe beeldvormende techniek voor prostaatweefsel en prostaatcarcinoom (hoofdstuk 8-11).

Ter introductie hebben we de huidige meest gebruikte technieken om prostaatcarcinoom in beeld te brengen op een rij gezet. In hoofdstuk 2 worden de nieuwste echo en MRI technieken voor patiënten selectie, sturing van de behandeling en follow-up na de focale therapie in 2012 samengevat. Het artikel benadrukt dat standaardisatie van de manier waarop beeldvorming van prostaatcarcinoom wordt verricht, essentieel is voor protocol en richtlijnenontwikkeling.

Het proces van standaardisatie van data acquisitie en richtlijnenontwikkeling begint met expert-opinion. Hoofdstuk 3 is het verslag van een consensus project tussen radio-
logen, urologen en onderzoekers uit Europa en Noord-Amerika. Het doel was om de vereisten voor een optimaal uitgevoerde mpMRI te definiëren. Een tweede doel was om tot consensus te komen over de huidige status van een optimaal uitgevoerde mpMRI met betrekking tot i) het vaststellen van de lokalisatie van prostaatkanker (dit betekent het kunnen lokaliseren van “target laesies” ≥ 0.5mL), ii) het kunnen monitoren en vaststellen van de uitkomsten van focale therapie iii) het identificeren van diagnostische voordelen van nieuwe MRI methodes. Over de belangrijkste onderwerpen werd consensus bereikt: mpMRI is de optimale beeldvormende techniek om de doelen te bereiken die nodig zijn om focale therapie mogelijk te maken. Een mpMRI moet vervaardigd worden op een 3 Tesla (T) machine met of zonder endorectale spoel of een 1.5 T machine met endorectale spoel, én moet worden beoordeeld door een ervaren radioloog. MpMRI is in staat kleine tumoren voor focale therapie te lokaliseren, echter gestructureerde en ge-standaardiseerde beoordeling van mpMRI is van vitaal belang. Als laatste concludeerde het panel dat een template geleide saturatie biopt niet langer noodzakelijk is als een state-of-the-art mp MRI beschikbaar is. Verdachte laesies op beeldvorming, moeten nog wel worden bevestigd met een (gericht) biopt.

Met de kennis uit hoofdstuk 3, zijn we gestart met een groter en meer gestructureerd consensusproject in hoofdstuk 4. Het doel van het project was het definiëren van de rol van mpMRI voor het plannen van focale therapie, sturing van de behandeling en follow-up na de focale therapie. Een vragenlijst werd gecirculeerd volgens de Delphi methode naar een 48 leden tellend panel van urologen, radiologen en technici. Na 3 vragenrondes werd het project afgesloten met een vergadering. Over 41% van de onderwerpen werd consensus bereikt. Patiënten die in aanmerking komen voor focale therapie moeten biopt bewezen prostaatcarcinoom hebben. Biopten moeten, indien mogelijk, pas worden afgenomen na het vervaardigen van een mpMRI van de prostaat. Standaardisatie van protocollen voor beeldvorming en beoordelen van beeldvorming is essentieel en mpMRIs dienen te worden beoordeeld door een ervaren radioloog. In de follow-up na focale therapie dient na 6 maanden een mpMRI gemaakt te worden, gevolgd door een jaarlijkse mpMRI. De afwijkingen op een mpMRI dienen eerst te worden bevestigd met een gericht biopt voorafgaand aan een hernieuwde behandeling.

Omdat focale therapie van prostaatkanker een relatief nieuw concept is, is er nog weinig bekend over de follow-up van patiënten na de behandeling. Standaardisatie van deze follow-up is noodzakelijk voor het creëren van uniform vergelijkbare data in klinische studies. Daarom hebben we in hoofdstuk 5 een Delphi consensus project uitgevoerd over dit onderwerp. De onderwerpen waren: (1) algemeen, (2) biopten, (3) PSA, (4) rectaal toucher, (5) beeldvorming, (6) kwaliteit van leven en (7) registratie en verzamelen van data. De volgende conclusies werden geformuleerd: De follow-up na focale therapie moet ten minste een periode van 5 jaar beslaan. De volgende modaliteiten moeten worden meegenomen in het beoordelen van de behandeluitkomsten: mpMRI, biopten,
beoordeling van de erectiele functie, kwaliteit van leven, mictieklachten en incontinentie. Na 1 jaar dienen 12 systematische transrectale echo (TRUS) geleide biopten gecombineerd te worden met 4-6 biopten van het behandelde gebied en elke verdachte laesie op beeldvorming moet eveneens gebiopteerd worden. Hierna dienen alleen biopten te worden afgenomen indien er op beeldvorming verdenking op een recidief bestaat. De ideale manier om een gericht biopt te nemen is mpMRI-TRUS fusie biopten. PSA dient te worden afgenomen voor onderzoeksdoeleinden, elke 3 maanden in het eerste jaar en daarna elke 6 maanden. MpMRI is de optimale beeldvormende techniek voor follow-up van patiënten na focale therapie. Een mpMRI dient te worden vervaardigd na 6 maanden en 1 jaar na de behandeling, vervolgens jaarlijks tot 5 jaar na de behandeling. Ideaal gezien dienen de uitkomsten van focale therapie in een wereldwijde database te worden verzameld.

In 2016 werden de Prostate Imaging – Reporting and Data System (PI-RADS) V2.0 richtlijnen voor het vervaardigen en de interpretatie van mpMRI van de prostaat gepubliceerd. In hoofdstuk 6 hebben wij de nauwkeurigheid en de variabiliteit tussen waarnemers getest van deze nieuwe versie van PI-RADS in een biopt naïeve groep patiënten. 101 patiënten met een verhoogd serum PSA ondergingen een mpMRI en vervolgens mpMRI-TRUS gefuseerde biopten van de prostaat. Verdachte laesies werden gescoord door 5 geblindeerde beoordelaars volgens PI-RADS v.2.0. 87 (54%) van de laesies bleek positief voor prostaatcarcinoom. De PI-RADS scores waren voor zowel laesies in de perifere zone als laesies in de transitie zone in overeenstemming met pathologie (Kendall τ voor laesies in de perifere zone, 0.51 [P < 0.0001] en voor laesies in de transitie zone, 0.45 [P = 0.0008]). Geen van de 12 laesies welke gescoord waren als PI-RADS 2, vertoonden klinisch significant prostaatcarcinoom bij pathologie. Met andere woorden, geen significant prostaatcarcinoom werd gemist. Voor PI-RADS v.2.0 werd slechts een matige overeenstemming gevonden tussen waarnemers (κ voor totale PI-RADS score, 0.46). Dit is vergelijkbaar met studies naar eerdere versies van PI-RADS.

Na de behandeling van prostaatcarcinoom kunnen patiënten een recidief ontwikkelen. Vroege detectie en behandeling van deze recidieven verbetert de behandeluikomst van deze recidieven. In hoofdstuk 7 beschrijven we het gebruik van mpMRI transrectale echo gefuseerde biopten voor de detectie van recidief prostaatcarcinoom na radicale prostatectomie. Patiënten met een stijgend PSA na radicale prostatectomie en geen aanwijzingen voor metastasen elders, ondergingen een 3T mpMRI en vervolgens mpMRI-TRUS gefuseerde biopten. De gemiddelde laesiediameter op mpMRI was 1.12 cm (bereik: 0.40-2.20 cm). Alle verdachte laesies (16/16 100%) waren positief op de T2 gewogen opnames, 14 (89%) waren positief op de diffusie gewogen opnames, en 16 (100%) waren positief op dynamische contrast MRI. MpMRI-TRUS gefuseerde biopten waren positief in 10/16 (62.5%) van de laesies en in 8/10 (80%) van de patiënten. We concludeerden dat het mogelijk was om met mpMRI-TRUS gefuseerde biopten recidie-
ven van prostaatcarcinoom na radicale prostatectomie vast te stellen. Deze techniek kan bijdragen aan de vroege detectie van recidief prostaatcarcinoom en verbetert mogelijk de behandeluitkomsten van deze recidieven.

In het tweede gedeelte van dit proefschrift onderzoeken we de mogelijk toegevoegde waarde van OCT als nieuwe beeldvormende techniek voor prostaatweefsel en prostaatcarcinoom, waardoor deze techniek mogelijk een rol kan spelen bij de indicatiestelling voor focale therapie. Om tot betrouwbare metingen te komen dient eerst het systeem gekalibreerd te worden. In hoofdstuk 8 wordt de kalibratie van het OCT systeem beschreven. Een op maat gemaakt computerprogramma werd ontworpen voor automatische bepaling van de optische attenuatiecoëfficiënt. Er werden metingen verricht in prostaatweefsel: in goedaardige gebieden zag het prostaatweefsel er homogeen uit, terwijl in kwaadaardige gebieden kleine glandulaire structuren werden gezien. De optische attenuatiecoëfficiënt van prostaatweefsel werd bepaald. Niet alle gebieden met een hoge attenuatiecoëfficiënt kwamen overeen met gebieden van prostaatcarcinoom.

Met een gekalibreerd systeem konden we de optische eigenschappen van prostaatweefsel verder verkennen. In hoofdstuk 9 bepaalden we de diagnostische accuratesse van de optische attenuatiecoëfficiënt voor de detectie van prostaatcarcinoom in 6 patiënten. De gemiddelde attenuatiecoëfficiënt (benigne OCT data; maligne OCT data; p-waarde) was: (3.56 mm⁻¹; 3.85 mm⁻¹; p < 0.0001) voor alle patiënten gecombineerd. Het gebied onder de receiver operating characteristic (ROC) curve was 0.64. Om een mogelijke mismatching met histopathologie te omzeilen, deden we een sub-analyse van OCT data waar de tumor zichtbaar was in 2 opeenvolgende histologie plakken. Deze analyse kon uitgevoerd worden bij slechts 3 patiënten. De gemiddelde attenuatiecoëfficiënt (benigne OCT data; maligne OCT data; p-waarde) was: (3.23 mm⁻¹; 4.11 mm⁻¹; p < 0.0001) voor alle patiënten gecombineerd. Het gebied onder de ROC curve was 0.89.

In hoofdstuk 9 kwamen we tot de ontdekking dat de methode die we gebruikten voor het matchen van de OCT metingen met histopathologie niet voldoende accuraat is om OCT als een beeldvormende techniek voor prostaatcarcinoom te valideren. Dit probleem werd opgelost in hoofdstuk 10 met de ontwikkeling van een op maat gemaakt hulpmiddel dat OCT metingen zeer nauwkeurig met histopathologie kan matchen. Met dit hulpmiddel werd de prostaat in plakken van 4 mm gesneden, precies door het OCT meetraject heen. Driedimensionale OCT metingen werden gefuseerd met gedigitaliseerde histopathologie coupes en de beelden werden vergeleken. Een variëteit aan structuren als Gleason graad 3, Gleason graad 4, stroma, benigne klieren, cysteuze atrofie en atrofie met septae konden zowel in de pathologie als op de OCT beelden op dezelfde plaats worden herkend.

In hoofdstuk 11, analyseerden we de resultaten van 106 OCT metingen in 20 patiënten met gebruik van het op maat gemaakte hulpmiddel voor histopathologie matching. De resultaten werden zowel kwantitatief als kwalitatief geanalyseerd. OCT kan betrouwbaar
differentiëren tussen vet, cysteuze atrofie, atrofie en benigne klieren. De overall sensitiviteit en specificiteit voor de detectie van kwaadaardige structuren was respectievelijk 79% en 88% voor beoordelaar 1 en 88% en 81% voor beoordelaar 2. Kwantitatieve analyse voor het differentiëren tussen stroma en maligniteit met de optische attenuatiecoëfficiënt liet een significant verschil zien (4.6 mm⁻¹ vs. 5.0 mm⁻¹ p<0.0001). Er werd ook een significant verschil waargenomen in de attenuatiecoëfficiënt wanneer er werd gedifferentieerd tussen stroma, ontsteking, Gleason graad 3 en Gleason graad 4 (respectievelijk 4.6 mm⁻¹, 4.1 mm⁻¹, 5.9 mm⁻¹, 5.0 mm⁻¹). Echter, de attenuatiecoëfficiënten verschilden per patiënt en bij een intra-patiënt analyse werd geen significant verschil waargenomen. We verwachten dat als in de toekomst de resolutie van OCT systemen verbetert, ook de diagnostische accuratesse omhoog gaat.

Tot slot biedt hoofdstuk 12 een overzicht van de belangrijkste bevindingen uit dit proefschrift en wordt een toekomstvisie gegeven.
Part IV

Appendices
**PHD PORTFOLIO**

Name PhD student: Berrend G. Muller  
PhD period: 2012-2019  
Affiliation: Amsterdam University Medical Centers, AMC location, Department of Urology and Department of Biomedical Engineering & Physics  
Name supervisors: dr. TM de Reijke, prof. dr. AGJM van Leeuwen

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<td><strong>Muller BG</strong>, van den Bos W, de Bruin DM, Brandt MJ, Faber DJ, Zondervan PJ, Laguna-Pes MP, van Leeuwen TG, de la Rosette JJMCH: <em>Van lichtverstrooiing tot Gleason-score: ex-vivo optische coherentietomografie (OCT) van de menselijke prostaat na radicale prostatectomie</em> - NVU - presentation</td>
<td>2013</td>
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<td><strong>BG Muller</strong>, W van den Bos, DM de Bruin, MJ Brandt, DJ Faber, MP Laguna-Pes, TG van Leeuwen, JJMCH de la Rosette: <em>Ex-Vivo Optical Coherence Tomography of the Human Prostate After Radical Prostatectomy: Preliminary Results from a Pilot Study</em>. SPIE Medical Imaging San Diego 2014 – 20 min oral presentation</td>
<td>2014</td>
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<td><strong>BG Muller</strong>, W van den Bos, DM de Bruin, MJ Brandt, DJ Faber, MP Laguna-Pes, PJ Zondervan, TM de Reijke, TG van Leeuwen, JJMCH de la Rosette: <em>From Gleason Score to Changes in Scattering: Optical coherence Tomography in Prostate Cancer – a Prospective Human ex-vivo Study</em>. EAU Stockholm 2014 - poster presentation</td>
<td>2014</td>
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<td><strong>Consensus meeting 1: Focal Therapy: Follow-up Modalities</strong>, Moderator: <strong>BG Muller</strong> Chairmen: Thomas Polascik (Durham, USA) - Usamnu Ukimura (Los Angeles, USA); 7th international symposium on Focal Therapy and Imaging in Prostate &amp; Kidney Cancer, Los Angeles California, USA, 21-23 august 2014</td>
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<td><strong>BG Muller</strong>, A Swaan, RAA van Kollenburg, ECH Zwartkruis, DM de Bruin, M.J.Brandt, W van den Bos, AW Schreurs, DJ Faber, L Rozendaal, AN Vis, JA Nieuwenhuijzen, MP Laguna, RJA van Moorselaar, TG van Leeuwen, JJMCH de la Rosette: <em>Optical Coherence Tomography in Prostate Cancer: Results in 20 Patients Validated with a Customized Pathology Matching Tool</em>. SIU Annual Conference Buenos Aires Argentina, 20-23 October, E-poster and video presentation</td>
<td>2016</td>
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### Teaching and Tutoring

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<th>Name</th>
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<tr>
<td>Juliette Velu (September 2012 - November 2012)</td>
<td>2012</td>
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<tr>
<td>Student Technical Medicine, University of Twente, Enschede, The Netherlands, 10 week combined internship Technical Medicine. Department of Biomedical Engineering &amp; Physics and department of Urology, AMC Amsterdam. Title Bachelor thesis: Towards Diagnostic Accuracy of Optical Coherence Tomography in Diagnosis and Staging of Prostate Cancer</td>
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<td>Suzanne van Huystee (May 2013 - September 2013)</td>
<td>2013</td>
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<tr>
<td>Student Medicine, VU Medisch Centrum, Amsterdam, the Netherlands 14 week scientific internship, department of urology, AMC Amsterdam Title Master thesis: Shining Light on Prostate Cancer: Towards Diagnostic Accuracy of Optical Coherence Tomography in Diagnosis and Staging of Prostate Cancer</td>
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<td>Coen van Hessen (May 2014 - September 2014)</td>
<td>2014</td>
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<tr>
<td>Student Medicine, AMC Amsterdam, the Netherlands Writing bachelor thesis Title bachelor thesis: Optical Diagnostics for Prostate Cancer: Technology, Diagnostic Accuracy, and Future Applications</td>
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<td>Rob van Kollenburg (December 2015 - April 2016)</td>
<td>2015</td>
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<td>Student Medical Doctor/Clinical Investigator, Maastricht University, the Netherlands 20 week scientific internship Department of Biomedical Engineering &amp; Physics and department of Urology, AMC Amsterdam. Title Master thesis: Validation of needle based optical coherence tomography for the detection of prostate cancer: a qualitative and quantitative analysis in 20 patients</td>
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### Parameters of Esteem

<table>
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<th>Awards</th>
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<tr>
<td>Winner AUA Review Knowledge Quiz Award</td>
<td>2012</td>
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### Other

| Organization Board Member AMC Field Hockey Tournament                      | 2013         |
| 5 day course in Healthcare finances in the Netherlands                       | 2016         |
| 5 day course Leadership in Healthcare                                       | 2016         |
AUTHORS CONTRIBUTIONS

Study conception and design: 1
Acquisition of data: 2
Analysis and interpretation of data: 3
Drafting the manuscript: 4
Critical revision: 5

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Chapter 7  Multiparametric magnetic resonance imaging-transrectal ultrasound fusion-assisted biopsy for the diagnosis of local recurrence after radical prostatectomy
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P Yan, S Xu, JJMCH de la Rosette, MJ Merino, BJ Wood, PA Pinto 2,5
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Chapter 8  Prostate cancer diagnosis: the feasibility of needle-based optical coherence tomography
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Chapter 9  Prostate cancer diagnosis by optical coherence tomography: first results from a needle based optical platform for tissue sampling
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MJ Brandt, S van Huystee, DJ Faber  3,5
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Chapter 10  Customized tool for validation of optical coherence tomography in differentiation of prostate cancer
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Chapter 12  Concluding remarks and future perspectives
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TM de Reijke, TG van Leeuwen, DM de Bruin, DJ Faber  5
**LIST OF PUBLICATIONS**

**Peer-reviewed full-text publications**

*This thesis*


**Additional publications**


Book Chapters:

About the author

Berrend Muller was born on January 18th 1986 in Weesp, the Netherlands. In 2004 he graduated from the Goois Lyceum in Bussum and continued his education at the “Liberal Arts & Sciences Honors College” Roosevelt Academy in Middelburg. There, his interest in medicine and health-care was sparked. In 2006, he did a 4 month medical internship at the “Universidad de Buenos Aires” in Buenos Aires, Argentina, where he studied neurology and neuroanatomy under the supervision of dr. Horacio Conesa. After graduation in Middelburg, Berrend went to Maastricht, where he completed the research master “Medical Doctor/ Clinical investigator”. During his internships in urology at the Maxima Medisch Centrum in Veldhoven and the Maastricht University Medical Center, he developed a profound interest in urology.

After graduation at the university of Maastricht in 2011, Berrend started his medical career by working for a short period as a resident not in training (ANIOS) in the department of urology in the Academic Medical Center in Amsterdam, before starting his PhD project, in January 2012. He started his PhD project under the supervision of prof.dr. JJMCH de la Rosette and later dr. De Reijke, in the Urology department, and prof.dr. AGJM van Leeuwen in the Biomedical Engineering & Physics department, during which he was involved in several projects, concerning prostate cancer diagnostics, focal treatment of the prostate and patient follow-up. During his PhD, he spent 3.5 months in Bethesda, MD, USA, in the National Institutes of Health (NIH), conducting shared projects on prostate MRI between the departments “Urologic Oncology Branch” and “Molecular Imaging Program”, under the shared supervision of dr. PA Pinto, MD and dr. B Turkbey, MD respectively.

January 2015, Berrend started his residency in urology. First as a surgical resident in the “Westfriesgasthuis” in Hoorn, to continue as a urology resident in the “Spaarne Gasthuis” in Hoofddorp in 2017. In 2018, he performed a 6 weeks clinical fellowship at the “Muljibhai Patel Urological Hospital”, in Nadiad, Gujarat, India, under the supervision of dr. MR Desai, MD. Berrend is currently appointed as a 5th year resident in urology in the Radboudumc in Nijmegen.
**DANKWOORD**

In 7 jaar kan veel gebeuren. Met trots schrijf ik hier nu de laatste woorden aan het resultaat van het proefschrift dat u nu in handen heeft. Dit boek had nooit tot stand kunnen komen zonder de betrokkenheid van heel veel mensen. Ongetwijfeld zullen er mensen zijn die ik vergeet, maar weet dat ik je dankbaar ben voor je interesse en betrokkenheid.

Allereerst gaat mijn dank uit naar de patiënten die hebben bijgedragen aan onderzoek en deel hebben genomen aan onze studies of toestemming hebben gegeven dat uw weefsel voor onderzoek werd gebruikt. Zonder u was de data in dit proefschrift niet gegenereerd en was dit proefschrift niet tot stand gekomen. Hartelijk dan voor het vertrouwen in ons en de bereidwilligheid uw weefsel ter beschikking te stellen of deel te nemen.

Dank aan alle co-auteurs. Mede dankzij jullie harde werk en kritische feedback is dit proefschrift tot stand gekomen.

Geachte promotiecommissie, geachte Prof dr. Beerlage, Prof dr. Aalders, Prof dr. Van de Vijver, Prof dr. Fütterer, dr Van Soest, en Dr. van Oort, hartelijk dank voor jullie zorgvuldige beoordeling van mijn proefschrift en jullie bereidheid zitting te nemen in mijn promotiecommissie.

Al eerste wil ik mijn (co-promotores) bedanken. prof dr. Ton van Leeuwen, dr. Theo de Reijke, dr. Martijn de Bruin, dr. Dirk Faber:

Beste Ton, Dank voor je vertrouwen en voor de ruimte die je mij en mijn collega’s gegeven hebt het onderzoek op onze eigen manier vorm te geven. Het was zowel een verrijking als een genot om onderzoek te doen zowel op de afdeling Biomedical Engineering & Physics als op de afdeling urologie. Je bent een voorbeeld voor mij als leider van een technische afdeling waarbij je schijnbaar moeiteloos een veelvoud aan contacten met clinici onderhoudt en ook van iedereen zijn vakgebied iets afweet, maar toch ook meedogenloos precies bent in het technische aspect van de studies. Ik weet nog dat ik baalde dat de analyses van een artikel dat reeds in de laatste fase was, helemaal vanaf nul opnieuw moest omdat je vond dat de methode niet inzichtelijk genoeg was. Je had uiteraard gelijk. Dank voor je gezeligheid en het feit dat je voor ons PhD studenten altijd benaderbaar bent. Dit heeft geleid tot het proefschrift dat er nu ligt.

Beste Theo, jij hebt het laatste gedeelte van de begeleiding van mijn proefschrift vanuit de klinische kant op je genomen. De afgelopen periode in het AMC is rumoerig gewe-

Beste Martijn, vanaf het eerste moment dat we elkaar tegenkwamen in het AMC toen ik een dag mee kwam lopen om te kijken of onderzoek in het AMC iets voor mij was, hadden we gelijk al een klik. Zelfde humor en no-nonsense gezelligheid. Sinds die tijd hebben we samen veel meegemaakt tijdens onze periode in het AMC. Het was een genot om naar congressen te gaan en samen met jou ons onderzoek te presenteren. Waar jij begon met het begeleiden van enkele PhD studenten (zelf ook nog even je promotie officieel afronden), heb je nu een hele vloot onder je hoede. Ik ben zeer trots om jou als onderzoeksbegeleider, co-promotor en goede vriend te hebben.

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Geachte professor de la Rosette, beste Jean, jij was mijn supervisor in de eerste fase van mijn onderzoeksperiode in het AMC. Uit de schoolbanken nam je me in dienst, eerst als ANIOS en daarna als fulltime PhD student. Dank voor alle mooie kansen die ik heb gekregen en alle deuren die je voor me geopend hebt.

Stichting Cure for Cancer is een stichting die fondsen werft voor de strijd tegen urologische oncologische aandoeningen. Mijn salaris als arts-onderzoeker is deels betaald door stichting Cure for Cancer. Hartelijk dank voor deze ondersteuning, zonder jullie was dit proefschrift niet mogelijk geweest. Wilt u meer weten of donateur worden? Kijk dan op www.cureforcancer.nl.

Hester Scheffer en Tim Buddingh, beiden collega ANIOS in het AMC, bedankt voor jullie plezier en gezelligheid. Samen begonnen we in het AMC, jullie hadden al enige werkvrijheid, ik had urologie ervaring als semi-arts, maar we waren nog relatief bleu. Samen runden we de afdeling en de consulten in huis en SEH, het was een mooie tijd.

Onderzoekers van het eerste uur: Kurdo, Miki, Martijn Smeenge. Wat hebben we hebben veel Dumpert gekeken in het hok, maar ook hard gewerkt en veel lol samen gemaakt. Martijn jij bent de volgende!

Arnoud, Peter en in het speciaal Willemien, dank voor jullie gezelligheid en hulp bij de artikelen. Samen stonden we sterk. Natuurlijk Mieke, mijn kamergenoot voor 3 jaar.
We hebben elkaar door en door leren kennen. Ik ben enorm trots dat jij ook recent je proefschrift hebt verdedigd. Je heb het geweldig gedaan.

Fellows in the UMC urology department: Dr. Hiren Sodha, Dr. Anastasios Anastasiadis, Dr. Ernesto Cordeiro, Dr. Mathias Westendarp and Dr. Alexandre Ingels. Because of your presence, I learned a lot about urology all over the world and moreover, I made a lot of new international friends. In 2016, I visited Argentina to see Ernesto and in 2018, I was in Mumbai to visit Hiren. All of you are great clinicians and friends and I hope to keep seeing you in the future.

People from the “Urologic Oncology Branch”, and “Molecular Imaging Program” in the “National Institutes of Health” in Bethesda Maryland, USA, especially Baris Turkbey, Peter Pinto and Peter Choyke, thank you for taking me by the hand for 3,5 months and show me how excellent research in de field of uro-oncology is done. Special thanks to the fellows from both departments, and all the personnel involved.

Urologen uit het AMC in mijn onderzoeksperiode: Guido, Patricia, Joyce, Lara, Eric, Andreas, dank voor jullie interesse en steun.

Ondersteuners van de afdeling, Martine, Laura, Sonja, Alice, Annemarie, Natasha, dank voor het de gezellige gesprekken tijdens de koffiepauzes op het voetenplein. Annelies, elke keer werd het UDO spreekuur door jouw ondersteuning een feestje.

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Pathologie afdeling AMC, met name Dilara Savci, uro-patholoog, maar ook al het ondersteunend personeel, dank voor jullie inzet en harde werk.

Wim Schreurs, instrumentmaker in het AMC, bedenker van de klapschaats, maar ook ontwerper van de prostaatsnijder. Door jouw uitvinding konden we histopathologie
exact met de OCT beelden koppelen, iets wat anders praktisch onmogelijk is. Dit heeft de laatste twee hoofdstukken van dit proefschrift mogelijk gemaakt.

Mensen van de pathologie uit het VUMC, met name Rence Rozendaal, en Evita Zwartkruis, maar ook alle ondersteunende analisten, mensen uit het mortuarium en fotograaf. Dank voor jullie bereidheid om mee te werken met onderzoek uit het AMC, dank voor jullie eindeloze geduld met het intekenen van de resultaten en voor jullie harde en moeilijke werk met het maken van de whole mount coupes, dat is echt lastig werk. Bovenal dank voor de gezelligheid tijdens de metingen en het uitwerken van de resultaten op locatie!

Dank afdeling Cardiologie uit het VUMC voor het lenen van jullie OCT meetapparatuur, dit heeft het onderzoek in het VUMC mede mogelijk gemaakt.

Dr. André Vis, dr. Jakko Nieuwenhuijzen en prof.dr. Jeroen van Moorselaar van de urologie uit het VUMC bedankt voor de hulp op de operatiekamers voor het doen van de metingen in de 20 prostaten. Door jullie is het onderzoek in een stroomversnelling geraakt.

Wetenschapsstudenten tijdens de masterfase van jullie studie, Juliëtte Velu (technische geneeskunde), Suzanne van Huystee (geneeskunde) en Rob van Kollenburg (A-KO master). Dank voor de gezelligheid en jullie bijdragen tijdens jullie stages aan de wetenschap. Stuk voor stuk zijn de projecten waar jullie aan meegewerkt hebben zonder veel moeite gepubliceerd. Iets waar jullie trots op kunnen zijn! Goed om te zien dat jullie allemaal goed terecht zijn gekomen.

Beste vrienden van de vooropleiding in het Westfriesgasthuis in Hoorn. Bedankt voor de geweldig leuke tijd van 2 jaar! Waar ik van tevoren dacht dat ik nooit algemeen chirurg zou willen worden, heb ik nog 1,5 jaar de blues gehad toen ik weer aan de urologie was begonnen. Jullie zijn geweldig!

Urologen, ANIOS en ondersteuners van de urologie uit het Spaarne Gasthuis. Dank voor de leerzame periode!

Dankwoord

Uiteraard wil ik ook mijn vrienden niet vergeten, mijn vrienden uit mijn jeugd in Weesp, vrienden van mijn studie in Middelburg en Maastricht, en vrienden uit Amsterdam. Al veel te lang hebben jullie moeten aanzien dat het proefschrift nu echt, echt, echt bijna klaar was. Dank voor jullie interesse en steun wanneer dat nodig was.

Mijn paranimfen, Abel, medeonderzoeker uit het AMC, en technisch geneeskundige. Jouw optimisme en Amsterdamse manier van communiceren en aanpakken werkt aanstekelijk. Jij ziet geen problemen maar vooral oplossingen en maakt van alles een feestje. Samen deden we metingen in het mortuarium van de VU, gingen we op congres, naar Manchester voor het uitwerken van onderzoeksresultaten, maar ook zaten we samen op de racefiets van Londen naar Amsterdam. Je bent een heel goede vriend van me geworden en ben vereerd dat je mijn paranimf wil zijn. Coen, studievriend uit Middelburg en dispuutsgenoot. Jij hebt mij meegemaakt in een vormende periode van mijn leven en daarom kennen we elkaar door en door. Ik kan met jou alles bespreken en meestal hebben we al aan een half woord genoeg. Dank dat je mijn paranimf wil zijn, jij gaat ook nog wel een keer promoveren en waarschijnlijk sneller dan je nu denkt.

Lieve familie Muller en Vogels, lieve oma’s, dank voor alle interesse en steun de afgelopen jaren. Eindelijk is het zover!

Lieve familie Brummelhuis, dank dat jullie mij hebben opgenomen in jullie familie, het voelt als een warm bad.

Lieve Jorran, als broers kennen wij elkaar door en door. Ik ben trots op wat je tot nu toe allemaal hebt bereikt. Dank voor je nuchtere opmerkingen en je frisse no-nonsense kijk op zaken.


Lieve Iris, we kennen elkaar nu ruim twee jaar maar het voelt voor mij alsof je er altijd al was. Jouw spontaniteit, openheid, frisse kijk op dingen en jouw onbevooroordeelde blik op de wereld maken elke dag met jou een feest. Ik hoop dat we samen heel oud worden.
uitnodiging voor het bijwonen van de openbare verdediging van mijn proefschrift:

Prerequisites for patient-tailored treatment in localized prostate cancer

Vrijdag 20 december 2019 om 11.00
Aula der Universiteit van Amsterdam,
Oude Lutherse Kerk,
Singel 411 (thuin Spui), Amsterdam

Na afloop bent u van harte welkom op de receptie
En 's avonds vanaf 20:00 voor het promotiefeest
in bar The Tara
Rokin 85-89
Amsterdam

Berrend Muller
berrend@gmail.com

PARANIMFEN
Coen Huizinga
coenhuizinga@gmail.com
Abel Swaan
abelswaan@hotmail.com

Prerequisites for patient-tailored treatment in localized prostate cancer

B E R R E N D  M U L L E R

Berrend G. Muller