mpMRI BASED TARGETED BIOPSY OF THE PROSTATE

Is there a preferred technique?

OLIVIER WEGELIN

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COLOPHON

Cover design: James Jardine | www.jamesjardine.nl
Layout: James Jardine | www.jamesjardine.nl
Print: Ridderprint | www.ridderprint.nl
ISBN: 978-94-93108-12-7

Dit proefschrift werd (mede) mogelijk gemaakt met financiële steun van het St. Antonius ziekenhuis onderzoeksfonds, het Canisius Wilhelmina ziekenhuis wetenschapsfonds, de maatschap Urologen voor U, de maatschap urologie Canisius Wilhelmina ziekenhuis, stichting urologie 1973, Ipsen Farmaceutica B.V., Astellas Pharma B.V., ChipSoft B.V., Hoogland Medical B.V., ABN AMRO en Erbe Nederland B.V.

mpMRI based targeted biopsy of the prostate: Is there a preferred technique?

Gerichte prostaat biopten op basis van mpMRI beeldvorming: Is er een voorkeurstechniek?
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

woensdag 13 mei 2020 des middags te 4.15 uur

door

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geboren op 28 januari 1986
te Jakarta, Indonesië

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Chapter 1

General introduction to thesis

PROSTATE CANCER

General epidemiology

Prostate cancer (PCa) is the second most common malignancy in men worldwide.[1] PCa incidence varies more than 25-fold worldwide, with the highest incidence occurring in Australia, New Zealand, North America, Northern and Western Europe.[1] Similarly, PCa is the most common malignancy among Dutch men, with an absolute incidence of 12.646 in 2018.[2] The prevalence of incidental PCa increases with each decade of age.[3] Due to increased PSA testing and aging of the population in general, the incidence of PCa is increasing.[1]

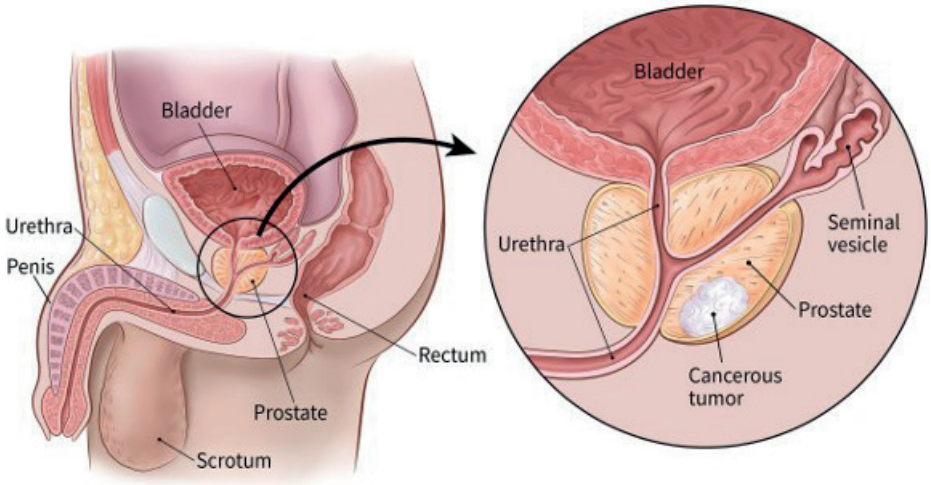

FIGURE 1: Position of the prostate.

Although PCa is a most common malignancy, PCa specific mortality is relatively low compared to other forms of cancers. In 2017, 2.862 Dutch men died due to PCa, which is considerably lower than the mortality rate of 10.391 for lung cancer.[2] This suggests an indolent natural history of localised prostate cancer.[4]

Clinically significant and insignificant prostate cancer

PCa can be classified as clinically significant or insignificant PCa. Clinically significant PCa (csPCa) is a likely cause of death in men with a life expectancy of >10 years when left

untreated, whereas insignificant PCa (iPCa) is unlikely to lead to clinical symptoms and PCa-related death during their lifetime. Commonly, many men diagnosed with iPCa die of competing causes of death.[5]

For decades, the Epstein criteria have been the mainstay tool for the definition of iPCa.[6,7] These criteria are based on clinical parameters such as PSA (and PSA derivatives such as PSA-density), clinical stage using digital rectal examination, and histopathological analysis of systematic biopsy cores (core positivity rate, percentage of cancer involvement per core and Gleason grade). The Epstein criteria can be used to predict the presence of low-grade, organ confined disease with volume ≤ 0.5 cm^3 at the time of radical prostatectomy, which is considered very unlikely to lead to prostate cancer related death in the long-term when left untreated. The Protect trial recruited 1643 men with (predominantly low-grade) localised PCa and could not demonstrate a difference in PCa specific mortality between active monitoring, radical prostatectomy (RP) and radiotherapy, even after 10 years follow-up.[8] As such active surveillance (AS) has been introduced as a management option for patients with iPCa to prevent overtreatment of iPCa, but inclusion criteria for AS protocols are stringent and will only prevent treatment in very low-risk cases. Therefore, these inclusion criteria are unable to correct for all cases of overdiagnosis of iPCa.

The ideal diagnostic tool would have a high detection rate of csPCa and a low detection rate of iPCa, thus preventing overtreatment of iPCa whilst identifying all cases of csPCa requiring treatment. A histological diagnosis of PCa by prostate biopsy remains the cornerstone of diagnosis of any PCa. Traditionally, PSA driven transrectal ultrasound (TRUS) guided systematic biopsy (SB) of the prostate has been used to diagnose PCa. Unfortunately, TRUS-SB carries a high risk of over-diagnosis of iPCa, and consequently over-treatment of iPCa.[9] At the same time, TRUS-SB misses a substantial number of csPCa.[10]

More recently, multiparametric MRI (mpMRI) and subsequent mpMRI based targeted biopsy (TB) of tumour suspicious lesions have become the mainstay of prostate cancer diagnosis. Therefore, the aforementioned Epstein criteria for iPCa and csPCa are very likely to have become obsolete as they incorporate characteristics of SB.

Nowadays the definition of csPCa is often based solely on a Gleason sum score of 3+4 or higher, although the definition of csPCa has undergone changes over time.[11-13] There is an urgent need to determine a universal definition of csPCa in the era of TB and to determine the best technique to obtain these TB, as several options are available. In this introduction, the historical context of prostate biopsy is briefly described and the most recent developments on TB are outlined, as a background to the ensuing chapters on techniques of TB.

HISTORICAL CONTEXT OF PROSTATE BIOPSY

Transperineal biopsy

The first prostate biopsy was described by Young in 1909 using an open perineal biopsy technique.[14,15] Open perineal biopsy required general anaesthesia and a lengthy post-operative hospital stay. Furthermore, it carried significant risks regarding urinary incontinence and erectile dysfunction. Consequently, open perineal biopsy was not routinely performed.

In 1930, Martin and Ellis described a technique called needle puncture and aspiration for soft tissue tumours.[16] Later that year Ferguson described the first application of the needle puncture and aspiration technique for the diagnosis of PCa using a transperineal approach.[17] Effectively this was the first percutaneous transperineal prostate biopsy. Using this technique, tissue was successfully obtained for analysis in approximately 30% of the cases.

In subsequent years, biopsy needles underwent significant alteration. In 1938, Silverman described a needle that shows similarities to contemporary biopsy needles. In 1943, Peirson and Nickerson described the usage of the Silverman needle in prostatic disease using the perineal route.[18] Guided by a finger in the rectum the Silverman needle was inserted though the perineum into the desired spot in the prostate. This technique allowed for office-based biopsy. In their study, Peirson and Nickerson describe a success rate of 86% in obtaining tissue for analysis.

Transrectal biopsy

In 1937, Astraldi described the open transrectal prostate biopsy.[19] A rectal speculum was introduced to identify the target region of the rectal wall, followed by disinfection of the rectal wall. The extractor instrument was introduced into the desired depth, opened, rotated by 180 degrees and closed. In doing so, tissue was cut off and stored in a separate compartment. Remarkably, the author states in his publication that after 12 years of usage of this technique he has never observed any infections following punctures.

Transrectal ultrasound imaging

Ultrasound imaging is based on the generation and transmission of high frequency sound waves by a transducer into a patient's body. The sound waves travel through the body and are reflected by tissue boundaries. These echoes travel back into the transducer probe and are relayed to a computer. The computer processor calculates the distance from the probe

to the tissue using the speed of sound and the time of each sound echo's return. Based on the distances and intensities of the echoes a two dimensional image can be generated, see **figure 2**.

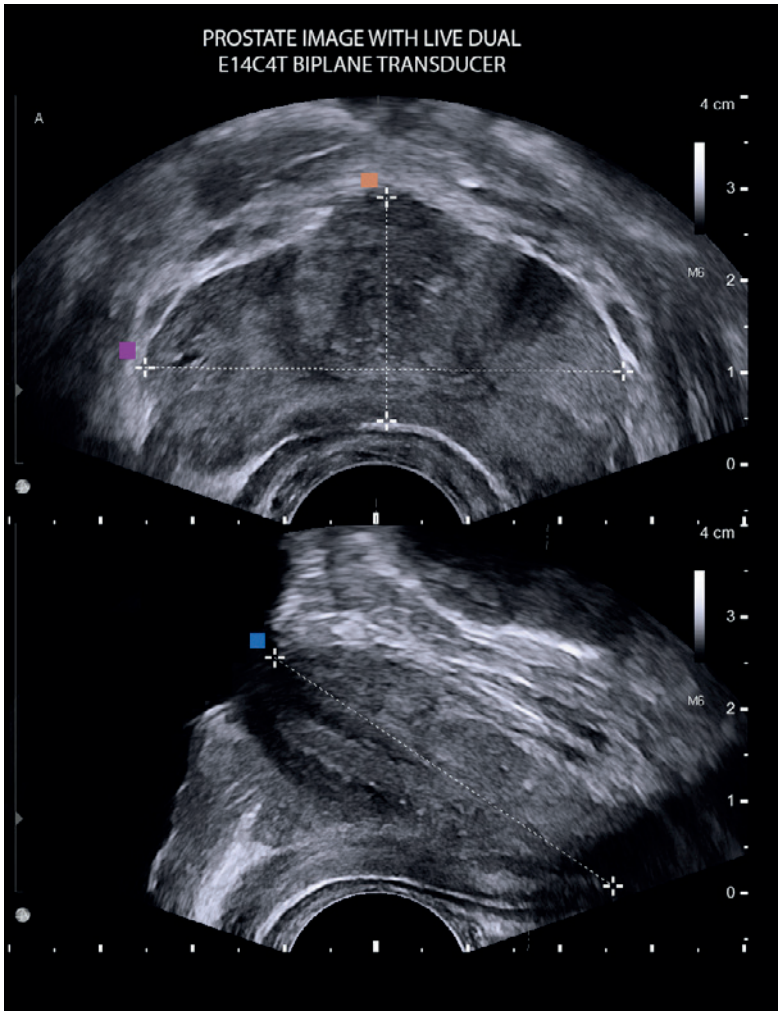

Figure 2: Biplane TRUS imaging of the prostate

In 1965 Gotoh published a feasibility study of TRUS usage in the diagnosis of prostatic disease.[20] The quality of imaging in this initial report on TRUS was poor, but at the time this was considered a breakthrough in urologic imaging. The years following the initial

concept, researchers developed TRUS into a more useful application. In 1973 Watanabe described the assembly of a chair incorporating a transrectal ultrasound transducer.[21] With the ultrasound image projected by this equipment, the prostate could be discerned from surrounding tissue such as the rectal wall and the bladder. Unfortunately, the imaging technique using the chair with an incorporated ultrasound transducer could not be used for the purpose of prostate biopsy. However, it did not take long before TRUS was used as a method to guide prostate biopsies.

Transrectal ultrasound guided biopsy

In 1983 Fornage described ultrasound-guided prostatic biopsy using a transrectal linear-array probe and aspiration biopsy.[22] In 1989 Hodge described the usage of a spring-loaded biopsy gun and TRUS imaging to perform biopsies of hypo-echoic lesions in patients with palpably abnormal prostates.[23] The authors found PCa detection rate of 66% in patients with abnormal digital examination and hypo-echoic lesions on TRUS. That same year Hodge et al published a landmark paper describing the comparison of 6 (sextant) random systematic TRUS biopsies versus directed biopsies of specific hypo-echoic lesions on TRUS.[24] The authors found that sextant biopsy had an increased detection rate of PCa compared to directed biopsies of hypo-echoic lesions.

In the decades following the introduction of sextant biopsy other biopsy schemes were proposed, including 5 region prostate biopsy (13 biopsy cores)[25], 8 core extended biopsy scheme[26], 11 core extended biopsy scheme[27] and saturation biopsy scheme (total of 23 cores)[28]. All these schemes further increased detection rates of PCa compared to conventional sextant biopsy schemes. The evidence from these various studies led to the advice of sampling the prostate using 8-12 biopsy cores (depending on prostate volume) formulated in international guidelines as recent as 2013.[29]

As early as 1995, Stamey had warned that sextant biopsy could lead to an over-diagnosis and over-treatment of iPCa, especially in men with normal digital rectal examination, normal TRUS and an elevated PSA (>4).[30] Data from the European Randomized Study of Screening for Prostate Cancer (ERSPC) suggested that PSA screening in combination with sextant biopsy schemes has a rate of over-diagnosis of iPCa as high as 50%.[9,31] Furthermore, the usage of TRUS-guided biopsy increased the knowledge of the sensitivity of TB of hypo-echoic lesions, and revealed this to be as low as 9%.[32] Consequently, TRUS does not seem to be a reliable instrument for accurate diagnosis or staging of PCa.

MAGNETIC RESONANCE IMAGING

Multiparametric MRI

Magnetic resonance imaging (MRI) makes use of the fact that all atomic nuclei consist of protons and neutrons, with a net positive charge. Certain atomic nuclei, such as the hydrogen nucleus, possess a property known as "spin". This can be conceived as the nucleus spinning around its own axis, generating a local magnetic field with north and south poles. Application of a strong, external magnetic field aligns the nucleus either in parallel with or perpendicular to the external field. The absorption of energy by the nucleus causes a transition from higher to lower energy levels and vice versa on relaxation. The energy absorbed (and subsequently emitted) by the nuclei induces a voltage that can be detected by a suitably tuned coil of wire.[33]

The initial paper describing the application of MRI in urological disorders date from 1983.[34] In this feasibility study, the authors concluded that MRI may play a prominent role in the clinical evaluation of prostate and bladder cancer. Since its introduction, MRI sequences have undergone significant developments.

Initially, imaging was performed using solely multiplane T1 and T2 weighted (T2W) imaging, see **figure 3**.[35,36] Functional MRI modalities, such as diffusion weighted imaging (DWI), dynamic contrast enhanced imaging (DCE) and magnetic resonance spectroscopic imaging (MRSI) were later developed. The central concept of functional MRI modalities is that they can make a more accurate distinction between malignant (even csPCa and iPCa) and benign lesions based on tissue density (DWI), tissue perfusion (DCE) and metabolism (MRSI), compared to anatomic structural imaging (T2W) alone. In 2009, a European consensus meeting was held and the first recommendations on MR imaging in prostate cancer diagnosis were formulated.[37] One of the main recommendations was that multiparametric (mp)MRI should consist of T1W, T2W, DWI and DCE imaging modalities, see **figure 4**. Furthermore, it was recommended that mpMRI imaging should be performed using at least a 1.5-T scanner but preferably at 3.0-T.

PIRADS grading system

In 2012, the European Society of Urogenital Radiology (ESUR) described a standardised scoring system for reporting on mpMRI called the Prostate Imaging Reporting and Data System (PIRADS).[38] Using the PIRADS grading system, lesions are graded 1-5 on each imaging modality (T2W, DWI and DCE). The overall PIRADS grade indicates an increasing suspicion of tumour presence in a lesion, see **table 1.** Initial clinical studies using mpMRI and the PIRADS grading system indicate that PIRADS was a useful tool for decision making

for targeting suspicious lesions.[39] Since its conception the PIRADS grading system has been revised and simplified in 2015, resulting in PIRADS version 2.[40] Main alteration in PIRADS v2 is that lesion location (peripheral or transition zone) determines which imaging modality should be dominant in the overall PIRADS score and that DCE has a secondary role compared to DWI and T2W.[41]

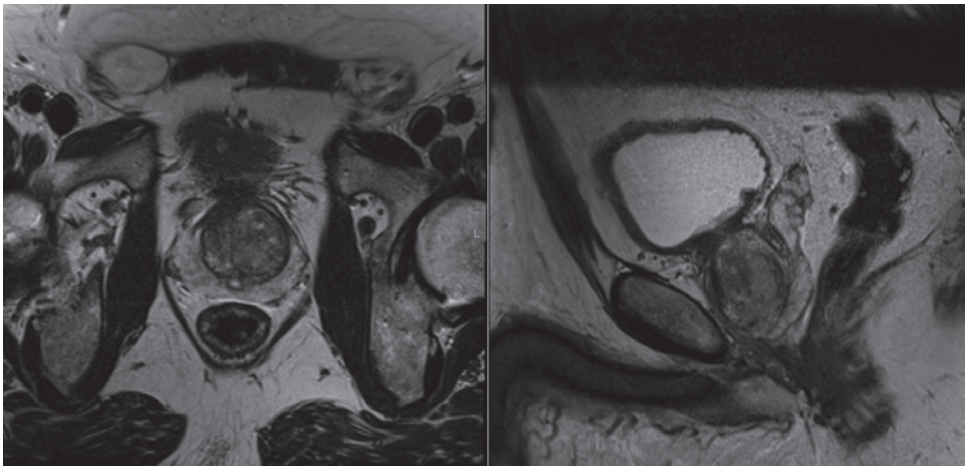

Figure 3: Axial and sagittal T2 weighted MR imaging of the prostate

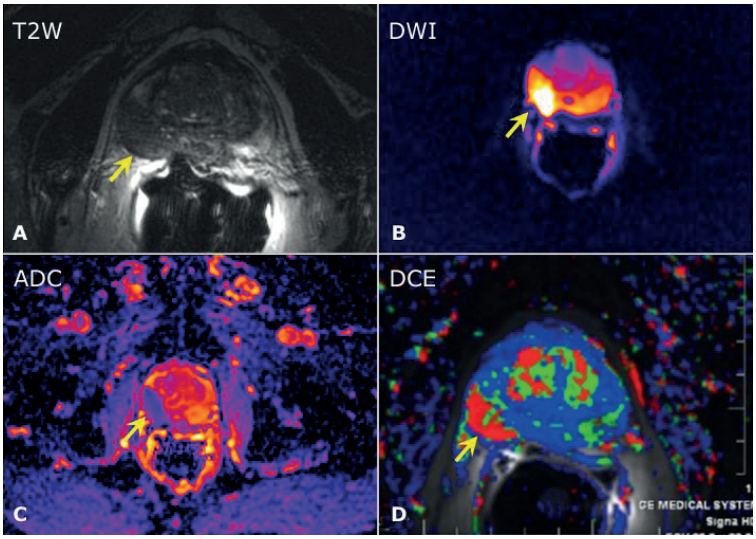

Figure 4: Multiparametric MRI of the prostate

Table 1: PIRADS grade

PIRADS 1	Very low: clinically significant cancer is highly unlikely to be present
PIRADS 2	Low: clinically significant cancer is unlikely to be present
PIRADS 3	Intermediate: the presence of clinically significant cancer is equivocal
PIRADS 4	High: clinically significant cancer is likely to be present
PIRADS 5	Very high: clinically significant cancer is highly likely to be present

Role of mpMRI in the diagnostic pathway

Since the introduction of mpMRI, clinicians have been confronted with the question when to apply mpMRI diagnostics in the diagnostic pathway of PCa. Clinical studies typically compare the yield of TB of mpMRI identified lesions with the yield of TRUS-SB in various settings (biopsy naïve patients, patients with prior negative TRUS-SB and patients with biopsy proven low-grade disease). Several meta-analyses of these studies have been published over time.[13,42,43] These meta-analyses indicate that the benefit of mpMRI and subsequent TB of mpMRI identified lesions, compared to repeated TRUS-SB, is most significant in patients with prior negative TRUS-SB and a persistent clinical suspicion of PCa.[42] Until recently, clinical guidelines have been recommending the usage of mpMRI diagnostics and subsequent TB in patients with prior negative TRUS-SB and a persistent clinical suspicion of PCa.[29] In light of recent evidence from clinical trials, the latest update of the European guidelines on PCa advice performing MRI diagnostics and subsequent TB in biopsy naïve patients as well.[44] The impact of the revision of the guidelines on the outcomes of the current thesis will be discussed in the general discussion chapter of the thesis.

MRI BASED TARGETED BIOPSY PROCEDURES

Although mpMRI does reliably predict the presence of csPCa, it should always be combined with histopathological analysis of biopsy cores obtained from tumour suspicious lesions identified by mpMRI. Currently there are several techniques available to perform TB based on mpMRI imaging. There is, however, no consensus on which technique of TB should be preferred.

In-bore MRI targeted biopsy

The first feasibility studies on transperineal targeted prostate biopsy of MRI identified lesions using real-time 0.5-T MRI guidance were published in 2000.[45,46] This technique evolved into transrectal 3-T in-bore MRI targeted biopsy (MRI-TB).[47] With MRI-TB the entire

biopsy procedure takes place in the MRI-scanner itself. A meta-analysis of 10 clinical studies on MRI-TB published in 2013 reports a median detection rate of PCa of 42%, with 81-93% of the detected tumours being csPCa.[48]

MRI-TRUS fusion targeted biopsy

Another technique to target mpMRI identified lesions is the MRI-TRUS fusion technique. A feasibility study of this technique was published in 2002.[49] The main principle of MRI-TRUS fusion is the alignment of a pre-biopsy MRI to an intra-procedural real-time TRUS image. Using this software aided image fusion, biopsy needles can be accurately directed onto pre-defined tumour suspicious lesions. Consequently, this enables real-time MRI-TRUS fusion targeted biopsy (FUS-TB).

Various platforms enabling FUS-TB employing either transrectal or transperineal biopsy approach are commercially available. The method of fusion is either rigid (predefined prostate contours on MRI are simply overlaid on the prostate contour on TRUS) or elastic (where organ contours on MRI and TRUS are dynamic, allowing for correction of prostate deformation during biopsy). A recently published meta-analysis found that FUS-TB detected more PCa (median 50.5% vs 43.4%) and more csPCa (median 33.3% vs 23.6%) compared to TRUS-SB.[43]

Cognitive TRUS targeted biopsy

A third technique of MRI based TB is cognitive TRUS target biopsy (COG-TB). Following the introduction of mpMRI this technique was first described in 2011.[50,51] With COG-TB the pre-interventional mpMRI is reviewed directly prior to biopsy, and used to target tumour suspicious lesions of the prostate using real-time biplane TRUS guidance. COG-TB is considered the most basic form of TB of mpMRI-identified lesions. In a large cohort of patients with suspected PCa (with and without prior negative SB) transperineal COG-TB detected comparable csPCa (57% vs 62%) and less iPCa (9.3% vs 17.0%) compared to transperineal template biopsy.[12]

THESIS OBJECTIVES AND STRUCTURE

The primary objective of this thesis is to gain insight into which technique of mpMRI based TB of the prostate should be preferred in men with a persistent clinical suspicion of PCa following SB (according to clinical guidelines at time of thesis design) by comparing the diagnostic efficacy of MRI-TB, FUS-TB and COG-TB.

Secondary objectives of this thesis include the evaluation of contemporary literature on the subject of mpMRI based TB, the ex-vivo evaluation of the accuracy of FUS-TB, the comparison of detection rates of (cs)PCa of mpMRI based TB with detection rates of repeated TRUS-SB, and the evaluation of morbidity following mpMRI based TB.

This thesis is structured into five parts:

Part I

In **chapter 2** a systematic review and meta-analysis of the literature on three techniques of mpMRI based TB will be presented. The aim of this systematic review and meta-analysis is to evaluate whether mpMRI based TB has increased detection rates of csPCa compared with TRUS-SB in men at risk for PCa. Furthermore, it evaluates whether there is a difference in detection rates of (cs)PCa among the three TB techniques based on the available literature.

Part II

In pursuit of the main objective of this thesis, a clear understanding of the factors influencing accuracy during TB procedures of the prostate is required. In **chapter 3** an ex-vivo validation study will be presented. This study evaluates the accuracy of a perineal MRI-TRUS fusion device for TB of mpMRI-derived targets and identifies the origin of errors. Furthermore, the study assesses the likelihood that lesions with incremental diameters can be accurately targeted.

The literature directly comparing the three available techniques of mpMRI based TB is limited. Therefore, a randomized controlled trial (RCT) was designed directly comparing the outcomes of MRI-TB, FUS-TB and COG-TB among men with a prior negative TRUS-SB and a persistent clinical suspicion on PCa. In **chapter 4** the research protocol of this trial (FUTURE trial) will be presented. In this chapter an abbreviated version of (the medical ethical review board approved) research protocol details the applied research methodology of this multicenter RCT.

Part III

In **chapter 5** the primary outcomes of the FUTURE trial are presented. The aim of this study is to assess if there is a superior technique of TB regarding diagnostic efficacy in a repeat biopsy setting by comparing overall PCa and csPCa detection rates of the three (MRI-TB, FUS-TB and COG-TB) TB techniques. Furthermore, several sub-group analyses will be presented to assess if there is an increased diagnostic efficacy in specific sub-groups of patients for any one technique.

In **chapter 6** a secondary outcome of the FUTURE trial will be presented. The aim of this study is to evaluate what the additional value of repeat SB is in men with negative prior SB and a persisting clinical suspicion of PCa undergoing TB of mpMRI identified lesions. In this study the detection rates of (cs)PCa of mpMRI based TB are compared with the detection rates of repeated TRUS-SB, in a subgroup of patients (who underwent both TB and SB) from the FUTURE trial. Furthermore, Gleason score concordance of both TB and SB with final radical prostatectomy specimens will be presented for another subgroup of FUTURE trial participants.

In **chapter 7** another secondary outcome of the FUTURE trial will be presented. The aim of this study is to assess if there is a significant difference in the occurrence of post-biopsy adverse events (AE) among patients undergoing MRI-TB, FUS-TB and COG-TB. Furthermore, univariate and multivariate analyses will be performed for suspected factors influencing the occurrence AE's. Finally, the influence of TB procedures on self-reported functional outcomes relating to urinary and erectile function will be reported.

Part IV

Chapter 8 of this thesis contains a general discussion of the studies presented in chapters 2-7. The studies presented in this thesis have been prepared in accordance with the prevailing guidelines at the time of initiation of each study. However, since then guidelines have been updated according to the latest evidence. The impact of these guideline updates is presented in this chapter, which ends with a discussion of future perspectives in prostate cancer diagnosis and management.

Chapter 9 contains English and Dutch summaries of this thesis.

Part V

This part contains several appendices to this thesis.

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2

Chapter 2

Comparing three different techniques for MRI targeted prostate biopsies: a systematic review of in-bore versus MRI-TRUS fusion versus cognitive registration. Is there a preferred technique?

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European Urology 2017; 71 (4): 517-531

ABSTRACT

Context: The introduction of MRI guided biopsies (MRI-GB) has changed the paradigm concerning prostate biopsies. Three techniques of MRI-GB are available: in-bore MRI target biopsy (MRI-TB), MRI-TRUS fusion (FUS-TB) and cognitive registration (COG-TB)

Objective: To evaluate whether MRI-GB has increased detection rates of (clinically significant) prostate cancer (PCa) compared to TRUS guided biopsy (TRUS-GB) in patients at risk for PCa, and which technique of MRI-GB has the highest detection of (clinically significant) PCa.

Evidence acquisition: We performed a search of the literature in PubMed, Embase and CENTRAL databases. Studies were evaluated using the QUADAS-2 checklist and START recommendations. Initial search identified 2562 studies, 43 were included in the meta-analysis.

Evidence synthesis: Among the included studies 11 used MRI-TB, 17 used FUS-TB, 11 used COG-TB, and 4 used a combination of techniques. In 34 studies concurrent TRUS-GB was performed. There was no significant difference between MRI-GB (all techniques combined) and TRUS-GB for overall PCa detection (RR 0.97 (0.90-1.07)). MRI-GB had higher detection rates of clinically significant PCa (csPCa) compared to TRUS-GB (RR 1.16 (1.02-1.32)), and a lower yield of insignificant PCa (RR 0.47 (0.35-0.63)). There was a significant advantage (p=0.02) of MRI-TB compared to COG-TB for overall PCa detection. For overall PCa detection there was no significant advantage of MRI-TB compared to FUS-TB (p=0.13), and neither for FUS-TB compared to COG-TB (p=0.11). For csPCa detection there was no significant advantage of any one technique of MRI-GB. The impact of lesion characteristics such as size and localization could not be assessed.

Conclusions: MRI-GB had similar overall PCa detection rates compared to TRUS-GB, increased rates of csPCa, and decreased rates of insignificant PCa. MRI-TB has a superior overall PCa detection compared to COG-TB. FUS-TB and MRI-TB appear to have similar detection rates. Head-to-head comparisons of MRI-GB techniques are limited, and needed to confirm our findings.

Patient summary: Our review shows that MRI guided biopsy detects more csPCa, and less insignificant PCa compared to systematic biopsy in men at risk for PCa.

INTRODUCTION

Prostate cancer (PCa) is the most common malignancy among European men.[1] PCa incidence is expected to increase due to PSA testing and aging of the general population.[1] The introduction of PSA testing led to an increased PCa incidence while mortality from PCa has decreased.[2,3] Disadvantages of PSA screening are the risks of over-diagnosis and over-treatment of clinically insignificant PCa.[3]

The current standard technique for PCa detection is transrectal ultrasound guided biopsy (TRUS-GB). Using TRUS-GB the prostate is randomly sampled for the presence of PCa, and has its limitations due to the inability of grey-scale ultrasonography to distinguish PCa from benign tissue.[4,5] Consequently TRUS-GB is renowned for its low sensitivity and specificity for PCa. This is underlined by the fact that repeat TRUS-GB due to persisting clinical suspicion on PCa, leads to the diagnosis of PCa in 10-25% of the cases following a prior negative biopsy.[6,7] Furthermore Gleason grading in radical prostatectomy specimens demonstrates upgrading in 36% when compared to pre-operative grading using TRUS-GB.[8] Developments of multiparametric MRI (mpMRI) techniques have increased the sensitivity of imaging for PCa.[9-12] According the European Society of Urogenital Radiology (ESUR) guidelines an mpMRI consists of T2-weighted images (T2W), Dynamic Contrast Enhanced (DCE) imaging and Diffusion Weighted Imaging (DWI).[13] Usage of a 3 Tesla (3-T) magnet has further enhanced resolution and quality of imaging compared to 1.5-T.[13] Clinical guidelines advise performing an mpMRI when initial TRUS biopsy results are negative but the suspicion of PCa persists.[4]

A standardised method for mpMRI evaluation was developed in order to increase inter-reader reliability and meaningful communication towards clinicians.[13] The PI-RADS (Prostate Imaging-Reporting and Data System) classification was introduced in 2012 by the ESUR, and has recently been updated to version 2.0.[13-15] It evaluates lesions within the prostate on each of three imaging modalities (T2W, DWI, and DCE) using a 1-5 scale, and additionally each lesion is given an overall score between 1-5 predicting its chance of being a clinically significant cancer.[13-15]

Classically the definition of clinically significant PCa (csPCa) was based on the Epstein criteria[16,17] and d'Amico classification[18,19]. These classifications are based on random TRUS-GB outcomes. Due to the introduction of target biopsy procedures the pre-operative definition of csPCa has changed. For that reason a number of new definitions of csPCa have been proposed, though as yet none has been widely adopted.[20-23]

Various strategies for targeted biopsy of lesions on MRI have been developed, and demonstrate increased detection rates of csPCa compared to TRUS-GB.[24-28] Currently no consensus exists on which strategy of targeted biopsy should be preferred. Existing strategies of MRI guided biopsy (MRI-GB) include:

a) in-bore MR target biopsy (MRI-TB) which is performed in the MRI suite using real-time MRI guidance.[26,28]
b) MRI-TRUS fusion target biopsy (FUS-TB) were software is used to perform MRI and TRUS image fusion, which allows direct target biopsies of MRI identified lesions using MRI-TRUS fusion image guidance.[29-32]
c) cognitive registration TRUS targeted biopsy (COG-TB) were the MRI is viewed preceding the biopsy, and is used to 'cognitively' target the MRI identified lesion using TRUS guidance.[33,34]

The aim of this systematic review is to answer the following questions. In men at risk for PCa (based on an elevated PSA (>4.0 ng/ml) and/or abnormal DRE (Digital Rectal Examination))

- Does MRI-GB lead to increased detection rates of (cs)PCa compared to TRUS-GB?
- Is there a difference in detection rates of (cs)PCa between the three available strategies of MRI-GB?

EVIDENCE ACQUISITION

Search strategy

A search strategy was designed using the STARLITE methodology.[35] A comprehensive search of the literature was performed. A range of the last 10 years was used since mpMRI has evolved rapidly in the last decade, and literature dating further back is not considered useful for current practise. No other search limits were applied. The search terms used were '*Prostate OR Prostatic Neoplasm' AND 'Biopsy' AND 'Magnetic Resonance Imaging OR Image-Guided Biopsy'* (see appendix 1 for the complete search query). The search was assisted by an information specialist on October 27th 2014 using the PubMed, Embase and CENTRAL databases.

Published primary diagnostic studies reporting on PCa detection rates among patients at risk of PCa using MRI-TB, or FUS-TB, or COG-TB were included. A direct comparison of MRI-GB techniques was not obligatory. Studies were excluded if they reported detection rates of PCa among patients with prior diagnosed PCa (including active surveillance populations, and mixed populations if data for subjects with no or negative prior biopsies was not

separately reported upon); if the MRI acquisition was not in accordance to the 2012 ESUR guidelines[13]; if the language was other than English, and if studies used alterative target biopsy strategies (such as contrast enhanced TRUS).

Since the interval between data presentation and initial search was significant, a cursory repeat search was performed on December 15th 2015. This search identified an additional 4 studies which were not included in the meta-analysis, but are incorporated in the discussion section of this paper.

Selection procedure

Following initial identification of studies, duplicates were removed by a single reviewer (OW). Titles and abstract of all studies were screened for relevance by two reviewers (OW, RS). Full text review of eligible studies was performed by three reviewers (OW, RS, HM). Any disagreement was handled by consensus, refereed by a fourth reviewer (RB).

The selection procedure followed the Preferred Reporting Items for Systematic Reviews and Mete-Analysis (PRISMA) principles and is presented using a PRISMA flow-chart.[36]

Quality assessment

The methodological quality of studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 checklist by two reviewers in consensus (OW, LH).[37] Using the QUADAS-2 checklist the risk of bias and concerns of applicability to the review questions was assessed. A sensitivity analysis was performed excluding the studies assessed to have high risk of bias or high concerns regarding applicability to the review questions.

Data extraction

The data for quantitative assessment was extracted by a single reviewer (OW) in accordance to the START recommendations.[38] Data was collected on the method of recruitment; population investigated; methods of MRI acquisition and evaluation; MRI findings and/or PI-RADS score; threshold applied for MRI positivity; methods of biopsy procedure; number of (systematic and target) cores taken; detection rates of (clinically significant) PCa (per subject and per core); and the applied definition of csPCa.

Data analysis

For the first review question on the difference in accuracy between TRUS-GB and MRI-GB, we combined the data of the three MRI-GB techniques. For this analysis, we focused on paired studies reporting results of both TRUS-GB and MRI-GB separately. The main accuracy

measure was the sensitivity of each technique, which was defined as the number of patients with detected cancer by TRUS-GB (or MRI-GB), divided by the total number of patients with detected cancer by the combination of TRUS-GB and MRI-GB. In other words, 1 minus the sensitivity of a technique is the percentage of patients with a cancer missed by this technique. We calculated the relative sensitivity for each study by dividing the sensitivity of MRI-GB by the sensitivity of TRUS-GB. We used the formula for the standard error of a relative risk without taking the paired nature into account because not all studies reported their data in a paired format.[39] A random effects pooled estimate of this relative sensitivity was calculated using the generic inverse variance method.[40] All sensitivity analyses were done twice: once for all PCa detected as the condition of interest and once focussing on csPCa only. For the per core analysis and detection of insignificant PCa we performed a yield analysis as accuracy measure, which was defined as the number of patient with detected cancer, divided by the total number of patient that underwent biopsy. We calculated the relative yield for each study by dividing the yield of MRI-GB by the yield of TRUS-GB.

For the second review question on the difference in accuracy between the various techniques of MRI-GB, we used studies reporting on at least one of the MRI-GB techniques (MRI-TB or FUS-TB or COG-TB). The applied accuracy measurement was the sensitivity of each MRI-GB technique as defined earlier. These proportions were meta-analysed using a random effects model, incorporating heterogeneity beyond chance due to clinical and methodological differences between studies. The within-study variances (i.e. the precision by which yield has been measured in each study) was modelled using the exact binomial distribution. Differences in sensitivity between MRI-GB techniques were assessed by adding the type of MRI-GB technique as covariate to the random effects meta-regression model. These analyses were performed for all PCa and csPCa. Extracted data was analysed using SPSS version 22.0 (SPSS Inc, IBM), and the random effects models were analysed in SAS version 9.2 (SAS Institute Inc).

EVIDENCE SYNTHESIS

Search and selection

Using the three databases 2562 studies were identified. Following removal of duplicates, abstract and title screening, and full text assessment a total of 43 articles were deemed relevant for the current review question. For an overview of the selection procedure and reason for exclusion see the PRISMA flow-chart (see **illustration 1**).

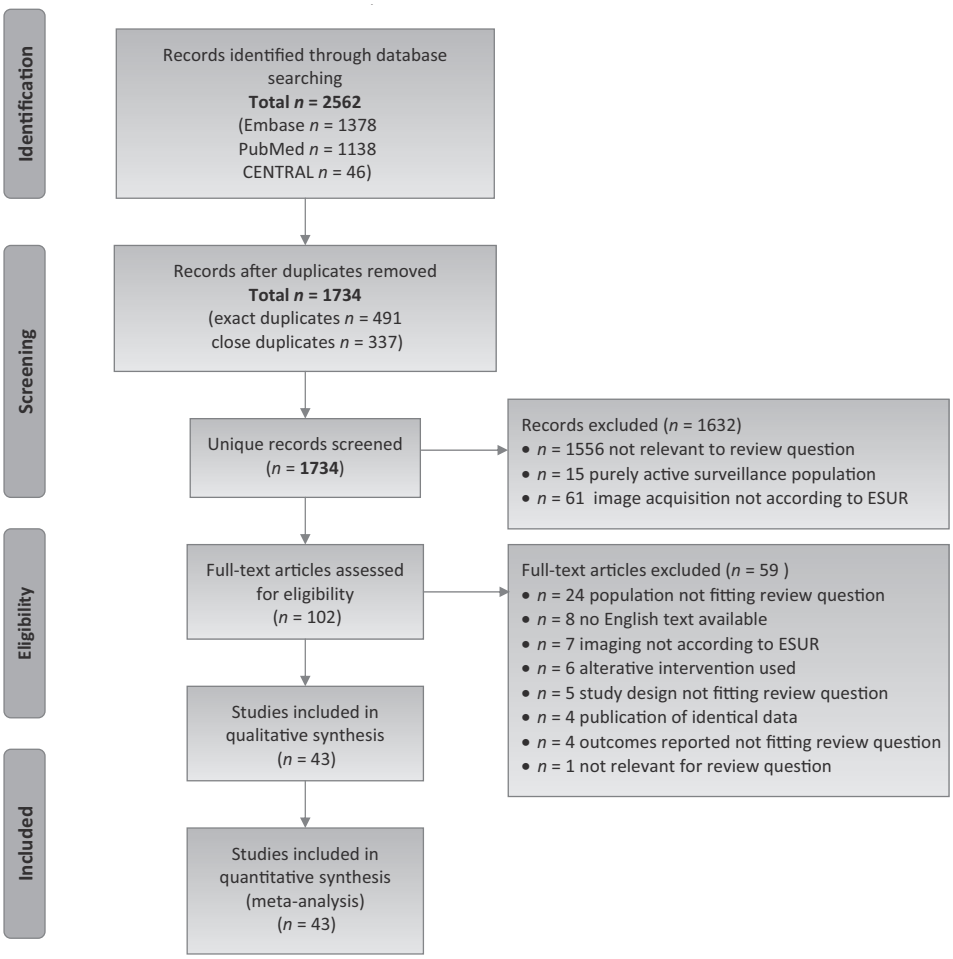

ILLUSTRATION 1: PRISMA Flow Chart

Quality assessment

Of the 43 studies subjected to quality assessment 54% (n=23) were estimated to have a low risk of bias, 40% (n=17) had a high risk of bias, and 7% (n=3) had an intermediate risk of bias.

Regarding the applicability to the current review 65% (n=28) had low concerns on applicability, and 35% (n=15) had high concerns. Causes for concerns regarding applicability and bias included whether TRUS-GB was performed in conjunction to MRI-GB, whether the operator of TRUS-GB was blinded for MRI results, the number of TRUS-GB cores taken, what

radiological threshold was applied to perform MRI-GB, and the population investigated. Of the 43 included studies 35% (n=15) had both a low risk of bias and low concerns regarding the applicability.

Population

The 43 included studies demonstrate significant variation in cohort size, ranging from 16-1003 (median 106) subjects. The mean PSA value ranged from 5.1-15.3 ng/ml and the mean age ranged from 61.8-70.0 years. The populations varied with respect to biopsy history. For all subsequent analysis, we used clinical homogenous data on detection rates among subjects with no or negative prior biopsies.

A 3-Tesla scanner was used in 72% (n=31) of the included studies. Of the included studies 58% (n=25) applied PI-RADS classification for the evaluation of the mpMRI. The above-mentioned heterogeneity in the evaluation and reporting of imaging is reflected by the variation of thresholds applied for performing a targeted biopsy.

Of the included studies 21% (n=9) performed MRI-GB exclusively, whilst 79% (n=34) combined it with TRUS-GB. Most studies applied a single technique of targeting, though 4 studies used both COG-TB and FUS-TB within the same population.

Finally considerable heterogeneity was found with respect to the applied definition of csPCa. Therefore we performed the analysis on csPCa detection using the definitions as applied in each original paper. Furthermore several studies did not present a definition of csPCa, and consequently did not report data on detection of csPCa. See **table 1** for an overview of all included studies, baseline characteristics, methodology applied for MRI imaging, and biopsy procedures.

MRI outcome

An overall estimate of all studies (n=20) reporting on the number of patients with tumour suspicious findings on MRI in subjects with a clinical suspicion on PCa yielded 73% (2225/3053) with MRI abnormalities. An overall estimate of studies reporting on the number of patients with tumour suspicious MRI abnormalities exclusively among subjects with no prior biopsies (n=6) resulted in a yield of 68% (734/1080), and a yield of 79% (567/716) exclusively among subjects with prior negative biopsies (n=7).

TABLE 1: Baseline characteristics and applied methodology of included studies

Author; year of publication	Population investigated	Recruitment criteria	No. of subjects	Mean age (yrs)	Mean PSA (ng/ml)	MRI used; magnet strength	Coil used (No. channels)	Threshold for target biopsy	Biopsy method; approach	SB and TB cores	Definition of clinically significant PCa
Hambrock et al, 2008(48)	Negative prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	21	62,0	15,0	Trio Tim (Siemens); 3 Tesla	ERC	In tumour suspicious/ abnormal MRI; no threshold defined	In-bore MRI; transrectal	No	No criteria for significance applied
Hambrock et al, 2010(49)	Negative prior biopsy	Elevated PSA and abnormal MRI	68	63,0	13,0	Trio Tim (Siemens); 3 Tesla	Combined ERC and PPA	In tumour suspicious/ abnormal MRI; no threshold defined	In-bore MRI transrectal	No	Epstein criteria
Miyagawa et al, 2010(50)	Negative prior biopsy	Elevated PSA and abnormal MRI	85	69,0	9,9	Interna pulsar (Philips); 1.5 Tesla	PPA	No threshold defined	MRI/TRUS fusion; transperineal	Yes	No criteria for significance applied
Franiel et al, 2011(51)	Negative prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	54	68,0	12,1	Avanto (Siemens); 1.5 Tesla	Combined ERC and PPA	PIRADS 2 or higher	In-bore MRI; transrectal	No	No criteria for significance applied
Park et al, 2011(52)	No prior biopsy	Elevated PSA and/or abnormal DRE	44	63,0	6,1	Interna Achieva (Philips); 3 Tesla	PPA	In tumour suspicious/ abnormal MRI; no threshold defined	cognitive TRUS; transrectal	Yes	No criteria for significance applied
Hadaschik et al, 2011(29)	Mixed population	Elevated PSA and/or abnormal DRE	95	66,0	8,0	Magnetom Trio (Siemens); 3 Tesla	PPA	Irrespective of MRI findings	MRI/TRUS fusion; transperineal	Yes	No criteria for significance applied
Hoeks et al, 2012(28)	Negative prior biopsy	Elevated PSA and abnormal MRI	265	66,0	11,4	Magnetom Trio (Siemens) and Magnetom Skyra (Siemens); Both 3 Tesla	PPA	In tumour suspicious/ abnormal MRI; no threshold defined	In-bore MRI; transrectal	No	d' Amico classification (intermediate and high risk) and Epstein criteria
Portalez et al, 2012(53)	Negative prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	129	64,7	9,6	Achieva (Philips) and Avanto (Siemens); Both 1.5 Tesla	PPA (8)	Irrespective of MRI findings	MRI/TRUS fusion; transrectal	Yes	No criteria for significance applied
Rouse et al, 2012(54)	Negative or no prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	114	63,6	13,4	Avanto (Siemens); 1.5 Tesla	Unclear	PIRADS 3 or higher	cognitive TRUS; transrectal	Yes	-Gleason score ≥ 3 + 4 -or Gleason 3+3 and MMCL ≥3mm;

TABLE 1: Continued

Author; year of publication	Population investigated	Recruitment criteria	No. of subjects	Mean age (yrs)	Mean PSA (ng/ml)	MRI used; magnet strength	Coil used (No. channels)	Threshold for target biopsy	Biopsy method; approach	SB and TB cores	Definition of clinically significant PCa
Arsov et al, 2012(55)	Negative prior biopsy	Elevated PSA and/or abnormal DRE	16	67,0	9,3	Magnetom Trio (Siemens); 3 Tesla	PPA (6)	No threshold defined	cognitive TRUS; transrectal	Yes	d' Amico classification (intermediate and high risk)
Vourganti et al, 2012(56)	Negative prior biopsy	Elevated PSA and/or abnormal DRE	195	62,0	9,1	Achieva (Philips); 3 Tesla	Combined ERC and PPA (16)	Irrespective of MRI findings	MRI/TRUS fusion; transrectal	Yes	Gleason score ≥ 3 + 4
Puech et al, 2013(34)	Negative or no prior biopsy	Elevated PSA and abnormal MRI	95	65,0	10,1	Gyroscan Intera, (Philips) and Symphony (Siemens); Both 1.5 Tesla	PPA	PIRADS 3 or higher	Cognitive TRUS and MRI/ TRUS fusion; transrectal	Yes	SB: -Gleason score ≥ 3+4 -Gleason score =3 + 3 and MMCL >3mm; TB: Gleason score ≥ 3+4
Wysock et al, 2013(42)	Mixed population	Elevated PSA and/ or abnormal DRE and abnormal MRI	67	65,0	5,1	Magnetom Trio (Siemens); 3 Tesla	PPA	PIRADS 2 or higher	Cognitive TRUS and MRI/ TRUS fusion; transrectal	Yes	Gleason score ≥ 3 + 4
Nagel et al, 2013(57)	Negative prior biopsy	Abnormal MRI	88	63,0	11,0	Trio Tim (Siemens); 3 Tesla	PPA	In tumour suspicious/ abnormal MRI; no threshold defined	In-bore MRI; transrectal	No	Gleason score ≥ 3 + 4
Quentin et al, 2013(58)	Negative or no prior biopsy	Elevated PSA	59	65,0	8,0	Magnetom Trio (Siemens); 3 Tesla	PPA (6)	PIRADS sum score ≥10	In-bore MRI; transrectal	No	No criteria for significance applied
Kasivivanathan et al, 2013(22)	Mixed population	Elevated PSA and/ or abnormal DRE and abnormal MRI	110	63,3	6,7	Avanto (Siemens) and Magnetom Verio (Siemens); 1.5 and 3 Tesla	PPA	PIRADS 3 or higher	cognitive TRUS; transperineal	Yes	Multiple definitions; applied definition: -Gleason score ≥ 3 + 4 or Gleason score = 3 + 3 and MCCL >4mm
Junker et al, 2013(59)	Negative prior biopsy	Elevated PSA	73	62,0	6,4	Magnetom Skyra (Siemens); 3 Tesla	PPA (18)	PIRADS sum score ≥7	MRI/TRUS fusion; transrectal	Yes	Gleason score ≥ 4 + 3
Rosenkrantz et al, 2013(60)	Negative or no prior biopsy	Elevated PSA	42	63,0	7,4	Unknown; 3 Tesla	PPA	In tumour suspicious/ abnormal MRI; no threshold defined	cognitive TRUS; transrectal	Yes	d' Amico classification (intermediate and high risk)

TABLE 1: Continued

Author; year of publication	Population investigated	Recruitment criteria	No. of subjects	Mean age (yrs)	Mean PSA (ng/ml)	MRI used; magnet strength	Coil used (No. channels)	Threshold for target biopsy	Biopsy method; approach	SB and TB cores	Definition of clinically significant PCa
Delongchamps et al, 2013(61)	No prior biopsy	Elevated PSA and/or abnormal DRE	391	63,9	8,5	Unknown; 1.5 Tesla	Combined ERC and PPA	Sum score of ≥ 4 and ≥ 6	Cognitive TRUS and MRI/ TRUS fusion; transrectal	Yes	Microfocal disease = Gleason score = 3 + 3 and MCCL <5mm and single core positve.
Fiard et al, 2013(62)	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE	30	64,0	6,3	Achieva (Philips); 3 Tesla	PPA (32)	PIRADS sum score ≥ 5	MRI/TRUS fusion; transrectal	Yes	-d' Amico classification (intermediate and high risk) -or Gleason score ≥ 3 + 4 -or TCCL ≥10mm
Kuru et al, 2013(31)	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE	347	65,3	9,9	Magnetom Trio (Siemens); 3 Tesla	PPA	Irrespective of MRI findings	MRI/TRUS fusion; transperineal	Yes	NCCN criteria (intermediate and high risk)
Kauffman et al, 2014(63)	Negative prior biopsy	Elevated PSA and abnormal MRI	35	68,0	9,4	Magnetom Espree (Siemens); 1.5 Tesla	ERC	Irrespective of MRI findings	In-bore MRI; transrectal	Yes	d' Amico classification (intermediate and high risk) and Epstein criteria
Penzkofer et al, 2014(64)	Mixed population	Abnormal MRI	52	65,0	15,3	Signa (GE); 3 Tesla	Combined ERC and PPA	No threshold defined	In-bore MRI; transperineal	No	Gleason score ≥ 3 + 4
Schimmoller et al, 2014(65)	Negative or no prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	235	65,7	9,9	Magnetom Trio (Siemens); 3 Tesla	PPA (6)	No threshold defined	In-bore MRI; transrectal	No	Gleason score ≥ 4 + 3
Shakir et al, 2014(66)	Negative or no prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	1003	62,1	6,7	Achieva (Philips); 3 Tesla	Combined ERC and PPA (16)	In tumour suspicious/ abnormal MRI; no threshold defined	MRI/TRUS fusion; transrectal	Yes	Gleason score ≥ 4 + 3
Rastinehad et al, 2014(30)	Negative or no prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	105	65,8	9,2	Magnetom Verio (Siemens); 3 Tesla	Combined ERC and PPA (16)	Low risk using NIH criteria	MRI/TRUS fusion; transrectal	Yes	SB: Epstein criteria (SB) TB:-Gleason score ≥3 + 4 -or MRI lesion > 0.2cc
Mozer et al, 2014(67)	No prior biopsy	Elevated PSA and abnormal MRI	152	63,0	6,0	Achieva (Philips); 1.5 Tesla	PPA	PIRADS 2 or higher	MRI/TRUS fusion; transrectal	Yes	-Gleason score ≥ 3 + 4 -or Gleason score = 3 + 3 and MCCL ≥4mm

TABLE 1: Continued

Author; year of publication	Population investigated	Recruitment criteria	No. of subjects	Mean age (yrs)	Mean PSA (ng/ml)	MRI used; magnet strength	Coil used (No. channels)	Threshold for target biopsy	Biopsy method; approach	SB and TB cores	Definition of clinically significant PCa
Salami et al, 2014(68)	Negative or no prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	175	64,9	7,1	Magnetom Verio (Siemens); 3 Tesla	Combined ERC and PPA (16)	PIRADS 2 or higher	MRI/TRUS fusion; transrectal	Yes	SB: Epstein criteria TB:-Gleason score ≥ 3+ 4 -or MRI lesion > 0.2cc
Salami et al, 2014(69)	Negative prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	140	65,8	9,0	Magnetom Verio (Siemens); 3 Tesla	Combined ERC and PPA (16)	PIRADS 2 or higher	MRI/TRUS fusion; transrectal	Yes	SB: Epstein criteria TB:-Gleason score ≥ 3+ 4 -or MRI lesion > 0.2cc
Shoij et al, 2014(70)	No prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	20	70,0	7,4	Signa (GE); 1.5 Tesla	PPA (8)	PIRADS 2 or higher	MRI/TRUS fusion; transperineal	Yes	-Gleason score ≥ 3 + 4 -MCCL >4mm
Roethke et al, 2014(27)	Negative or no prior biopsy	Elevated PSA and abnormal MRI	64	64,5	8,3	Magnetom Trio (Siemens); 3 Tesla	PPA	No threshold defined	MRI/TRUS fusion; transperineal	No	Gleason score ≥ 3 + 4
Ploussard et al, 2014(71)	Negative or no prior biopsy	Elevated PSA and/ or abnormal DRE and abnormal MRI	91	63,0	6,0	Intera (Philips); 1.5 Tesla	PPA	PIRADS 3 or higher	cognitive TRUS; transrectal	Yes	Epstein criteria
Kuru et al, 2014(72)	Negative prior biopsy	Elevated PSA and abnormal MRI	74	64,0	11,3	Unknown; 3 Tesla	PPA	In tumour suspicious/ abnormal MRI; no threshold defined	MRI/TRUS fusion; transperineal	Yes	Gleason score ≥ 4 + 3
Radtke et al, 2014(46)	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE	294	64,0	7,3	Unknown (Siemens); 3 Tesla	PPA	PIRADS 2 or higher	MRI/TRUS fusion; transperineal	Yes	Gleason score ≥ 3 + 4
Iwamoto et al, 2014(73)	No prior biopsy	Elevated PSA	238	69,2	9,6	Achieva (Philips) and Magnetom Skyra (Siemens); 1.5 and 3 Tesla		In tumour suspicious/ abnormal MRI; no threshold defined	cognitive TRUS; transrectal	Yes	Gleason score ≥ 3 + 4

TABLE 1: Continued

Author; year of publication	Population investigated	Recruitment criteria	No. of subjects	Mean age (yrs)	Mean PSA (ng/ml)	MRI used; magnet strength	Coil used (No. channels)	Threshold for target biopsy	Biopsy method; approach	SB and TB cores	Definition of clinically significant PCa
Thompson et al, 2014(20)	Negative or no prior biopsy	Elevated PSA and/or abnormal DRE	150	62,0	5,6	Unknown; 1.5 and 3.0 Tesla	PPA (32)	PIRADS 3 or higher	Cognitive TRUS and MRI/ TRUS fusion; transperineal	Yes	Multiple definitions; applied definition: -Gleason score ≥ 3 + 4 and >5% grade 4 component and <50% cores positive -or Gleason score ≥ 3 + 3 and <5% grade 4 component and <30% cores positive -or MCCL ≥8mm
Pokorny et al, 2014(23)	No prior biopsy	Elevated PSA and/or abnormal DRE	142	63,0	5,3	Magnetom Skyra (Siemens); 3 Tesla	PPA	PIRADS 3 or higher	In-bore MRI; transrectal	Yes	-Gleason score = 3 + 3 and MCCL ≥6 mm -or Gleason score = 3 + 4 and MCCL ≥4mm -or Gleason score ≥ 4 + 3
Jambor et al, 2014(74)	No prior biopsy	Elevated PSA	53	66,0	7,4	Magnetom Verio (Siemens); 3 Tesla	PPA	PIRADS 4 or higher	cognitive TRUS; transrectal	Yes	-Gleason score ≥ 3 + 4 -or Gleason score = 3 + 3 and MCCL ≥3mm
Boesen et al, 2014(75)	Negative prior biopsy	Elevated PSA and/or abnormal DRE	83	63,0	11,0	Achieva (Philips); 3 Tesla	PPA (6)	No threshold defined	cognitive TRUS; transrectal	Yes	Epstein criteria
Habchi et al, 2014(76)	Mixed population	Elevated PSA and/or abnormal DRE	204	61,8	8,3	Discovery (GE); 3 Tesla	PPA	PIRADS 2 or higher	cognitive TRUS; transrectal	Yes	Gleason score ≥ 3 + 4
Sonn et al, 2014(77)	Negative prior biopsy	Elevated PSA	105	65,0	7,5	Trio Tim (Siemens); 3 Tesla	PPA	PIRADS 2 or higher	MRI/TRUS fusion; transrectal	Yes	-Gleason score ≥ 3 + 4 -or Gleason score = 3 + 3 and MCCL ≥ 4mm
Quentin et al, 2014(45)	No prior biopsy	Elevated PSA	128	66,1	6,7	Magnetom Trio (Siemens); 3 Tesla	PPA (6)	No threshold defined	In-bore MRI; transrectal	Yes	-Gleason score ≥ 3 + 4 -or Gleason score = 3 + 3 and TCCL >5mm
Pepe et al, 2015(78)	Negative prior biopsy	Elevated PSA	100	64,0	8,6	Achieva (Philips); 3 Tesla	PPA (16)	PIRADS 4 or higher	cognitive TRUS; transperineal	Yes	-Gleason score ≥ 3 + 4 -or Gleason score = 3 + 3 and TCCL >50%

DRE = digital rectal examination; PPA = Pelvic Phased Array; ERC= Endorectal coil; PIRADS = prostate imaging reporting and data system; TRUS = transrectal ultrasound; MMCL = maximum cancer core length; SB = systematic biopsy; TB = target biopsy; TMCL = total cancer core length

MRI-GB versus TRUS-GB

Does MRI-GB result in a higher overall PCa detection rate compared to TRUS-GB?

For this analysis we evaluated 25 studies that reported on both MRI-GB (any technique) and TRUS-GB results separately within the same population. The pooled estimates of detection rates on a per patient basis demonstrates that MRI-GB and TRUS-GB did not significantly differ in overall PCa detection with a relative sensitivity of 0.98 (95% CI 0.90-1.07) (sensitivity for MRI-GB of 0.81 (95% CI 0.76-0.85); sensitivity for TRUS-GB of 0.83 (95% CI 0.77-0.88)). In other words MRI-GB missed 19% of all cancers, whilst TRUS-GB missed 17% (**see illustration 2A**).

In addition to detection on a per patient basis, 14 included studies presented detection rates on a per core basis for both MRI-GB and TRUS-GB. A pooled analysis on detection rates of PCa per core demonstrates that MRI-GB cores have a significant higher yield of PCa detection compared to TRUS-GB biopsy cores (relative yield 3.91 (95% CI 3.17-4.83) (yield of MRI-GB 0.41 (95% CI 0.33-0.49); yield of TRUS-GB 0.10 (95% CI 0.08-0.13)).

Does MRI-GB result in a higher detection rate of csPCa and a lower detection rate of insignificant PCa compared to TRUS-GB?

For this analysis we evaluated 14 studies that reported on the detection of csPCa for both MRI-GB and TRUS-GB separately within the same population. A pooled analysis of the detection rates of csPCa on a per patient basis, demonstrates that MRI-GB detected significantly more csPCa than TRUS-GB with a relative sensitivity of 1.16 (95% CI 1.02-1.32) (sensitivity for MRI-GB of 0.90 (95% CI 0.85-0.94); sensitivity for TRUS-GB of 0.79 (95% CI 0.68-0.87)). In other words MRI-GB missed 10% significant cancers whilst TRUS-GB missed 21% (**see illustration 2B**).

A pooled analysis of the detection rates of insignificant PCa demonstrates that MRI-GB detected significantly less insignificant PCa than TRUS-GB with a relative yield of 0.47 (95% CI 0.35-0.63) (yield for MRI-GB 0.07 (95% CI 0.04-0.10); yield for TRUS-GB of 0.14 (95% CI 0.11-0.18)). In other words TRUS-GB alone detected twice as many clinically insignificant cancers as MRI-GB alone (**see illustration 2C**).

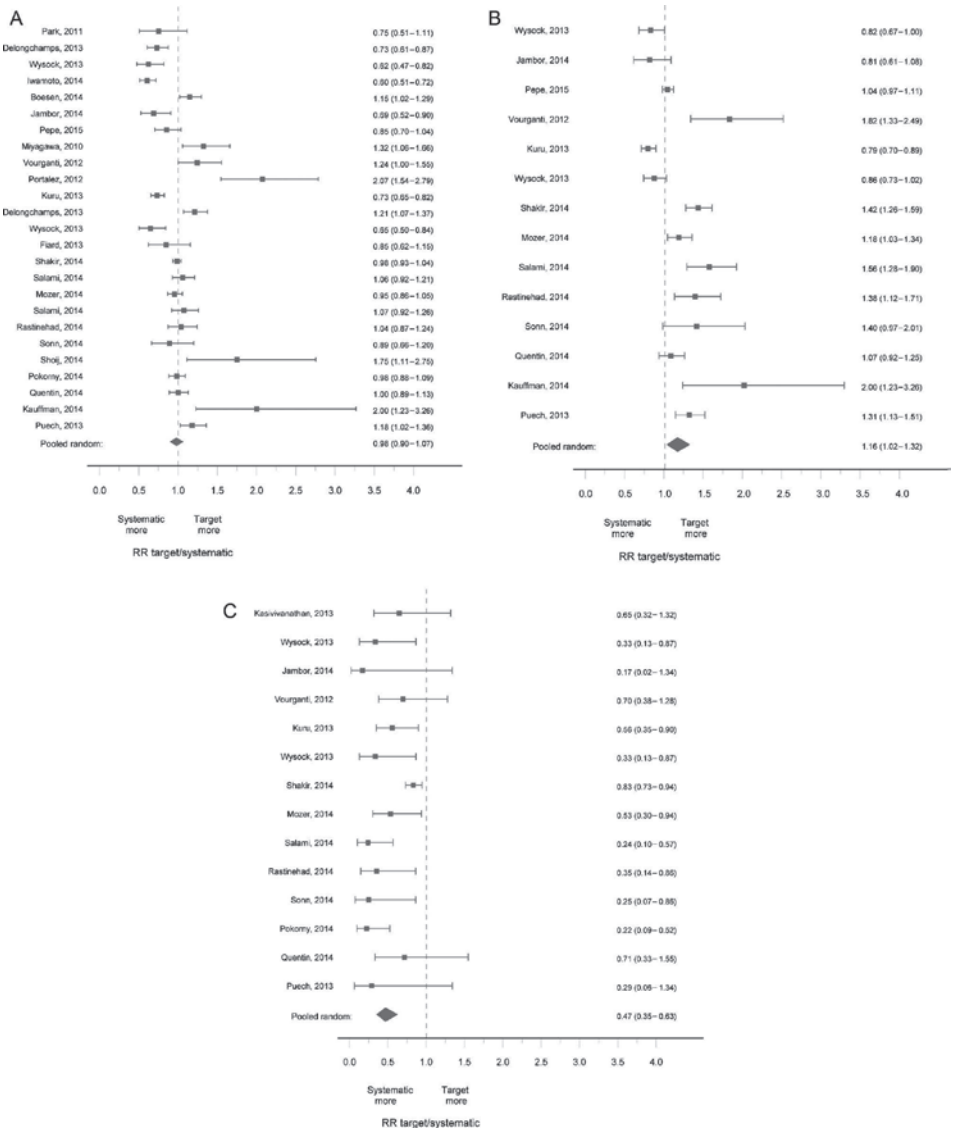

ILLUSTRATION 2A: Forest plot of pooled relative sensitivity of MRI-GB and TRUS-GB for all PCa. **B:** Forest plots of pooled relative sensitivity of MRI-GB and TRUS-GB for significant PCa. **C:** Forest plots of pooled relative yield of MRI-GB and TRUS-GB for insignificant PCa.

RR = relative risk

Sensitivity analysis

When regarding the overall PCa detection rates exclusively in publications with low risk of bias, and low concerns regarding applicability, which reported on TRUS-GB in conjunction with MRI-GB within the same population (n=10), we found a relative sensitivity of 0.86 (95% CI 0.74-0.99). When looking at csPCa detection rates in publications with low risk of bias, and low concerns regarding applicability (n=4), we found a relative sensitivity of 0.97 (95% CI 0.71-1.33).

MRI-TB versus FUS-TB versus COG-TB

Which technique of targeting has the highest overall detection rate of PCa?

Of the included studies that reported on the outcomes of both MRI-GB and TRUS-GB within the same population, 7 used COG-TB to perform targeting (n=712), 14 used FUS-TB (n=2817) and 3 used MRI-TB (n=305). The pooled sensitivity for COG-TB was 0.72 (95% CI 0.62-0.81). The pooled sensitivity for FUS-TB was 0.81 (95% CI 0.75-0.85). The pooled sensitivity for MRI-TB was 0.89 (95% CI 0.78-0.95) (**see illustration 3A**). Based on the above-mentioned pooled sensitivities there is a significant (p=0.02) advantage of usage of MRI-TB compared to COG-TB for overall PCa detection. There were no significant differences in the performance of FUS-TB compared to MRI-TB (p=0.13), and FUS-TB compared to COG-TB (p=0.11).

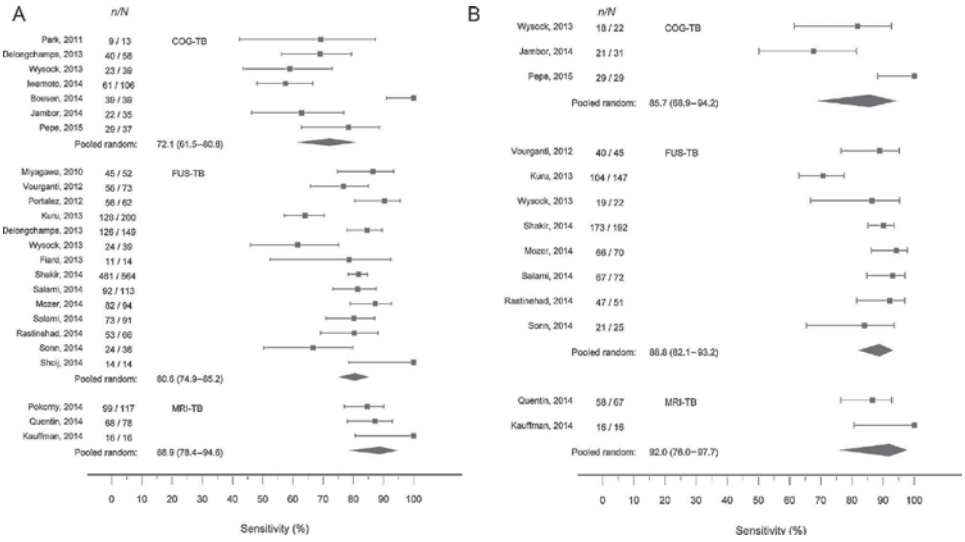

ILLUSTRATION 3A: Forest plots of pooled sensitivity of COG-TB, FUS-TB and MRI-TB for all PCa.
B: Forest plots of pooled sensitivity of COG-TB, FUS-TB and MRI-TB for significant PCa

Which technique of targeting has the highest detection rate of csPCa?

Of the included studies that reported on the detection rates of csPCa of both MRI-GB and TRUS-GB within the same population, 3 used COG-TB to perform targeting (n=220), 8 used FUS-TB (n=2114) and 2 used MRI-TB (n=163). The pooled sensitivity for csPCa for COG-TB was 0.86 (95% CI 0.69-0.94). The pooled sensitivity for FUS-TB was 0.89 (95% CI 0.82-0.93). The pooled sensitivity for MRI-TB was 0.92 (95% CI 0.76-0.98) (**see illustration 3B**). Based on the above-mentioned pooled sensitivities there was no significant advantage of usage of any one technique of MRI-GB for the detection of csPCa; MRI-TB vs FUS-TB (p=0.60); MRI-TB vs COG-TB (p=0.42); FUS-TB vs COG-TB (p=0.62).

DISCUSSION

Summary of findings

The paradigm on biopsy strategies in men with increased risk for PCa is shifting, and the optimal biopsy strategy is yet to be determined. The optimal biopsy technique presumably has a near 100% detection rate of csPCa, whilst simultaneously have a low detection rate of clinically insignificant PCa.

The direct comparison of MRI-GB and TRUS-GB within the same population demonstrates that there is no statistically significant difference for overall PCa detection. Though a per core analysis demonstrates a statistically significant increased incidence of PCa in target biopsy cores when compared to systematic biopsy cores, with a relative yield of 3.91 (95% CI 3.17-4.83). When focussing on the detection of csPCa MRI-GB has a statistically significant advantage over TRUS-GB, with a relative sensitivity of 1.16 (95% CI 1.02-1.32), indicating that MRI-GB significantly detects more clinically significant cancers than TRUS-GB. Consequently MRI-GB has a statistically significant lower yield of insignificant PCa compared to TRUS-GB, with a relative yield of 0.47 (95% CI 0.35-0.63). These results support MRI-GB as a superior alternative to TRUS-GB. These findings are similar to findings of a previous meta-analysis comparing TRUS-GB to MRI-GB in which the authors found a relative sensitivity for MRI-GB of 1.05 (95% CI 0.94–1.19) for overall PCa, and a relative sensitivity of 1.20 (95% CI 1.09–1.32) for csPCa.[41]

Are we ready to abandon systematic TRUS-GB and completely replace it for MRI-GB? Based on this meta-analysis, omitting TRUS-GB would result in missing 19% of all PCa, and 10% of the csPCa. Simultaneously by omitting TRUS-GB 50% of the insignificant PCa would not

be detected and would thereby decrease over-diagnosis of these tumours. The debate on whether this is acceptable or not is ongoing, and a definite conclusion is beyond the scope of this review.

Which technique for MRI-GB should then be preferred? The results of this current meta-analysis indicate that MRI-TB has an advantage over COG-TB in overall PCa detection (p=0.02). There does not seem to be a significant advantage of MRI-TB compared to FUS-TB, or FUS-TB compared to COG-TB for overall PCa detection. When focussing on the detection of csPCa, there does not seem to be a significant advantage of any particular technique, though the number of studies used for this specific meta-analysis was limited. When comparing various techniques of MRI-GB essential components are targeted lesion characteristics, such as PI-RADS classification, lesion size and lesion location. Of 43 included studies only 5% (n=2) presented data regarding lesion diameter, and 58% (n=25) applied PI-RADS classification. Furthermore the applied threshold for target biopsy will directly impact the found tumour yield, and as mentioned earlier the included studies demonstrate significant heterogeneity regarding applied threshold. Consequently the results of this meta-analysis are indicative at best: the number of randomised controlled trials directly comparing one technique to another is limited. Within the cohort presented in this meta-analysis there were only two studies directly comparing 2 techniques.[34,42] Both studies were not able to demonstrate significant differences between COG-TB and FUS-TB on overall cancer and clinically significant cancer detection. Though a multivariate analysis in one study demonstrated increased cancer detection in smaller MRI lesions using FUS-TB when directly compared to COG-TB.[42] Importantly a large RCT comparing all three techniques of MRI-GB is underway.[43]

Strengths and limitations

The number of studies investigating MRI-GB was quite large, but there was considerable heterogeneity in applied methodology. The majority of studies report on subsequent cohorts of patients undergoing target biopsy procedures. The number of studies that applied a comparative test (such as TRUS-GB) in conjunction with target biopsy is limited. And finally the quality of MRI acquisition seems to demonstrate significant heterogeneity, directly influencing the outcome of MRI-GB.

The major strength of this meta-analysis is that all included studies have used MRI acquisition protocols in accordance to the latest imaging guidelines. Hereby safeguarding some level of homogeneity in the selection procedure for subsequent MRI-GB. Furthermore only studies performing both MRI-GB and TRUS-GB within the same population were included in the meta-analysis. As a consequence the number of eligible studies was limited, especially for MRI-TB where lack of simultaneous TRUS-GB seems to be most common.

The heterogeneous usage of definitions for csPCa incorporating PSA (density), clinical stage and histology among the different series is a major concern for this current meta-analysis and even more so because most definitions have their origin in the systematic biopsy setting. As such they are, at least partially, based on variables such as cancer core length, and number of positive cores and therefor might significantly overestimate the number of detected csPCa in a targeted biopsy setting. Consequently commonly used definitions such as the Epstein criteria seem to become outdated, whereas new generally accepted criteria have yet to be formulated for MRI-GB. Of the 14 studies used for the analysis on csPCa in this systematic review only 3 used a definition of csPCa solely based on the presence of a Gleason 4 component on biopsy.[42,44,45]

Furthermore the method of MRI evaluation, and the applied threshold for MRI-GB seems to demonstrate heterogeneity. This will directly impact tumour detection yields, as studies that incorporate subjects with benign finding on MRI will demonstrate lower tumour yields than studies that only incorporate subjects with very suspicious findings on MRI. Potentially the PIRADS grading system can solve this problem, but it has only been introduced several years ago. Therefore the number of studies using this grading system is as yet limited. Thirdly we found significant variation concerning biopsy conduct, especially concerning comparative testing. Not only did the number of cores on TRUS-GB vary, but also whether systematic biopsy was performed prior to or following MRI-GB. Moreover several techniques of FUS-TB are commercially available, and this variation can impact accuracy of targeting. Rigid image fusion (where the MRI prostate contour is projected over the TRUS image, and used to match landmarks during the planning phase of biopsy) is likely to be less accurate when compared to elastic image fusion (where the prostate is contoured on both the MRI and the TRUS image, and the contours are fused correcting for prostate deformation and movement during the entire biopsy procedure).[32] Finally the absence of lesion specific descriptive characteristics, such as size, in the majority of studies limits the ability to perform accurate comparison of the various MRI-GB techniques. If only larger lesions are biopsied, this may negatively affect the potential of MRI-TB.

A cursory repeat search on December 15th 2015 identified another 4 major relevant publications.[46-49] All studies performed MRI-GB in conjunction with TRUS-GB. 3 studies used FUS-TB, and 1 paper used MRI-TB to perform MRI-GB in subjects at risk for PCa. The 3 studies using FUS-TB concluded that MRI-GB detects more csPCa compared to TRUS-GB whist decreasing the detection of clinically insignificant PCa.[46,48,49] Though one paper concluded that omitting TRUS-GB would miss some clinically significant cancers.[46] The fourth paper performed MRI-TB in conjunction with TRUS-GB in biopsy naïve subjects. The authors concluded that MRI-GB and TRUS-GB have equivalent high detection yield, though MRI-GB

required significantly less biopsy cores compared to TRUS-GB to accomplish this diagnostic yield.[47] These results are in accordance to the findings of this current meta-analysis, and are summarised in appendix 2.

CONCLUSION

In men at risk for PCa who have tumour suspicious lesions on MRI subsequent MRI-GB of these lesions demonstrates similar overall tumour detection rates compared to systematic TRUS-GB, although the incidence of PCa is increased in targeted cores when compared to systematic cores. Moreover the sensitivity of MRI-GB is increased for the detection of csPCa, and decreased for clinically insignificant PCa when compared to TRUS-GB.

Based on the studies included in this meta-analysis MRI-TB demonstrates a superior performance in overall PCa detection when compared to COG-TB. For overall PCa detection and detection of csPCa FUS-TB has a similar performance compared to MRI-TB. Though the current number of RCTs performing a head to head comparison of the various techniques for MRI-GB is limited, and comparative analysis is restricted by the absence of data on lesion characteristics.

Acknowledgements

None

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APPENDICES

Appendix 1: Complete search query

Complete search query.
Date of search: 27-10-2014
Search performed by: Carla Sloof (c.sloof@antoniusziekenhuis.nl).

PubMed

("Prostate"[Mesh] OR "Prostatic Neoplasms"[Mesh] OR prostat*[tiab]) AND ("Biopsy"[Mesh] OR biops*[tiab]) AND ("Magnetic Resonance Imaging"[Mesh] OR "Image-Guided Biopsy"[Mesh] OR magnetic resonance[tiab] OR MRI*[tiab] OR MR imag*[tiab] OR MR guid*[tiab] OR MR target*[tiab] OR MR-US[tiab] OR MRUS[tiab] OR MR-TRUS[tiab] OR mpMR*[tiab] OR image guid*[tiab] OR imaging guid*[tiab] OR fusion-guid*[tiab] OR multiparametric[tiab] OR image fusion[tiab] OR ultrasound fusion[tiab] OR US fusion[tiab]) *NOT (review[pt] OR case reports[pt]) AND (2004:2014[pdat])*

1138 hits

Embase

'prostate'/de OR 'prostate tumor'/exp OR prostat*:ab,ti AND ('biopsy'/exp OR biops*:ab,ti) AND ('nuclear magnetic resonance imaging'/exp OR 'image guided biopsy'/exp OR 'magnetic resonance':ab,ti OR mri*:ab,ti OR (mr NEXT/1 (imag* OR guid* OR target* OR us OR trus)):ab,ti OR mrus:ab,ti OR mpmr*:ab,ti OR ((image OR imaging OR fusion) NEXT/1 guid*):ab,ti OR multiparametric:ab,ti OR 'image fusion':ab,ti OR 'ultrasound fusion':ab,ti OR 'us fusion':ab,ti) *NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [review]/lim OR 'case report'/de) AND [1-1-2004]/sd*

1378 hits

CENTRAL

prostat* and biops* and ('magnetic resonance' or mri* or (mr next/1 (imag* or guid* or target* or us or trus)) or mrus or mpmr* or ((image or imaging or fusion) next/1 guid*) or multiparametric or 'image fusion' or 'ultrasound fusion' or 'us fusion')

Filters: Publication Year from 2004 to 2014

46 hits

Total hits 3 databases: 2562 referenties

Appendix 2: Summary of results of additional papers from cursory repeat search.

Author; year of publication	Population investigated	No. of subjects	Mean age (yrs)	Mean PSA (ng/ml)	MRI used; magnet strength	Threshold for target biopsy	Biopsy method; approach	Definition of clinically significant PCa	No. of subjects SB No. of subjects TB	Sensitivity all cancer	Sensitivity significant cancer
Peltier, 2015	No prior biopsy	110	65.1	8.4	Magnetom Verio (Siemens); 3 Tesla	In tumour suspicious/ abnormal MRI; no threshold defined	MRI/TRUS fusion; transrectal	-Gleason score ≥ 3 + 4 -or Gleason 3+3 and MMCL ≥6mm;	SB: n=110 TB: n=100	SB: 72.5% (50/69) TB: 82.6% (57/69)	SB: 61.5% (32/52) TB: 98.1% (51/52) *P = 0.0008*
Quentin, 2014	No prior biopsy	128	66.1	8.7	Magnetom Trio (Siemens); 3 Tesla	No threshold defined	In-bore MRI; transrectal	-Gleason score ≥ 3 + 4 -MCCL >5mm	SB: n=128 TB: n=128	SB: 87.25% (68/78) TB: 87.25% (68/78)	SB: 80.6% (54/67) TB: 86.6% (58/67)
Radtke, 2015	Negative or no prior biopsy	294	64	7.3	Unknown (Siemens); 3 Tesla	PIRADS 2 or higher	MRI/TRUS fusion; transperineal	-Gleason score ≥ 3 + 4	SB: n=294 TB: n=196	SB: 90% (135/150) TB: 74.7% (112/150) *P = 0.001*	SB: 79.1% (68/86) TB: 87.2% (75/86)
Siddiqui, 2015	Negative or no prior biopsy	1003	62.1	6.7	Achieva (Philips); 3 Tesla	In tumour suspicious/ abnormal MRI; no threshold defined	MRI/TRUS fusion; transrectal	-Gleason score ≥ 4 + 3 -or Gleason score = 3 + 4 and >50% core positivity	SB: n=1003 TB: n=1003	SB: 83.2% (469/564) TB: 81.7% (461/564)	SB: 69.4% (211/304) TB: 81.6% (248/304) *P < 0.001*

PIRADS = prostate imaging reporting and data system; TRUS = transrectal ultrasound; MMCL = maximum cancer core length; SB = systematic biopsy; TB = target biopsy; TCCL = total cancer core length

3

Chapter 3

An ex-vivo phantom validation study of an MRI-TRUS fusion device for targeted prostate biopsy

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Journal of Endourology 2016; 30 (6): 685-691

ABSTRACT

Objectives: To evaluate the ex-vivo accuracy of an MRI-TRUS fusion device for guiding targeted prostate biopsies, to identify the origins of errors, and to evaluate the likelihood that lesions can be accurately targeted.

Materials and Methods: Three prostate phantoms were used to perform 27 biopsies using transperineal MRI-TRUS fusion. All phantoms underwent 3-T MRI. The prostate contour and nine lesions were delineated onto the MRI. A 3D-US dataset was generated and fused with the MRI. Per lesion one needle was virtually planned. The post-biopsy needle location was virtually registered. The needle trajectory was marked using an MRI-safe guidewire. Post-interventional MRI was performed. The coordinates of the lesion on pre-interventional MRI, the virtually planned needle, the virtually registered needle, and the marked needle trajectory on post-interventional MRI were documented and used to calculate the planning error (PE), targeting error (TE), and overall error (OE). Using the OE in the transversal plane an upper one-sided tolerance interval was calculated to assess the likelihood that a biopsy needle was on target.

Results: In the transversal plane the mean PE, TE, and OE were 1.18 mm, 0.39 mm and 2.33 mm respectively. Using a single biopsy core the likelihood that lesions with a diameter of 2 mm can be accurately targeted is 26%; lesions of 3 mm 61%; lesions of 4 mm 86%; lesions of 5 mm 96%, and lesions of 6 mm 99%. The likelihood of accurate sampling increases if more biopsy cores are used.

Conclusion: MRI-TRUS fusion allows for accurate sampling of MRI identified lesions with an overall error of 2.33mm. Lesions with a diameter of 3 mm or more can be accurately targeted. These results should be considered the lower limit of in-vivo accuracy.

INTRODUCTION

Prostate cancer is the most commonly diagnosed malignancy amongst men.[1] The standard detection technique for prostate cancer is transrectal ultrasound (TRUS) guided biopsy. TRUS is an office-based investigation using grey-scale ultrasonography, but has limited abilities to distinguish prostate cancer from benign tissue.[2] Therefore TRUS biopsies are performed in a random, systematic manner in contrast to imaging guided, targeted biopsies as used in other solid malignancies. The low sensitivity of systematic TRUS biopsy is demonstrated by the fact that repeat TRUS biopsy reveals prostate cancer in 10-25% of the cases following prior negative biopsy.[3-5] Furthermore radical prostatectomy specimens demonstrate tumour upgrading in 36.3% of the cases compared to pre-operative grading using systematic TRUS biopsy as a result of sampling error in a heterogeneous tumour.[6] Evidently targeted prostate biopsy has great potential in improving detection rates compared to random, systematic biopsies.

The use of multiparametric MRI (mpMRI) techniques has dramatically increased the sensitivity of imaging for detection and staging of prostate cancer.[7-11] Clinical guidelines now advise performing mpMRI when the clinical suspicion on prostate cancer persists despite negative TRUS biopsy results.[12] There are several techniques available to utilize MRI information for direct targeted biopsies. All these techniques demonstrate increased detection rates of significant prostate cancer compared to systematic biopsy.[13-19] An upcoming technique is MRI-TRUS fusion targeted biopsy, which utilises the high diagnostic yield of mpMRI for prostate cancer in combination with the practicality and affordability of TRUS biopsy systems. Commercially available MRI-TRUS devices fuse pre-interventional mpMRI images, onto which tumour suspicious lesions are delineated, with real-time ultrasound images, enabling MRI-targeted biopsy. Various techniques exist to apply MRI-TRUS image fusion. In rigid image fusion the prostate is contoured on the MRI image and projected over the TRUS image, and is used to match paired landmarks during the planning phase of biopsy. In elastic image fusion the prostate is contoured on both the MRI and the TRUS image, and the contours are fused correcting for prostate deformation and movement during the entire biopsy procedure.[20-26] Additionally there are several ways to track the probe location compared to the target lesion. In sensor-based image fusion the probe contains a tracker which is used to determine the location of the probe compared to the target lesion.[20,26,27] In organ-based image fusion the contours of the prostate on imaging modalities are used to track location of the probe compared to the lesion.[20,21,25,28] Preliminary in-vivo investigations using various MRI-TRUS fusion devices uniformly show an increase in the detection of prostate cancer.[10,15,17] Furthermore a recent systematic review demonstrates that the various MRI-TRUS fusion devices detect more

significant prostate cancers compared to TRUS biopsy, using fewer biopsy cores.[29] In order to obtain representative tissue samples from tumour suspicious lesions accurate target biopsy procedures are essential. The literature evaluating the ex-vivo accuracy of MRI-TRUS fusion systems is limited.[25,26,30] The current study aims to evaluate the accuracy of a perineal MRI-TRUS fusion device (BiopSee® Medcom, Darmstadt, Germany) for target biopsy of MRI derived targets, and additionally to identify the origins of errors. Furthermore it aims to evaluate the likelihood that lesions with incremental diameters can be accurately targeted.

MATERIALS AND METHODS

Phantom models

We performed MRI-TRUS fusion perineal targeted biopsy on 3 prostate phantom models (CIRS Inc, Norfolk, Virginia, Model 066). Each model contains a prostate, 3 lesions within the prostate, a simulated perineal membrane, a simulated rectum within a clear acrylic container. (**See figure 1**). The lesions were not used for the current investigation due to their relative large diameter (10 mm).

Pre-interventional MRI

All phantoms underwent pre-interventional 3-T MRI (Siemens MAGNETOM ® Skyra) using transversal and sagittal T2 weighted imaging. Sequence parameters were TR 15.870 ms, TE 91 ms, FoV 180 mm x 180 mm and a slice thickness of 0.8 mm, resulting in a voxel size of 0.3x0.3x0.8 mm. The prostate was contoured and nine randomly placed fictive lesions per phantom were delineated onto the MR image. Each lesion was made as small as technically feasible using the device software, since the aim of the current investigation is to evaluate the accuracy of the system. Each lesion was cylindrically shaped with a diameter of 2 mm in the transversal plane (volume of 10 mm^3). The coordinates from the centre of each lesion as indicated in the pre-interventional MR images were documented (See figure 2), and used as reference standard for all subsequent measurements.

Ultrasound acquisition

A series of 2D-US transversal images was acquired by moving the TRUS probe from cranially to caudally, which were reconstructed resulting in a 3D-US dataset. The TRUS probe consists of 128 crystal arrays in both radial and longitudinal directions with a FoV of 165 degrees in the axial plane and 70 mm in the longitudinal plane. The maximum frequency of the probe is 8 MHz in the axial plane and 10 MHz in the longitudinal plane.

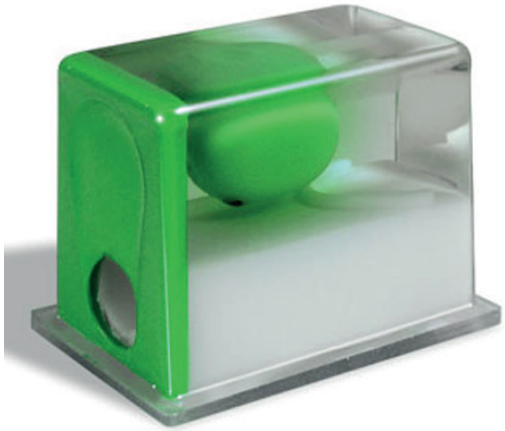

FIGURE 1. Prostate Phantom Model 066 (CIRS, Inc.), illustration supplied by CIRS, Inc.

Image fusion

MRI and US image fusion was performed using an automated rigid, organ-based image transformation.[15,20-22,24,28] This is done by projecting the contour of the prostrate on the MRI over the 3D-US image. The contour of the prostate on the MRI is then automatically matched with the 3D-US image, thereby performing automated rigid image fusion. Manual correction of the image fusion was performed using 3 degrees of translations and 3 degrees of rotation if necessary. Scaling was automated by the MRI-TRUS fusion device. Automated rigid image fusion is was applied instead of elastic image fusion because no tissue movement and deformation was expected during biopsy in this ex-vivo phantom setting. Segmentation was performed by a urologist with extensive experience in performing MRI-TRUS fusion biopsy (HvM).

Needle planning

One needle trajectory per lesion was planned virtually onto the 3D-US dataset towards the geometrical centre of each lesion. For each planned needle trajectory on the 3D-US image the coordinates of the centre of the biopsy core were documented before performing the biopsy procedure (**See figure 2**).

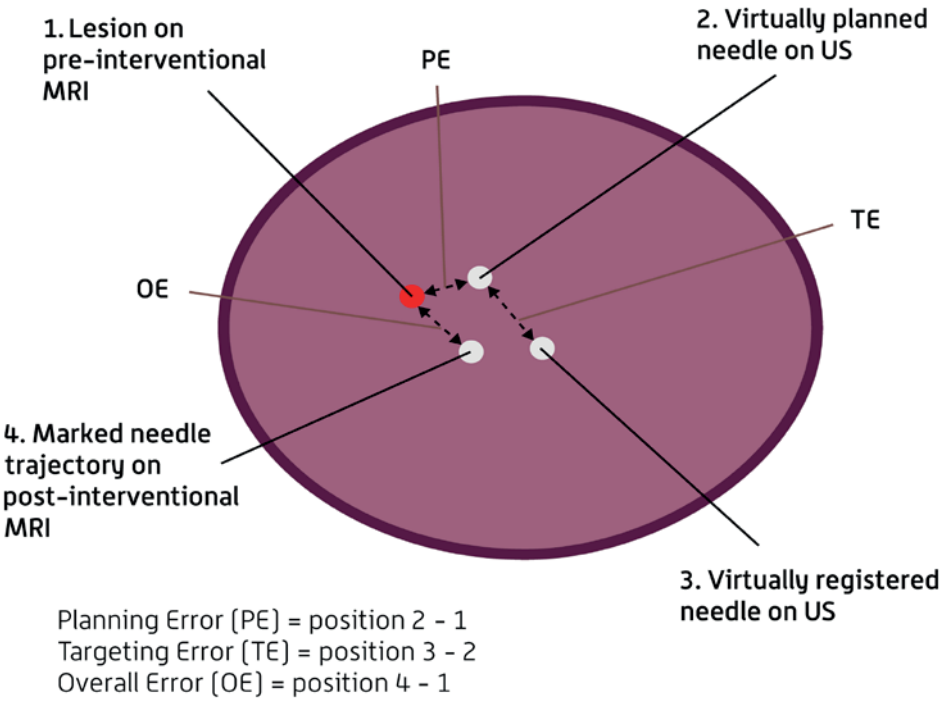

FIGURE 2. Schematic representation of the transversal plane of the prostate, including the main study parameters.

Biopsy procedure and registration

A total of 27 stereotactic perineal biopsy cores were taken from 3 phantoms using the BiopSee® MRI-TRUS fusion device. The device incorporates the mentioned TRUS probe, a stepper, a diagonal grid with a spacing of 2.5 mm, and a trolley containing the hardware needed (**See Figure 3**). The biopsy is guided by real-time MRI-TRUS fusion images. The depth and the axial rotation of the TRUS probe can be adjusted using the stepper and is tracked by the device. Biopsies were carried out using a Bard® Magnum® gun (Bard Inc, Tempe, Arizona), and 18G needles with a length of 250 mm with a bevelled tip, and a biopsy core length of 22 mm. Biopsies were performed by one experienced urologist (HvM). The needle location was virtually registered for each needle biopsy (**See figure 2 and figure 4**).

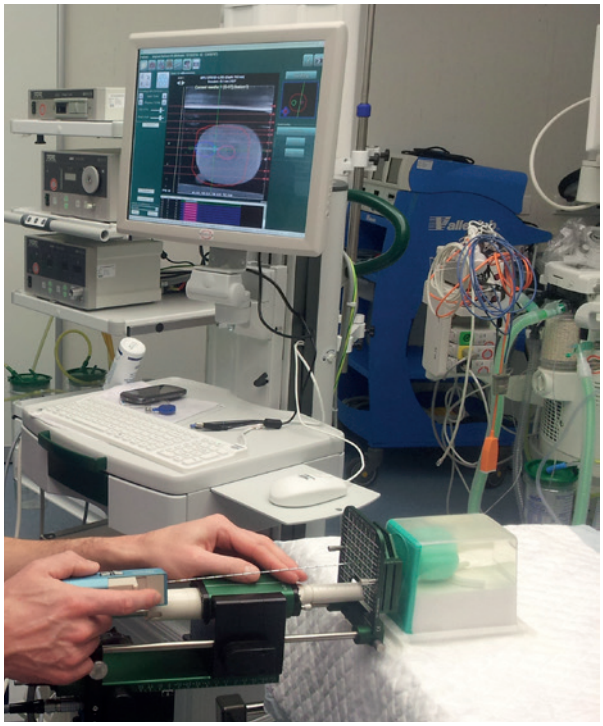

FIGURE 3. MRI-TRUS fusion biopsy procedure using the BiopSee device.

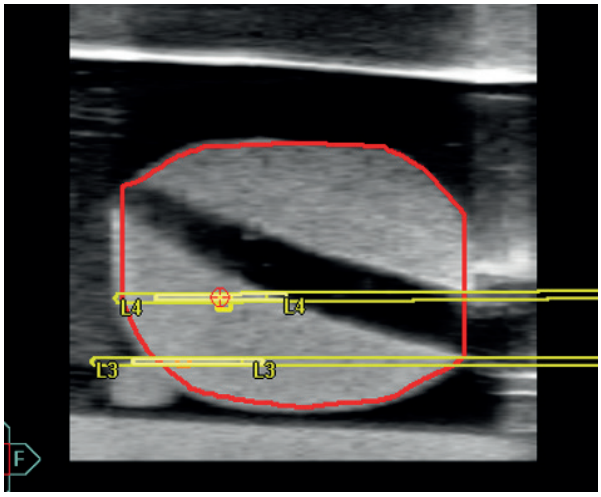

Figure 4. Sagittal view of 3D-US dataset with two registered needle trajectories (position 3).

Biopsy verification

Following virtual registration, the inner needle was removed leaving the outer sheath in place. An MRI-safe guidewire (Roadrunner® Hydrophilic PC Wire Guide 3 Fr, Cook® Medical, Bloomington, Indiana) was placed through the outer sheath whilst observing the US image for depth of the guidewire. Once in place the outer sheath was removed, and the guidewire was clipped at entry level of the needle. A post-interventional MRI was made of each phantom with the guidewires in place. The coordinates of each guidewire as indicated in the post-interventional MR images were documented (**See figure 2 and figure 5**). In order to compare the coordinates of the target lesion and the coordinates of the verification guidewire, the pre- and the post-interventional MR images were fused using the same method as for the fusion of the MR and US images. Segmentation was performed by the same operator.

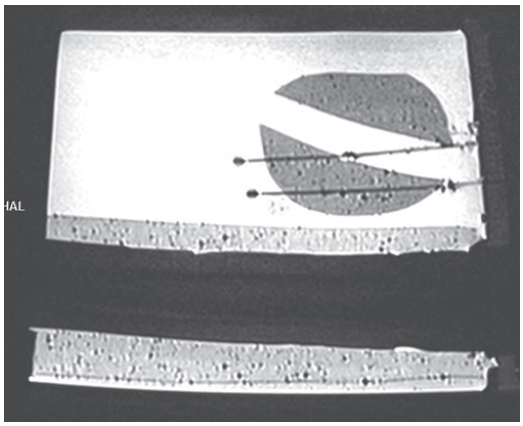

FIGURE 5. Sagittal view of postinterventional T2-weighted MRI of phantom with needle trajectory marked with guidewires (Roadrunner®) (position 4).

Statistical analysis

Needle positions were recorded in transversal and sagittal planes using the device software. The recorded needle positions were used to calculate the mean, standard deviation and range of three errors using SPSS 22 ® (IBM Corporation, Armonk, New York). (**See figure 2**)

1. The planning error (PE) was defined as the distance between the virtually planned needle on US and the target lesion on the pre-interventional MRI.
2. The targeting error (TE) was defined as the distance between the virtually registered needle on US and the virtually planned needle on US.

3. The overall error (OE) was defined as the distance between the marked needle trajectory on post-interventional MRI and the target lesion on the pre-interventional MRI.

Using the mean value and SD of the OE in the transversal plane an upper one-sided tolerance interval was calculated to assess the likelihood that a biopsy needle was on target for lesions with incremental diameters using an online statistics tool based on the Engineering Statistics Handbook.[31-33] The likelihood that a single needle biopsy was on target was calculated for lesions with a diameter of 2, 3, 4, 5, and 6 mm. Furthermore the likelihood that at least 1 out of 2 or 3 biopsy needles are on target was calculated using the following formula (*n* represents the number of needles used, and $P_{1*biopsy}$ represent the likelihood that a single needle biopsy was on target):

$$P_{n*biopsy} = 1 - (1 - P_{1*biopsy})^n$$

RESULTS

The mean OE in the transversal plane (X,Y) was 2.33 mm, while the PE and the TE were 1.18 mm and 0.39 mm, respectively. The OE in 3D (X,Y,Z) is obtained by including the error of insertion depth. The 3D OE is 5.42 mm, while the PE and the TE were 1.23 mm, and 1.71 mm, respectively. The TE and OE in the 3D plane are remarkably larger than in transversal plane**. See table 1** for an overview of the results concerning the PE, TE and OE in both the transversal and 3-D plane.

TABLE 1. Mean PE, TE, and OE Derived from the Various Needle Positions

	Transversal plane (X, Y)			**3D (X, Y, Z)**		
	Mean (mm)	**SD (mm)**	**Range (mm)**	**Mean (mm)**	**SD (mm)**	**Range (mm))**
PE (on US)	1.18	0.57	0.21–2.58	1.23	0.53	0.30–2.58
TE (on US)	0.39	0.30	0.07–1.46	1.71	1.22	0.33–6.34
OE (on MRI)	2.33	1.06	0.62–4.52	5.42	2.53	1.55–10.04

OE= overall error, PE = planning error, SD = standard deviation, TE = targeting error, US = ultrasound.

Using an upper one-sided tolerance interval and the OE in the transversal plane these results that lesion with a diameter of 5 mm in the transversal plane could be accurately sampled in 96% of the cases using a single biopsy core. The likelihood of accurate sampling using a single core increases with incremental diameters of the lesion targeted, and ranges

from 26% for a lesion of 2 mm up to 99% in lesions of 6 mm. Typically more than one target biopsy is performed per lesion, which increases the likelihood of accurate lesion sampling. For instance the likelihood that a lesion with a diameter of 3 mm will be adequately sampled using a single core is 61%, which would increase to 94% if three biopsy cores were to be employed. The likelihood that a biopsy needle was on target for lesions with incremental diameters is presented in **table 2**.

TABLE 2. Likelihood that lesions with incremental diameter are accurately sampled using an increasing number of needles based on the OE in the transversal plane

Diameter of the lesion targeted (mm)	Number of needles applied		
	1 (%)	2 (%)	3 (%)
2[a]	26	45	59
3[a]	61	85	94
4[a]	86	98	99
5[a]	96	99	99
6[a]	99	99	99

[a] 95% confidence interval.

DISCUSSION

Our findings demonstrate that the PE (consisting of errors due to restriction of resolution of imaging, the measurements of the biopsy grid, inaccuracies in needle planning and image fusion) significantly contributes to the OE. In the transversal plane the mean PE found in our investigation is 1.18 mm which represents over 50% of the OE. The resolution of imaging applied is relatively high compared to clinical practice. Furthermore image fusion in phantom prostates is likely to be more accurate than in-vivo due to the sharp image contours, the absence of tissue movement and deformation. Finally, planning accuracy is bounded by the resolution of the grid. When targeting lesions with a diameter of around 3 mm, the constraining effect of a grid with a spacing of 2.5 mm becomes apparent. An increased grid resolution could potentially decrease the established PE.

The TE is only a modest contributor to the OE, demonstrating a mean error of 0.39 mm in the transversal plane. Needle deflection, operator induced errors, tissue deformation, and errors in registration of needle position seem to play a minor role in the accuracy ex-vivo. Real prostatic tissue is inhomogeneous and demonstrates a different resistance compared

to phantom tissue. Consequently needle deflection in-vivo might play a more significant role. In the 3D plane the TE, with a mean error of 1.71 mm, is a significant contributor to the OE. This may be caused by the abrupt motion of the biopsy gun upon firing. Additionally inaccuracies are introduced by the inaccurate placement of the verification guide wire in this study. Though the accuracy with which the insertion depth can be determined is less relevant in clinical practice because the biopsy core contains a cylinder of tissue with a length of approximately 22 mm, which is larger than the 3D OE. Furthermore the depth recording (Z-axis) can be easily overestimated due to reduced tissue resistance of prostate phantoms.

Potential contributing factors of the OE that could not be recorded are the errors due to motion of the guidewires prior to post-interventional MRI, and the errors due to pre- and post-interventional MRI fusion. The errors resulting in movement of guidewires and fusion of post-interventional imaging obviously play a minor role in-vivo target biopsy procedures, and are only of value in an ex-vivo experiment such as this current study. These additional contributing factors of error could also explain why the mean OE is not identical to the geometrical summation of the mean PE and mean TE.

Two published phantom studies have been performed using MRI-TRUS fusion devices to assess targeting error. Kuru et al. performed a phantom study using the same fusion device we used, 5 phantom prostates and a mixture of ink and contrast to mark the needle trajectory. When comparing our series to the series by Kuru et al, we have to take into account that the applied definitions for TE and procedural TE (PTE) differ from our definitions. Kuru et al found an overall error of 0.83 mm for the TE (between the planned and performed biopsy) and 0.26 mm for the PTE (between the virtually planned biopsy trajectory and the manually registered 3D needle position).[30] We could not reproduce these findings, possibly due several methodological differences. Primarily the applied definitions are different as mentioned above. Also we used nine 'fictive' lesions per phantom prostate instead of the three MRI visible lesions in each prostate because we found that these lesions could also be visualised using TRUS, and are relatively large compared to typical lesion size. Furthermore, we used an alternative method to perform trajectory marking, as we were not able to reproduce the method used by Kuru et al.

Ukimura et al used a transrectal fusion device, 3 phantoms containing hypoechogenic lesions, 3 phantoms containing isoechogenic lesions and a mix of blue ink and MR contrast agent to assess the accuracy of targeted biopsy.[25] The authors found a mean targeting error of 2.09 mm (SD 1.28), a registration error of 0.83 mm (SD 0.54), and a total error of 2.92 mm in the 3d plane for 27 needle biopsies on isoechogenic lesions. A major difference between the current study and the study by Ukimura et al, is that the device employed in the current

study uses a transperineal route to the prostate whereas a transrectal device was used in the study by Ukimura et al. Furthermore the lesions used and method of needle trajectory marking are different. Despite the differences in methodology the reported errors are more or less similar to the errors found in this current investigation.

These ex-vivo results cannot be extrapolated to the in-vivo situation without caution, due to the fact that several additional factors (e.g. tissue deformation, inhomogeneous tissue resistance, and reduced precision of contouring) negatively influence the in-vivo accuracy that could not be simulated ex-vivo. Though the results of this ex-vivo experiment support further in-vivo studies using prostate MRI and target biopsy procedures because it provides an insight into the various causes of errors, and quantifies these errors in a way that cannot be done in-vivo. Further clinical studies on the detection of clinically significant prostate cancer using image fusion are necessary to validate MRI-TRUS fusion techniques in-vivo prior to incorporation into clinical guidelines and dissemination of these techniques.

CONCLUSION

This phantom study demonstrates that MRI-TRUS fusion allows for accurate sampling of MRI identified lesions, with a precision of 2.33 mm in the transversal plane. These results indicate that lesions with a diameter of 5 mm, and 6 mm can be accurately targeted in 96%, and 99% of the cases respectively using a single biopsy core. If more that one biopsy core is taken per lesion the likelihood of accurate sampling increases. The likelihood that a lesion with a diameter of 3 mm will be adequately sampled at least once using one biopsy core is 61%, which would be increased to 94% if three biopsy cores were to be employed. The overall error is predominantly determined by the planning error. Further advancement of fusion technology could contribute to an increased accuracy of the MRI-TRUS fusion systems in the future. Clinical investigations are necessary to evaluate the accuracy of MRI-TRUS fusion devices for the detection of significant prostate cancer.

Acknowledgements

We would furthermore like to thank the individuals of the “Back in the USA – fight cancer” initiative for funding this research.

Author disclosures statement

None of the authors have any conflicts of interest to disclose.

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4

Chapter 4

The FUTURE trial: Fusion target biopsy of the prostate using real-time ultrasound and MR images. A Multicenter RCT on Target Biopsy Techniques in the Diagnosis of Prostate Cancer

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Journal of Clinical Trial 2015; 5 (6)

ABSTRACT

Background: The current standard technique for prostate cancer detection is trans-rectal ultrasound (TRUS) guided biopsy, and is renowned for its low sensitivity. Developments of multiparametric MRI techniques have increased the detection of significant prostate cancer. Currently there are three techniques utilizing MRI for targeted biopsy: MRI-TRUS fusion, 'cognitive' TRUS, and in-bore MRI guided biopsy. There is no consensus which should be preferred. The current study aims to compare prostate cancer detection rates of three target biopsy procedures.

Methods: The FUTURE trial is a three-arm randomised controlled, multicentre trial comparing three techniques of MRI targeted biopsy of the prostate amongst subjects with one prior negative TRUS biopsy and a persisting suspicion on prostate cancer. All subjects undergo mpMRI imaging. Images will be centrally reviewed, and evaluated using the 'Prostate imaging reporting and data system'. An estimated 69% of the subjects will demonstrate tumour suspicious findings on mpMRI, and will be randomised 1:1:1. The primary objective is to compare (significant) tumor detection rates of the three techniques. Secondary objectives include histopathological validation of mpMRI imaging and PI-RADS classification, a cost-effectiveness analysis, and follow-up after a negative mpMRI or negative target biopsy. All biopsy cores will be evaluated by one dedicated uro-pathologists per center. Two sub-investigations were based on the hypothesis that MRI-TRUS fusion and in-bore MRI biopsy demonstrate similar tumor detection, whilst MRI-TRUS fusion demonstrates increased tumor detection compared to 'cognitive' TRUS biopsy. A total number of 466 subjects is needed for equal randomization. Assuming that 69% of subjects have tumor suspicious findings on MRI imaging, a total of 675 subjects are required for inclusion. Discussion: For target biopsy procedures of the prostate the ultimate comparator is histopathological examination of radical prostatectomy specimens, though this leads to insurmountable ethical objections and thus to a methodological dilemma concerning validation.

INTRODUCTION

Prostate cancer is the most commonly diagnosed malignancy amongst men in the Netherlands, with an increasing incidence under the influence of aging of males.[1,2] The current standard technique for prostate cancer detection is trans-rectal ultrasound (TRUS) guided biopsy of the prostate.[3,4] TRUS guided biopsy has its limitation due to the inability of grey-scale ultrasonography to distinguish prostate cancer from benign prostate tissue.[4,5] Consequently TRUS-guided biopsies are performed in a systematic manner in contrast to targeted biopsies, typically by taking 8-12 biopsy cores from the peripheral zone of the prostate. Due to these limitation TRUS guided biopsy is renowned for its high detection rates of insignificant cancers, and low sensitivity for significant cancers, which is underlined by the fact that repeat TRUS biopsy, due to a persisting clinical suspicion of prostate cancer, has a cancer detection rate (CDR) of 10-25% following prior negative biopsy.[6-10]

The combination of serum PSA (prostate specific antigen) screening and systematic TRUS biopsy has lead to an increased detection of early prostate cancer. A disadvantage of PSA screening is the risk of overdiagnosis and over-treatment of clinical insignificant or low-risk prostate cancer.[11] The Gleason score is the current standard grading system used to assess the differentiation grade of adenocarcinoma of the prostate. The Gleason score is the sum of the predominant and the highest most common histological pattern of tumor growth. Gleason scores 2-4 are not assigned on needle biopsy, thus Gleason sum score varies from 5 to 10.[3,4,12] Based on the serum PSA concentration, clinical stage, Gleason sum score, number of core positivity, and cancer core length a distinction is made between clinically significant and insignificant prostate cancer according to the Epstein criteria.[13,14] Clinically insignificant prostate cancers represent indolent, low-risk malignancies that require no immediate form of active treatment, whereas clinically significant disease represents intermediate and highrisk malignancies that warrant some form of active treatment.[3,13,14]

Development of multiparametric MRI (mpMRI) techniques has increased the detection of significant cancers and the sensitivity for the determination of its aggression.[15-22] Clinical guidelines advise performing an mpMRI when the clinical suspicion on prostate cancer persists despite prior negative TRUS biopsy results to investigate the possibility of ventrally located lesions.[3,4] According the European Society of Uro-Radiology (ESUR) 2012 and the ESUR/American College of Radiology (ACR) 2014 guidelines an mpMRI consists of high-resolution T2-weighted images (T2W), and at least two functional MRI techniques (such as Dynamic Contrast Enhanced (DCE) imaging and Diffusion Weighted (DWI) imaging).[3,4,15,23,24] Usage of a 3 Tesla (3-T) magnet has enhanced resolution and quality of imaging compared to 1.5-T, and possibly leads to an even better detection of prostate cancer using MRI

imaging.[23] A method to systematically evaluate mpMRI of the prostate is by using the 'Prostate Imaging Reporting And Data System' (PI-RADS) scoring system, by which imaging abnormalities are scored 1-5 based on each MR imaging modality.[15,23,24] The higher the PI-RADS score, the higher the risk of presence of malignancy.[25,26]

Following the development of enhanced quality of imaging, MRI guided interventions have been introduced. There are several techniques available to utilize MRI information for direct targeted biopsies of the prostate. Using in-bore MRI guided target biopsy (MRI-TB) real-time MR imaging is performed to guide the biopsy procedure. A recent systematic review demonstrated increased CDR of significant prostate cancer in a large cohort using MRI-TB.[17,22,27] Despite these results MRI-TB remains controversial due to impracticalities, as its low availability, required expertise and time consuming nature. An upcoming technique is MRI-TRUS fusion targeted biopsy (FUS-TB).[28-38] FUS-TB devices utilise the high diagnostic yield of the mpMRI for prostate cancer in combination with the practicality and affordability of TRUS biopsy systems by fusing the pre-interventional MR images with real-time ultrasound images. Thus enabling MRItargeted biopsy without the necessity of performing the biopsy in an MRI suite. A third commonly applied technique for MRI target biopsy is 'cognitive' TRUS target biopsy (COG-TB). The mpMRI information is used 'cognitively' by the physician to target tumour suspicious areas of the prostate using TRUS without applying image fusion.[39,40] All these techniques demonstrate an increased CDR of significant prostate cancer compared to systematic TRUS biopsy.[17,25-36,39-42] There is no consensus which technique for targeted biopsy should be preferred.

So far no multicenter, randomized controlled trials have been performed comparing prostate cancer detection rates of FUS-TB, COG-TB, and MRI-TB respectively.

METHODS/DESIGN

Objectives and hypothesis

The main objective of this study is to evaluate the clinical role of FUS-TB biopsy on prostate cancer detection, compared with MRI-TB and COG-TB, in men with a persistent clinical suspicion on prostate cancer and at least one negative TRUS guided biopsy session. The hypothesis is that FUS-TB demonstrates a similar CDR of prostate cancer compared to MRI-TB, whilst demonstrating an increased CDR compared to COG-TB.

Secondary objectives include histopathological validation of mpMRI imaging and PI-RADS classification in all subjects undergoing target biopsy of the prostate using biopsy cores

(and radical prostatectomy specimen), a cost-effectiveness analysis of all three target biopsy techniques, and an evaluation of the follow-up amongst subjects with a negative mpMRI or negative target biopsy outcome. It is hypothesized that all three techniques of targeted biopsy

demonstrate similar CDR compared to systematic biopsy, but an increased CDR of significant prostate cancer compared to systematic TRUS. Furthermore targeted biopsies are expected to predict the definitive Gleason sum score of radical prostatectomy specimens more accurately compared to systematic TRUS. Our hypothesis is that MRI is a crucial factor in patient selection for subsequent target biopsy procedures. Patients without tumour suspicious abnormalities on mpMRI will demonstrate a low CDR during follow-up.

Study design

The FUTURE trial is a three-arm randomized controlled, multicentre trial. Primarily all subjects will undergo mpMRI imaging of the prostate in accordance to the ESUR guidelines. If imaging does show abnormalities equivocal or suspicious for tumour (PI-RADS>2), subjects will be randomised to undergo one of three target biopsy strategies. If mpMRI imaging does not show abnormalities suspicious for tumour (PI-RADS ≤ 2) subjects will enter a biochemical follow-up course of at least 2 years. See **Figure 1** for a schematic overview of the trial design. Based on our hypothesis 2 sub-investigation were proposed; sub-investigation 1 consists of superiority study comparing the CDR of FUS-TB and COG-TB; and sub-investigation 2 consists of a non-inferiority study comparing the CDR of FUS-TB and MRI-TB. The study design and protocol drafting for the FUTURE trial was performed in adherence to the CONSORT, SPIRIT and START recommendations for reporting on interventional trials.[16,43,44]

Setting and participants

The FUTURE trial is conducted in two large, non-academic teaching hospitals and one academic hospital in the Netherlands. Eligible patients can be referred to inclusion centres from surrounding health care centres for study recruitment. Eligible patients for study participation must meet all the following inclusion criteria:

- Subject is at least 18 years old and mentally competent.
- Subjects have undergone at least one prior negative TRUS guided biopsy session within the last 4 years, with a minimum of 8 biopsy cores taken from the peripheral zone.
- Subjects have a persisting clinical suspicion on prostate cancer based on a PSA value of>4.0 ng/ml and/or suspicious digital rectal examination (DRE).

Subjects are excluded if one of the following criteria applies:

- Prior diagnosed or treated prostate cancer, including subjects with histologically proven low-risk prostate cancer submitted to active surveillance protocols.
- Prior targeted biopsy procedures of the prostate based on MR imaging.
- Proven urine tract infections (UTI).
- Contra-indications for MR imaging.
- Unwillingness or inability to undergo target biopsy procedures and biochemical follow-up.

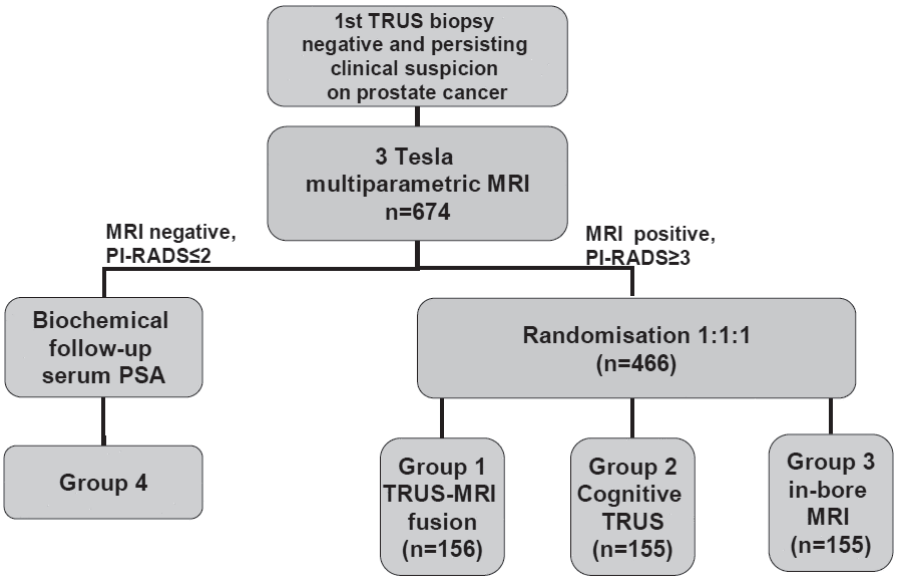

FIGURE 1: A schematic overview of the trial design.

Recruitment

Recruitment for study participation will be initiated by the treating urologist. If a subject is found to meet in- and exclusion criteria an appointment will be made at one of the inclusion centres for enrolment. At this appointment the study design will be discussed with subjects, inclusion and exclusion criteria will be reviewed, written informed consent will be obtained and all baseline data will be collected. Further appointments for study activities will be made (e.g., date of MRI imaging). By recruiting subjects from surrounding referral health care centres inclusion rates are to be boosted. In order to facilitate recruitment amongst

referral centres oral presentations will be held at for participating urologists per centre and during the annual meeting of the Dutch Uro-Oncological Studygroup (DUOS). Written and digital information concerning the trial is to be disseminated amongst urologists.

Intervention

Primarily all included subjects will undergo 3 T mpMRI imaging of the prostate in accordance to the ESUR guidelines using one of the following scanners (MAGNETOM Skyra® Siemens; MAGNETOM Trio® Siemens; Ingenia® Philips).[15] The imaging modalities used include high resolution T2W, DWI and DCE. Anti-peristaltic drugs (Buscopan®) and gadolinium intravenous contrast-agent will be administered during imaging. All images will be evaluated by a single experienced urogenital radiologists by applying central review. Images will be evaluated using the PI-RADS 2.0 scoring system.[23,24] Furthermore all subjects are required to fill in 5 sets of validated questionnaires at baseline. Questions are directed at micturition (IPSS), erectile function (IIEF-5), global health perception (EQ-5D-5L), medical consumption (iMCQ) and productivity (iPCQ). These questionnaires will be repeated one month following biopsy procedure.

If imaging demonstrates equivocal or suspicious findings (PIRADS> 2) subjects will be subjected to one of three targeted biopsy procedures. Axial T2W and DWI imaging are used to direct all biopsy procedures. Starting the day prior to the biopsy all subjects will receive a 3 day course of prophylactic antibiotics (typically a fluorchinolone).

MRI-TRUS fusion targeted biopsy (FUS-TB) is performed using the BiopSee® transperineal device for stereotactically navigated biopsies by Medcom. This system fuses pre-interventional mpMRI images with real-time ultrasound images, as described earlier. Using the BiopSee® fusion device a transperineal approach is used for prostate biopsies under ultrasound guidance. At least 2 biopsy cores are taken per identified lesion. Additionally this technique allows systematic biopsy cores to be taken during the same procedure as target biopsy. The systematic biopsy cores are taken using a predefined schema which includes at least 2 transition zone cores and 2 ventrally directed cores. The number of systematic cores taken varies between 8-12 depending on the volume of the prostate. The biopsy procedures are performed on the operating room under spinal or general anaesthesia, in day care clinical setting. Prior to biopsy subjects receive an enema (Mircolax®).

COG-TB using either the Hitachi Preirus®, Hitachi Avius® or BK UltraView 800® ultrasound system. Both systems are equipped with a bi-plane transrectal ultrasound transducer and a needle guidance application (end-fire and side-fire respectively). The prostate is biopsied using a transrectal approached under ultrasound guidance. The mpMRI images are reviewed directly prior to COG-TB. At least 2 biopsy cores are taken per identified lesion.

Additionally this technique allows systematic biopsy cores to be taken during the same procedure as target biopsy using the same biopsy scheme as described above. The biopsies are performed in the outpatient urology clinical setting without the use of anaesthesia.

In MRI-TB biopsy is performed in a 3-T MRI scanner (MAGNETOM Skyra® Siemens), as described earlier. The prostate is biopsied using a transrectal approached using an MRI compatible biopsy gun (Invivo®) under MRI guidance. At least 2 biopsy cores are taken per identified lesion. MRI-TB is performed in the out-patiënt clinical setting without the use of anaesthesia. This technique does not allow systematic biopsy cores to be taken during the target biopsy procedure.

All biopsy specimens will be reviewed by one dedicated uropathologists per centre. Biopsy cores will be potted with a maximum of three specimens per vial. Target cores will be potted, and analysed separately from systematic cores. Cores will be evaluated in accordance to the 2005 International Society of Urological Pathology (ISUP) conference on Gleason grading of prostatic carcinoma.[12] Evaluation of the biopsy cores will at least include histological diagnosis, Gleason sum score, length of core, length of prostate cancer within the core, and number of cores with/without cancer.

Follow-up

Subjects without tumour suspicious findings (PI-RADS ≤ 2) on mpMRI will enter a biochemical follow-up course consisting of annual PSA measurements. In case PSA measurements surpass a subject specific threshold (based on baseline value and prostate volume) a repeat mpMRI will be performed. Repeat biopsy will follow in case of rising PSA above predefined threshold and/or progression on mpMRI. Biochemical follow-up will be performed by principle referring urologist. Two years following inclusion a patient file review will be performed to determine whether the diagnosis prostate cancer has been made, what diagnostic tools have been used and their outcomes.

Subjects with equivocal findings (PI-RADS 3) on mpMRI and negative outcomes of subsequent targeted biopsy procedures will also enter a biochemical follow-up course consisting a biannual PSA measurement and repeat mpMRI after one year. Repeat biopsy will follow in case of rising PSA above the predefined threshold and/or progression on mpMRI. Two years following inclusion a patient file review will be performed to determine whether the diagnosis prostate cancer has been made, what diagnostic tools have been used and their outcomes.

Subjects with tumour suspicious findings (PI-RADS>3) on mpMRI and negative outcomes of subsequent targeted biopsy procedures are offered to undergo direct repeat MRI-

TB (cross-over). Two years following inclusion a patient file review will be performed to determine whether the diagnosis prostate cancer has been made, what diagnostic tools have been used and their outcomes.

Subjects with equivocal or tumour suspicious findings (PI-RADS>2) on mpMRI who have undergone subsequent targeted biopsy procedures will be contacted one month following the biopsy procedure. During this contact morbidity due to biopsy procedure will be discussed, and subjects will be required to complete a follow-up round of questionnaires.

Outcomes

The primary outcome of the FUTURE trial is overall prostate cancer CDR. Overall prostate cancer CDR will be presented per subject and per biopsy core for both target biopsy alone, systematic biopsy alone, and the combination of systematic and target biopsy. Target biopsy is assumed to demonstrate an increased CDR of significant prostate cancer. The definition of significant prostate cancer derived from the internationally accepted Epstein criteria and d'Amico risk classifications.[13,14,45,46]

Criteria for insignificant prostate cancer are:

- PSA<10 ng/ml.
- PSA-density<0.15ng/ml/ml.
- Gleason 3+3, <2 cores positive and maximum cancer core length<6mm.
- Gleason 3+4, <2 cores positive and maximum cancer core length<4mm.
- Clinically organ confined disease.

Primary parameters are histological diagnosis, Gleason sum score, cancer core length, and ratio of (systematic/targeted) core positivity. Secondary parameters include number of mpMRI suspicious lesions, PI-RADS score of lesions, imaging staging, and pathological staging (if applicable). Furthermore baseline data will be collected on PSA value, prostate volume (TRUS), clinical stage (based on DRE and TRUS), age, number of previous negative biopsy sessions, MR imaging parameters used, risk on prostate cancer based on the ERSPC algorithm[47], self-reported outcomes on micturition, erectile function, global health perception, medical consumption and productivity (prior/following biopsy). Furthermore data will be collected concerning the occurrence of adverse events following biopsy. See **Table 1** for an overview of outcomes and the moment of measurement.

TABLE 1: An overview of all outcome measures and the moment of measurement.

	T1	T2	T3	T4
Parameters	**Inclusion**	**Following MRI imaging**	**1 month following biopsy**	**Follow-up 2 years**
Age	X			
PSA value	X			
Biopsy history	X			
Prostate volume	X			
Clinical stage	X			
Risk algorithm	X			
EQ-5D-5L/IPSS/IIEF-5	X		X	
iPCQ/iMCQ	X			X
UTI screening	X			
MRI parameters used		X		
Lesion number, size		X		
PI-RADS score		X		
Imaging stage		X		
Biopsy allocation		X		
Histological diagnosis			X	
Gleason score			X	
Core positivity; cancer length			X	
Diagnosis prostate cancer			X	X
Adverse events/treatment			X	
Pathological stage				X
Follow-up				X

Sample size calculation

The sample size calculation was determined by the estimated CDR of the three biopsy techniques, an estimation of the incidence of tumour suspicious findings within our cohort and the applied subinvestigation. Based on a recent systematic review an estimated 69% of the subjects with prior negative biopsy outcomes and a persisting clinical suspicion on prostate cancer will demonstrate tumour suspicious findings on MRI (PIRADS ≥ 3).[41] Based on peer reviewed literature an estimated yield of CDR was 40% for MRI-TB, 40% for FUS-TB, and 25% for COG-TB within this population.[22,26,41] A power of 80%, a significance level of 5%, and a range of indifference of 15% were used for subsequent calculations. Sample size calculations were performed using WINPEPI software version 11.29.

For sub-investigation 1 (superiority study) group sample sizes of 152 per group achieve an 80% power to detect a difference of 0.15 between the null hypothesis (COG-TB) and alternative hypothesis (FUS-TB) using a two-sided Chi-square test without continuity correction and with a significance level of 0.05, assuming that COG-TB has a CDR of 0.25 and FUS-TB of 0.40.

In sub-investigation 2 (non-inferiority study) group sample sizes of 131 per group achieve an 80% power at a significance level of 0.05 using a one-sided equivalence test of proportions when the proportion in the standard group (MRI-TB) is 0.40 and the proportion in the experimental group (FUS-TB) being tested for non-inferiority is 0.40 and the maximum allowable difference between these proportions that still results in non-inferiority (the range of indifference) is 0.15. The range of indifference of 0.15 was chosen because the CDR of FUS-TB biopsy is estimated to lay in between the CDR of COG-TB (0.25) and the CDR of MRI-TB (0.40). The basis to perform a one-sided equivalence test instead of a two-sided equivalence test is that the FUS-TB performs biopsies on MRI derived targets, and consequently is not expected to show a superior CDR compared to MRI-TB.

A sample size of 152 per group for sub-investigation 1, and a sample size of 131 per group are needed to achieve statistical significance. To facilitate the randomization procedure identical group sizes were chosen for all three groups. This implicates 21 additional subjects in the MRI-TB group only and results in a sample size of 152 per group, and 456 subjects for all three biopsy procedures combined. 10 additional subjects are to be included to correct for possible lost-to follow up. By including subjects of the FUS-TB group for the analysis of both the superiority and non-inferiority study, a total number 466 of subjects is needed for equal randomization amongst the three target biopsy strategies. Assuming that within this population 69% of subjects demonstrate tumour suspicious findings on MRI imaging, a total of 675 subjects are required for inclusion.

Randomisation

All subjects with equivocal or tumour suspicious findings (PIRADS> 2) on mpMRI imaging will be randomized to undergo target biopsy strategy. Randomization is performed by applying bloc-randomization using a web-based randomization system. The administrator of the web-based system was not involved in any trial activities. The administrator of the web-based system generated a computer based random sequence assigning intervention arms. All subjects will be randomized 1:1:1 to undergo FUS-TB, MRI-TB or COG-TB. To prevent uneven distribution amongst the three intervention arms bloc-randomization was applied. The number of subjects per bloc varies. The investigators are blinded for the random sequence used and the bloc size used. Following randomization the allocated intervention will be revealed to both investigator and subject.

Data collection and management

Upon enrolment all subjects will be assigned a trial code. This code consist of the name of the trial, the inclusion centre were subject was enrolled, and a subject specific number. All data will be collected on a tailored CRF, under mention of the subject specific trial code. The key for encoding is stored by principle investigators at each of the inclusion sites. Access to data will be limited to main-investigators and supervising urologist. Collected data will be recorded digitally in the electronic patient file on secured hospital servers used by each inclusion site, as well as on the hardcopy CRF.

Statistical analysis

All analyses will be conducted using SPSS version 22.0 (Statistical Package for Social Sciences, IBM). A 0.05-significance level will be adopted in all statistical tests. Descriptive statistics will be used to describe baseline characteristics as means and standard deviation. To assess comparability between the three target biopsy groups baseline characteristics will be analysed using a Chi square test, or t-test (depending on variable type). The overall CDR, and clinically significant CDR will be compared between the three intervention groups using a t-test. If despite randomization confounding factors have been found in baseline characteristics a multivariate logistics regression test will be applied. Furthermore the overall CDR, and clinically significant CDR will be compared between the systematic biopsy outcomes and targeted biopsy outcomes in subjects that have undergone both systematic and targeted biopsies using a Mc Nemar test. A sub-group analysis will be performed on subjects with PI-RADS 3, 4, and 5 abnormalities on mpMRI imaging respectively. Statistical analysis will be performed on an intention-to-treat basis. Subjects with missing data will not be substituted for other subjects. Missing and incomplete data will be described.

Ethical considerations

This study will be conducted in accordance with the principles of the Declaration of Helsinki (version 10, amended in October 2013 by the 64th WMA General Assembly). The research protocol was examined and approved by the regional accredited Medical research Ethical Committee 'MEC-U' (Medical research Ethics Committees United) (reference R14.021, dossier NL48777.100.14). Institutional review board approval was granted for each of the participating centres. The research protocol was registered in the Dutch National Trial Register (reference NTR4988). All participating subjects will sign a written informed consent form.

DISCUSSION

The FUTURE trial is a multicentre randomized controlled trial on three target biopsy techniques in the diagnostic work-up of prostate cancer. Typically diagnostics are compared to a 'golden standard' as reference standard for the outcome of the diagnostic tool being investigated. For a diagnostic intervention such as biopsy the ultimate comparator would be histopathological examination of the target organ, in this case the prostate. Though this results in insurmountable ethical objections due to the fact that the reference standard of radical prostatectomy may harbour considerable morbidity, and on ethical grounds cannot be performed on subjects without histologically proven prostate cancer. Consequently a methodological dilemma is inevitable on how to validate the findings of biopsy procedures. An alternative methodological strategy is to perform a repeat of the current standard diagnostic procedure (systematic TRUS biopsy) on all subjects, but as previously described this intervention has a limited sensitivity. Furthermore it is technically not feasible to perform systematic biopsies in the MRI-TB group during in the same session. Consequently subjects would have to undergo MRI-TB followed by systematic TRUS biopsy in a subsequent session. Potentially this would result in significant resistance amongst subjects undergoing these procedures and could therefore negatively influence subject's willingness to participate in the trial.

In recent years a lot of experience has been gained using targeted biopsy strategies. From the three techniques currently being investigated the most experience has been acquired with MRI-TB. The medical scientific research validating this technique of targeted biopsy has been most extensive. For that practical reason this test was chosen as validation test in subjects with tumour suspicious findings on mpMRI (PI-RADS>3), and a negative outcome of primary targeted biopsy procedures of these lesions. Furthermore validation is performed by systematic biopsy during the same target biopsy session (in the FUS-TB and COG-TB groups), and by a serum PSA test follow-up course of at least 2 years.

In summary the current standard technique for prostate cancer diagnosis has its limitations. Improvement of mpMRI techniques has enabled targeted biopsy. There are three techniques of targeted biopsy. The main objective of this study is to evaluate prostate cancer detection rates of three target biopsy procedures by comparing FUS-TB with MRI-TB and COG-TB, in men with a persistent clinical suspicion on prostate cancer and at least one negative TRUS guided biopsy session. Furthermore target biopsy outcomes will be compared to systematic biopsy outcomes in subjects that have undergone both targeted and systematic biopsy procedures.

Trial Status

This trial is currently recruiting patients. The start date was December 2014. The initial patient inclusion is expected to take approximately 24 months. Patients will be followed for two years.

Acknowledgement

This research project has been funded by the St. Antonius Research fund and the St. Antonius Innovation Fund (reference BI13G04EA).

We would like to thank the following hospitals for their cooperation: Zuwe Hofpoort, Woerden; Diakonessehuis, Utrecht/Zeist; Rivierenland, Tiel; Rivas, Gorinchem; St. Jansdal, Harderwijk; VUmc, Amsterdam; Gelre, Apeldoorn; Slingeland, Doetinchem; Bernhoven, Uden; Gelderse Vallei, Ede; Rijnstate, Arnhem. Streekziekenhuis Koningin Beatrix, Winterwijk.

All authors participated in study design, writing, and final approval of the final manuscript.

Trial registration

The Dutch National Trial Register, reference: NTR4988, registration date: December 3rd 2014.

Conflict of Interest

The authors have no conflict of interests to declare.

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5

Chapter 5

The FUTURE trial: a multicenter randomized controlled trial on target biopsy techniques based on magnetic resonance imaging in the diagnosis of prostate cancer in patients with prior negative biopsies.

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European Urology 2019; 75 (4): 582-590

ABSTRACT

Background: Guidelines advise multiparametric MRI (mpMRI) before repeat biopsy in patients with negative systematic biopsies (SB) and suspicion of prostate cancer (PCa), enabling MRI targeted biopsy (TB). No consensus exists which of the three available techniques of TB should be preferred.

Objective: To compare detection rates for overall PCa and clinically significant (cs)PCa for three MRI based TB techniques.

Design, Setting and Participants: Multicenter RCT conducted between 2014-2017 in two non-academic teaching hospitals and an academic hospital among 665 men with prior negative SB and persistent suspicion of PCa.

Interventions: All subjects underwent 3-T mpMRI, evaluated with PIRADSv2. If imaging demonstrated PIRADS≥3 lesions patients were randomized 1:1:1 for one TB technique: MRI-TRUS fusion (FUS-TB), cognitive TRUS (COG-TB) or in-bore MRI (MRI-TB).

Outcomes and Statistical Analysis: Primary (overall PCa detection) and secondary outcomes (csPCa detection (Gleason score ≥3+4)) were compared using Pearson Chi square test.

Results and Limitations: On mpMRI 234/665 (35%) subjects had PIRADS≥3 lesion and underwent TB. There were no significant detection rate differences of overall PCa (FUS-TB 49%; COG-TB 44%, MRI-TB 55%, p=0.4). PCa detection rate difference between FUS-TB and MRI-TB was -5% (p=0.5, 95% CI -21% to 11%), between FUS-TB and COG-TB 6% (p=0.5, 95% CI -10% to 21%), between COG-TB and MRI-TB -11% (p=0.17, 95% CI -26% to 5%). There were no significant detection rate differences of csPCa (FUS-TB 34%; COG-TB 33%, MRI-TB 33%, p>0.9). csPCa detection rate difference between FUS-TB and MRI-TB was 2% (p=0.8, 95% CI -13% to 16%), between FUS-TB and COG-TB 1% (p>0.9, 95% CI -14% to 16%), between COG-TB and MRI-TB 1% (p>0.9, 95% CI -14% to 16%). Main study limitation was low rate of PIRADS≥3 lesion on mpMRI, causing under-powering for primary outcome.

Conclusion: We found no significant detection rate differences of (cs)PCa among three MRI based TB techniques.

Patient summary: In this study we compared the detection rates of (aggressive) prostate cancer among men with prior negative biopsies and a persistent suspicion of cancer

using three different techniques of targeted biopsy based on MRI. We found no significant differences in the detection rates of (aggressive) prostate cancer among the three techniques.

INTRODUCTION

Prostate cancer (PCa) is the most common malignancy among European men.[1] The standard diagnostic procedure, transrectal ultrasound (TRUS) guided systematic biopsy (SB), is limited by the inability to distinguish PCa from benign tissue using ultrasound.[2] Consequently, repeat TRUS-SB demonstrates PCa yields of 10-25%.[3,4]

Guidelines advise performing multiparametric (mp)MRI when suspicion of PCa persists despite negative TRUS-SB, followed by targeted biopsy (TB) of cancer suspicious regions (CSR).[5,6] Meta-analyses show that TB demonstrates higher detection rates of clinically significant (cs)PCa compared to TRUS-SB in repeat biopsy setting.[7-9] The recently published PRECISION trial demonstrates similar advantages of TB in biopsy naïve patients.[10]

TB was introduced with in-bore MRI targeted biopsy (MRI-TB), performed in the MRI-scanner using real-time MRI guidance.[11,12] MRI-TB demonstrates median PCa detection rate of 42%.[12] Nonetheless MRI-TB remains challenging due to impracticalities (as availability, required expertise, time-consuming and costly nature) forming barriers to widespread implementation, especially when pre-biopsy MRI and TB for all patients with a suspicion of PCa might become the new standard.[10] Consequently alternative techniques have been developed, as MRI-TRUS fusion targeted biopsy (FUS-TB)[13,14], and cognitive registration TRUS targeted biopsy (COG-TB)[15].

Obviously, increasing usage of TB necessitates answering the question which technique should be preferred. A meta-analysis on all three techniques demonstrated an advantage of MRI-TB compared to COG-TB for overall PCa detection, although this advantage was not apparent for csPCa.[8] However comparative trials are few.[17-21] Consequently little consensus exists on which technique should be preferred. This three-armed multicenter RCT compares overall PCa and csPCa detection rates of three TB techniques and aims to identify whether there is a superior technique regarding diagnostic efficacy in repeat biopsy setting.

MATERIAL AND METHODS

Recruitment

The trial protocol adheres to CONSORT, SPIRIT and START recommendations.[16-19] The trial was conducted between December 2014 and November 2017 in two non-academic teaching hospitals and an academic hospital. IRB approval was granted. Protocol was registered in the Dutch Trial Register (NTR4988). All subjects provided written IC.

Men were recruited with prior negative SB (<4 years) and persistent suspicion of PCa (PSA≥4 (ng/ml) and/or suspicious DRE). Exclusion criteria were prior diagnosed PCa, prior TB procedures, proven UTI, contra-indication for mpMRI or TB, imaging or TB not performed according to protocol, or withdrawal of consent.

MRI

All subjects underwent 3-T mpMRI according to PIRADSv2 standards.[20,21] Sequences included T2W, DWI and DCE (**appendix 1**). Images were centrally evaluated by one of two expert radiologists (20 and 5 years' experience in prostate MRI) using PIRADSv2 (**appendix 2**).[20,21] Radiologists were not blinded for clinical data. mpMRI outcome was reported using a written record incorporating marked images.

Randomisation

Subjects with PIRADS≥3 lesions were randomized 1:1:1 to undergo TB using FUS-TB, COG-TB or MRI-TB using a block-randomisation tool, generating a random sequence. Investigators were blinded for randomisation sequence. Following randomisation group allocation was revealed. If imaging demonstrated no CSR (PIRADS≤2) subjects entered biochemical follow-up.

Biopsy

MRI-TB was performed in the MRI-scanner (Magnetom Skyra® Siemens). CSR was re-identified using T2W and DWI. A rectally inserted needle guider was adjusted to aim towards the CSR. Transrectal biopsy was performed with a MR-compatible biopsy device.[11] After needle insertion, MR imaging verified its position. MRI-TB was performed by 10 expert-trained PhD candidates, with at least 6 months' experience at time of study commencement of which 3 months under expert supervision.

FUS-TB was performed in the operating-room under (general/spinal) anaesthesia using transperineal MRI/TRUS fusion (BiopSee® Medcom). Axial T2W images were imported, followed by prostate and CSR contouring. A biplane TRUS probe was inserted. 3D TRUS images were acquired. Using software, axial T2W and 3D ultrasound images were fused using rigid image fusion. Transperineal biopsy was performed using MRI/TRUS fusion guidance.[13] FUS-TB was performed by 5 urologists and expert-trained PhD candidates, with at least 6 months' experience of which 3 months under expert supervision.

COG-TB was performed in outpatient clinic using TRUS guidance (Hitachi Hi-Vision Preirus® or BK Pro-Focus®). Prior to biopsy the mpMRI was reviewed. A biplane TRUS probe was inserted. The CSR was re-identified. Transrectal biopsy was performed using biplane TRUS

guidance.[15] COG-TB was performed by 5 urologists and expert-trained PhD candidates, with at least 6 months' experience of which 3 months under expert supervision. A minimum of 2 TB cores per CSR was required for adequate sampling for all techniques.

Histopathology and definition of clinical significance

Biopsy cores were potted separately for each CSR and were evaluated by one uropathologist per centre (10, 11 and 17 years' experience in PCa diagnosis). Cores were processed according to ISUP standards.[22] The pathologist was blinded for applied TB technique.

csPCa was defined as Gleason score ≥3+4. Due to heterogeneity in the definition of csPCa in literature a second definition for csPCa was also applied (**appendix 3**).

Outcomes, sample size calculation and statistics

Primary outcome was detection rate of overall PCa for each TB technique. Secondary outcomes included csPCa detection rates, baseline clinical /mpMRI characteristics, procedural outcomes and adverse events (Clavien-Dindo).[23,24] Furthermore, exploratory subgroup analyses on (cs)PCa rates were performed, and a per core analysis.

We hypothesised that FUS-TB has an equivalent detection rate of PCa compared to MRI-TB, and that both MRI-TB and FUS-TB have a superior detection rate compared to COG-TB. Sample size was calculated using estimated PCa yields of TB techniques (40% FUS-TB, 25% COG-TB, and 40% MRI-TB) and 69% yield of CSR on mpMRI, based upon available literature at time of trial design.[4,7,12,13]

Two sub-investigations were formulated. Sub-investigation 1 is a superiority analysis comparing FUS-TB to COG-TB, and MRI-TB to COG-TB. Sample size of 152 per group was calculated to achieve 80% power to detect a difference of 15% between the null hypothesis (COG-TB) and alternative hypothesis (FUS-TB or MRI-TB) using a two-sided Chi-square test without continuity correction and significance levels 5%, assuming PCa yields of 25% for COG-TB and 40% for both FUS-TB and MRI-TB.[11,13]

Sub-investigation 2 is a non-inferiority study comparing PCa detection rates of FUS-TB and MRI-TB. Sample size of 131 per group was calculated to achieve 80% power at a 5% significance level using a one-sided equivalence test of proportions, when PCa yield in the standard group (MRI-TB) is 40% and yield in the alternative group (FUS-TB) tested for non-inferiority is also 40%, and the range of indifference still resulting in non-inferiority is 15%.[11-13]

To facilitate randomization identical groups of 152 were chosen, resulting in 456 subjects for all groups combined. 10 additional subjects were included, correcting for calculated losses, resulting in 466 subjects. Assuming 69% has CSR's on mpMRI 675 subjects are required for inclusion.[7]

All analyses were conducted with SPSS, 5% significance levels were adopted in all tests. To assess comparability between groups, baseline characteristics were analysed using one-way ANOVA or Kruskal-Wallis (for continuous variables) and Pearson Chi square test (categorical variables). Detection rates of PCa and csPCa were compared using Pearson Chi square test.[19]

RESULTS

695 men were recruited. 30 men were excluded following recruitment (**figure 1**), resulting in 665 subjects included in the final per protocol analysis.

Mean age was 64.7 (SD 6.6), mean PSA 10.4 ng/ml (SD 7.3), mean prostate volume (TRUS) was 56.9 ml (SD 24.0), median number of prior biopsies was 1 (IQR 1-2), and median interval between mpMRI and last SB was 9 months (IQR 4-22). Clinical stage (DRE) was cT1c in 80.9%, cT2a/b in 17.1%, cT2c in 0.8% and cT3a in 1.2% of cases (**table 1**).

In 234 subjects (35.2%) mpMRI demonstrated 263 PIRADS≥3 lesions, with mean CSR size of 13.5 mm (SD 7.0) (**table 2**). The remaining 431 subjects (64.8%) had PIRADS≤2 and entered follow-up.

234 subjects with PIRADS≥3 were randomised for TB; 79 for FUS-TB, 78 for COG-TB, and 77 for MRI-TB (**figure 1**). There were no significant differences in baseline characteristics, nor in mpMRI outcomes among groups (**table 3**). Using TB 115 PCas (49.1%) and 78 csPCas (33.3%) were detected.

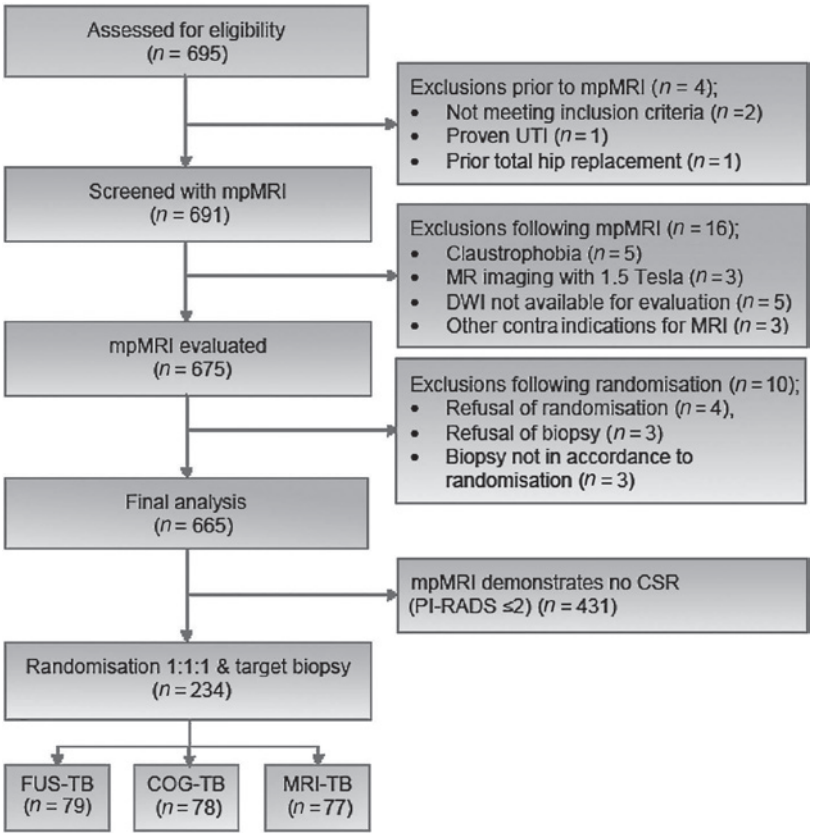

FIGURE 1: flow-chart of study.

COG-TB = cognitive registration TRUS TB; CSR = cancer suspicious region; DWI = diffusion weighted imaging; FUSTB = MRI-TRUS fusion TB; mpMRI = multiparametric MRI; MRI =magnetic resonance imaging; MRI-TB = in-bore MRI TB; PI-RADS = Prostate Imaging Reporting and Data System; TB = targeted biopsy; TRUS = transrectal ultrasound; UTI = urinary tract infection.

TABLE 1: Baseline characteristics

	Entire cohort (n=665)	**Cohort with CSR on mpMRI (PIRADS≥3) (n=234)**
Age, mean (SD)	64.7 (SD 6.6)	65.7 (SD 6.4)
PSA in ng/ml, mean (SD)	10.4 (SD 7.3)	11.2 (SD 8.5)
Volume on TRUS in ml, mean (SD)	56.9 (SD 14.4)	47.4 (SD 17.7)
Clinical stage (DRE), No. (%)		
• cT1c	538 (80.9%)	188 (80.3%)
• cT2a/b	114 (17.1%)	40 (17.1%)
• cT2c	5 (0.8%)	3 (1.3%)
• cT3a	8 (1.2%)	3 (1.3%)
Clinical stage (TRUS) , No. (%)		
• cT1c	535 (80.6%)	189 (80.8%)
• cT2a/b	109 (16.4%)	37 (15.8%)
• cT2c	10 (1.5%)	4 (1.7%)
• cT3a	6 (0.9%)	4 (1.7%)
• cT3b	4 (0.6%)	-
Number of prior negative biopsies, median (IQR)	1 (IQR 1-2)	1 (IQR 1-2)
Months between mpMRI and previous biopsy, median (IQR)	9 (IQR 4-22)	8 (IQR 4-23)

TABLE 2: mpMRI characteristics

Highest PIRADS grade on mpMRI (n=665), No. (%)	
• PIRADS 1	31 (4.7%)
• PIRADS 2	400 (60.2%)
• PIRADS 3	64 (9.6%)
• PIRADS 4	101 (15.2%)
• PIRADS 5	69 (10.4%)
CSR's per patient, mean (SD) (n=665)	1.1 (SD 0.3)
CSR size in mm's, mean (SD) (n=234)	13.5 (SD 7.0)
CSR location (n=234), No. (%):	
• Posterior	126 (53.8%)
• Anterior	90 (38.5%)
• Midline	18 (7.7%)
CSR location (n=234), No. (%):	
• Peripheral zone	137 (58.6%)
• Transition zone	29 (12.4%)
• Peripheral and transition	13 (5.6 %)
• AFS	8 (3.4%)
• Transition and AFS	42 (17.9%)
• Central	5 (2.1%)
Staging on mpMRI (n=234), No. (%):	
• T2a/b	141 (60.1%)
• T2c	24 (10.3%)
• T3a	62 (26.5%)
• T3b	7 (3.0%)

AFS = anterior fibromuscular stroma; CSR = cancer suspicious region; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; SD = standard deviation.

There were no significant differences in detection rates of overall PCa among groups (FUS-TB 49.4%; COG-TB 43.6% and MRI-TB 54.5%, p=0.4, **table 4**). PCa detection rate difference between FUS-TB and MRI-TB was -5.2% (p=0.5, 95%CI -20.6% to 10.5%), between FUS-TB and COG-TB 5.8% (p=0.5, 95%CI -9.8% to 21.1%), and between COG-TB and MRI-TB -11.0% (p=0.17, 95%CI -26.2% to 4.8%). Non-inferiority analysis comparing overall PCa detection rates of FUS-TB and MRI-TB was inconclusive (lower limit 95%CI being -20.6%). Both FUS-TB and MRI-TB were not significantly superior to COG-TB for overall PCa detection (p=0.5 and p=0.17 respectively).

There were no significant differences in detection rates of csPCa among groups (FUS-TB 34.2%; COG-TB 33.3% and MRI-TB 32.5%, p>0.9, **table 4**). csPCa detection rate difference between FUS-TB and MRI-TB was 1.7% (p=0.8, 95%CI -13.1% to 16.4%), between FUS-TB and COG-TB 0.8% (p>0.9, 95%CI -13.9% to 15.6%), and between COG-TB and MRI-TB 0.9% (p>0.9, 95%CI -13.9% to 15.6%). FUS-TB was non-inferior to MRI-TB for csPCa detection (lower limit 95%CI being -13.1%), and both FUS-TB and MRI-TB were not significantly superior to COG-TB for csPCa detection (p>0.9 and p>0.9 respectively).

TABLE 3: Baseline characteristics and mpMRI outcome of 3 groups of TB

	FUS-TB (n=79)	COG-TB (n=78)	MRI-TB (n=77)
Baseline characteristics			
Age, mean (SD)	64.6 (SD 6.9)	66.5 (SD 6.3)	66.0 (SD 5.9)
PSA in ng/ml, mean (SD)	11.6 (SD 9.0)	11.0 (SD 7.1)	11.0 (SD 9.4)
Volume on TRUS in ml, mean (SD)	45.4 (SD 14.4)	48.5 (SD 18.1)	48.3 (SD 20.2)
Clinical stage (DRE), No. (%):			
• cT1c	62 (78.5%)	64 (82.1%)	62 (80.5%)
• cT2a/b	16 (20.3%)	12 (15.4%)	12 (15.6%)
• cT2c	0 (0%)	2 (2.6%)	1 (1.3%)
• cT3a	1 (1.3%)	0 (0%)	2 (2.6%)
Number of prior negative biopsies, median (IQR)	1 (IQR 1-1)	1 (IQR 1-2)	1 (IQR 1-2)
Months between mpMRI and previous biopsy, median (IQR)	8 (IQR 3-23)	7 (IQR 4-23)	9 (IQR 4-25)
mpMRI outcome			
PIRADS score, No. (%):			
• PIRADS 3	23 (29.1%)	21 (26.9%)	20 (26.0%)
• PIRADS 4	34 (43.0%)	32 (41.0%)	35 (45.5%)
• PIRADS 5	22 (27.8%)	25 (32.1%)	22 (28.6%)
CSR size in mm's, mean (SD)	13.9 (SD 7.6)	12.9 (SD 6.1)	13.6 (SD 7.1)
Number of CSR, mean (SD)	1.1 (SD 0.3)	1.1 (SD 0.3)	1.1 (SD 0.4)
CSR location, No. (%):			
• Posterior	35 (44.3%)	46 (59.0%)	45 (58.4%)
• Anterior	37 (46.8%)	25 (32.1%)	28 (36.4%)
• Midline	7 (8.9%)	7 (9.0%)	4 (5.2%)

COG-TB = cognitive registration TRUS TB; CSR = cancer suspicious region; DRE = digital rectal examination; FUS-TB = MRI-TRUS fusion TB; IQR = interquartile range; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI TB; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; SD = standard deviation; TB = targeted biopsy; TRUS = transrectal ultrasound.

TABLE 4: Biopsy outcome of 3 groups of TB

	FUS-TB (n=79)	COG-TB (n=78)	MRI-TB (n=77)	
Days between mpMRI and biopsy, median (IQR)	53 (IQR 41-70)	27 (IQR 20-35)	39 (IQR 27-53)	p<0.05 [d]
Biopsy cores				
• Total TB cores, No.	358	275	197	
• Per subject, median (IQR)	4 (IQR 3-5)	3 (IQR 3-4)	2 (IQR 2-3)	p<0.05 [d]
• Per CSR, median (IQR)	4 (IQR 3-5)	3 (IQR 3-3)	2 (IQR 2-3)	p<0.05 [d]
• PCa positive cores, No.	128	88	94	
• Positivity rate, mean (SD)	31.3% (SD 37.8)	33.3% (SD 42.1)	47.7% (SD 46.4)	p<0.05 [b]
Detection rate of PCa, No. (%)	39 (49.4%)	34 (43.6%)	42 (54.5%)	p=0.4 [c]
Detection rate of csPCa [a], No. (%)	27 (34.2%)	26 (33.3%)	25 (32.5%)	p>0.9 [c]

ANOVA = analysis of variance; COG-TB = cognitive registration TRUS TB; csPCa = clinically significant PCa; CSR = cancer suspicious region; FUS-TB = MRI-TRUS fusion TB; IQR = interquartile range; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI TB; SD = standard deviation; PCa = prostate cancer; TB = targeted biopsy; TRUS = transrectal ultrasound.
[a] Kruskal-Wallis. [b] One-way ANOVA. [c] Pearson chi-square. [d] Gleason 3 + 4.

There were significant differences in number of cores taken per technique; median number for FUS-TB 4 (IQR 3-5); COG-TB 3 (IQR 3-4); and MRI-TB 2 (IQR 2-3), (p<0.05, table 4). Furthermore, core positivity rate was significantly different among groups (FUS-TB 31.3% (128/358), COG-TB 33.3% (88/275) and MRI-TB 47.7% (94/197), p<0.05, **table 4**). Various sub-analyses did not demonstrate statistically significant differences in (cs)PCa detection rates among groups (**table 5**).

Among 234 subjects that underwent TB 30.2% (n=70) experienced no adverse events. 63.2% (n=148) experienced grade I complications. Three subjects required hospitalisation due to gross haematuria. 6.0% (n=14) experienced grade 2 complications; eight UTI's occurred requiring antibiotics (four requiring hospitalisation), five subjects had LUTS progression for which treatment was initiated and one subject had atrial fibrillation. No grade 3, 4 or 5 events occurred.[23,24]

TABLE 5: Biopsy outcome of 3 groups of TB per sub-analysis.

Biopsy outcomes per sub-analysis						
			FUS-TB (n=23)	**COG-TB (n=21)**	**MRI-TB (n=20)**	
mpMRI outcome, No. (%)	PIRADS 3 (n=64)	PCa	6 (26.1%)	5 (23.8%)	5 (25.0%)	p>0.9 [b]
		csPCa [a]	2 (8.7%)	5 (23.8%)	4 (20.0%)	p=0.4 [b]
			FUS-TB (n=34)	COG-TB (n=32)	MRI-TB (n=35)	
	PIRADS 4 (n=101)	PCa	12 (35.3%)	7 (21.9%)	17 (48.6%)	p=0.07 [b]
		csPCa [a]	7 (20.6%)	5 (15.6%)	9 (25.7%)	p=0.6 [b]
			FUS-TB (n=22)	COG-TB (n=25)	MRI-TB (n=22)	
	PIRADS 5 (n=69)	PCa	21 (95.5%)	22 (88.0%)	20 (90.9%)	p=0.7 [b]
		csPCa [a]	18 (81.8%)	16 (64.0%)	12 (54.5%)	p=0.15 [b]
Small CSR (≤10 mm), No. (%) (n=91)			FUS-TB (n=29)	COG-TB (n=31)	MRI-TB (n=31)	
		PCa	7 (24.1%)	6 (19.4%)	9 (29.0%)	p=0.7 [b]
		csPCa [a]	3 (10.3%)	6 (19.4%)	5 (16.1%)	p=0.6 [b]
Anterior located CSR, No. (%) (n=90)			FUS-TB (n=37)	COG-TB (n=25)	MRI-TB (n=28)	
		PCa	23 (62.2%)	15 (60.0%)	18 (64.3%)	p>0.9 [b]
		csPCa [a]	18 (48.6%)	11 (44.0%)	10 (35.7%)	p=0.6 [b]
Posterior located CSR, No. (%) (n=126)			FUS-TB (n=35)	COG-TB (n=46)	MRI-TB (n=45)	
		PCa	14 (40.0%)	12 (26.1%)	21 (46.7%)	p=0.12 [b]
		csPCa [a]	7 (20.0%)	12 (26.1%)	13 (28.9%)	p=0.7 [b]
Peripheral zone CSR, No. (%) (n=130)			FUS-TB (n=39)	COG-TB (n=44)	MRI-TB (n=47)	
		PCa	16 (41.0%)	14 (31.8%)	23 (48.9%)	p=0.3 [b]
		csPCa [a]	8 (20.5%)	12 (27.3%)	15 (31.9%)	p=0.5 [b]
Transition zone CSR, No. (%) (n=29)			FUS-TB (n=10)	COG-TB (n=14)	MRI-TB (n=5)	
		PCa	6 (60.0%)	10 (71.4%)	5 (100.0%)	p=0.3 [b]
		csPCa [a]	5 (50.0%)	7 (50.0%)	3 (60.0%)	p>0.9 [b]
Small prostate volume (<50 ml), No. (%) (n=100)			FUS-TB (n=38)	COG-TB (n=33)	MRI-TB (n=29)	
		PCa	20 (52.6%)	21 (63.6%)	23 (79.3%)	p=0.08 [b]
		csPCa [a]	13 (34.2%)	17 (51.5%)	13 (44.8%)	p=0.3 [b]
Large prostate volume (≥50 ml), No. (%) (n=134)			FUS-TB (n=41)	COG-TB (n=45)	MRI-TB (n=48)	
		PCa	19 (46.3%)	13 (28.9%)	19 (39.6%)	p=0.2 [b]
		csPCa [a]	14 (34.1%)	9 (20.0%)	12 (25.0%)	p=0.3 [b]

COG-TB = cognitive registration TRUS TB; csPCa = clinically significant PCa; CSR = cancer suspicious region; FUS-TB = MRI-TRUS fusion TB; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI TB; PCa = prostate cancer; PIRADS = Prostate Imaging Reporting and Data System; TB = targeted biopsy; TRUS = transrectal ultrasound.
[a] Gleason 3 + 4. [b] Pearson chi-square.

DISCUSSION

Main findings

This is the first multicenter RCT comparing all three TB techniques based on mpMRI. There were no statistically significant detection rate differences of overall PCa nor csPCa among the three techniques. Though the highest yield of overall PCa was achieved with MRI-TB, followed by FUS-TB, these results were not significantly superior to COG-TB. This trend was not so apparent for csPCa, where the yields were very similar. The number of cores needed was lower for MRI-TB compared to other techniques, resulting in a higher core positivity rate. We expected an advantage of MRI-TB for small lesions and of transperineal FUS-TB for anterior lesions, but could not demonstrate such advantages in sub-analyses. Though these sub-analyses should be interpreted with caution due to small sample size per analysis.

Negative mpMRI and follow-up

Compared to published literature, the yield of mpMRI was relatively low (35.2%). This can partially be explained by the threshold applied for recruitment (persisting suspicion on PCa defined as PSA ≥4 (ng/ml) and/or suspicious DRE), accurately reflecting clinical thresholds for non-invasive diagnostic tools as mpMRI. Furthermore expert reading of mpMRI possibly contributes to low yields.

In 431 subjects with negative mpMRI (PIRADS≤2) nine (2.1%) PCas were detected during limited follow-up (median 12 months) including two (0.5%) csPCas. An elaborate analysis will be presented after completion of two and five years follow-up.

Current knowledge

The literature directly comparing TB techniques is limited, nonetheless conclusions drawn support findings of this RCT. Puech et al could not demonstrate an advantage of FUS-TB compared to COG-TB in 68 subjects undergoing both techniques, with a concordance of 84%.[15] Wysock et al performed both FUS-TB and COG-TB in 125 men and found PCa detection rates of 32.0% for FUS-TB vs. 26.7% for COG-TB (p=0.14), and csPCa rates of 20.3% for FUS-TB vs. 15.1% for COG-TB (p=0.05).[25] A RCT by Arsov et al compared MRI-TB to FUS-TB (+ SB) in 210 subjects. They found PCa detection rates of 37% for MRI-TB vs. 39% for FUS-TB (p=0.7), and csPCa rates of 29% for MRI-TB vs. 32% for FUS-TB (p=0.7).[26] Yaxley et al report on COG-TB and MRI-TB in 483 men, and found no advantage of one technique, neither for overall PCa (81.6% for COG-TB vs. 74.2% for MRI-TB, p=0.53) nor for csPCa detection (75.5% for COG-TB vs. 68.1% for MRI-TB, p=0.40).[27] Finally Kaufmann et al compared detection rates of (cs)PCa between COG-TB, MRI-TB and FUS-TB in a non-randomised cohort of 156 men,

and found no significant differences in detection rates of csPCa (COG-TB 23.7%, MRI-TB 40.0% and FUS-TB 25.6%, p=0.27), although they found a significant advantage of MRI-TB and FUS-TB over COG-TB for overall PCa detection (COG-TB 29.0%, MRI-TB 51.1% and FUS-TB 52.4%, p=0.04).[28]

Limitations

The main study limitation is powering. Primarily due to lower yield of PIRADS≥3 on mpMRI (50% lower than anticipated) and thus low availability for TB, causing under-powering for primary endpoint. This is partially counterbalanced by higher PCa detection rates (44-55%) than the anticipated yields (25-40%). Although no statistically significant differences were found among groups with the current sample size, clinically relevant differences cannot be ruled-out definitively based on broad 95% CI's. A larger trial might give more definitive results, although a post-hoc power analysis (based on the established yield of mpMRI and TB in this study) demonstrated that an overwhelming 9886 subjects would need to undergo mpMRI using the current study design. More importantly csPCa detection rate differences ranged between 0.8-1.7%, and as such even larger sample sizes would be necessary to find statistically significant differences among groups. Future studies could search for superior techniques for specific lesions (size and location).

The absence of consensus on csPCa definition limits any study on TB. We applied a commonly used definition of csPCa.[10,25] Furthermore, additional analysis was included using an alternative definition of csPCa.[29,30] With this conservative definition of csPCa (incorporating Gleason grade, tumour volume, PSA-density and stage) there were also no significant differences in detection rates (FUS-TB 43.0%, COG-TB 39.7% and MRI-TB 46.8%, p=0.68, **appendix 3**).

Inter-observer variability is a factor in PCa diagnosis, impacting quality and reliability of MRI evaluation, accuracy of biopsy procedures and histopathological evaluation. Due to logistical restrictions and institutional regulation we were not able to implement double readings of MR imaging or histopathology, which would have increased reliability. However our group represents an expert-team of urologists and radiologists regarding PCa diagnosis. Consequently the generalizability of this paper with regard to common practise might be limited, and should be implemented with caution. Nonetheless expertise and experience was similar in all groups and cannot explain the absence of statistical differences between techniques.

Finally each technique has its own strengths and limitations; FUS-TB was performed under anaesthesia, reducing movement potentially resulting in better targeting, while being invasive, expensive and time-consuming. COG-TB enables real-time correction for

movement, but requires experience with both TRUS and mpMRI. With MRI-TB post-biopsy scan with needle in situ can confirm adequate sampling, although is limited by availability, required expertise, and time-consuming and costly nature.

CONCLUSIONS

In men with prior negative prostate biopsies and a persistent suspicion of prostate cancer the rate of cancer suspicious regions (PIRADS≥3) on mpMRI was 35%. If targeted biopsy of these regions is performed the detection rate was 49% for prostate cancer, and 33% for clinically significant prostate cancer. Based on this multicenter RCT there were no significant differences in the detection rates of (clinically significant) prostate cancer among three techniques of mpMRI based targeted biopsy. Consequently other factors (as local experience, availability and costs) should be evaluated when determining which technique(s) to implement.

Take home message

In repeat biopsy setting mpMRI based targeted biopsy has a high detection rate of (clinically significant) prostate cancer. There were no significant differences in the detection rates of (clinically significant) prostate cancer among three techniques of mpMRI based targeted biopsy.

Acknowledgements and Funding

We would like to thank the urologists in the reference hospitals for presenting eligible subjects for recruitment in our recruitment centres: Beatrix Rivas Hospital Gorinchem, Bernhoven Hospital Uden, Canisius Wilhelmina Hospital Nijmegen, Diakonessenhuis Hospital Utrecht, Gelderse Vallei Hospital Ede, Gelre Hospital Apeldoorn/Zutphen, Rivierenland Hospital Tiel, Slingeland Hospital Doetinchem, St. Antonius Hospital Nieuwegein/Utrecht, St. Jansdal Hospital Harderwijk, Streekziekenhuis Koningin Beatrix Winterswijk, Zuwe Hofpoort Hospital Woerden. Furthermore we would like to thank the staff of the urology and radiology departments and the research bureaus of our recruitment centres, and obviously all the men recruited in the trial.

The sample size calculation and statistical analysis was performed with the help of dr. E. Tromp and dr. J.C. Kelder (Department of Epidemiology and Statistics, St Antonius Hospital, Nieuwegein/Utrecht)

This investigation was sponsored by the St. Antonius Hospital Research and Innovation Funds, Foundation Urology 1973 and Astellas Pharma.

Declaration of interests

None of the authors has financial interest to disclose with regard to this manuscript.

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APPENDICES

APPENDIX 1: specifications of applied mpMRI – scan protocol

	Magnetom Skyra® Siemens, Magnetom Trio® Siemens					
Sequence	**T2 TSE**	**T2 TSE**	**T2 TSE**	**EPI DWI**	**PD T1 Twist or Vibe or fl3d**	**DCE dynamic T1 Twist or Vibe or fl3d**
Orientation	Sagital	Coronal	Axial	Axial	Axial	Axial
TR (ms)	>5000	>5000	>5000	3200	40	3.62
TE (ms)	101	101	104	63	1.27	1.27
TI (ms)	-	-	-	-	-	-
Flip Angle (deg)	160	160	160	-	5	14
Freq FOV mm (Phase FOV)	180	192	192	256	192	192
Matrix size	320	320	384	128	224	224
# Slices/ Thickness(mm)	19 slices 3 mm	15 slices 3 mm	19 slices 3 mm	19 slices 3 mm	26 slices 3 mm	26 slices 3 mm
Gap	20%	0%	0%	0 %	-	-
Voxel size (mm)	0.6x0.6x3	0.6x0.6x3	0.5x0.5x3	2x2x3	0.9x0.9x3	0.9x0.9x3
Averages/NEX	2	2	4	8	-	-
Phase enc Dir	H>>F	R>>L	R>>L	R>>L	R>>L	R>>L
Fat suppres	None	None	None	Fat sat.	None	None
≅BW(Hz/Px)	200	200	200	1502	490	490
Flow Comp	-	-	-	-	-	-
≅ETL	13	13	11	-	-	-
b-values (sec/mm2) (Directions)	-	-	-	b 50, b 400, b 800, b 1400 (calculated)	-	-
Measurements	1	1	1	1	1	45
Contrast agent	-	-	-	-		15ml gadolinium

APPENDIX 1: Continued

	Ingenia® Philips					
Sequence	**T2 TSE**	**T2 TSE**	**T2 TSE**	**EPI DWI**	**PD THRIVE**	**DCE THRIVE**
Orientation	Sagital	Coronal	Axial	Axial	Axial	Axial
TR (ms)	4169	4200	4996	4188	40	3.2
TE (ms)	110	90	100	82	1.43	1.51
Flip Angle (deg)	90	90	90	90	10	10
Freq FOV mm (Phase FOV)	180	300	200	256	200	200
Matrix size	320	432	432	144	224	224
SENSE	Yes	Yes	Yes	Yes	yes	Yes
# Slices/ Thickness(mm)	28 slices 3 mm	25 slices 3 mm	26 slices 3 mm	26 slices 3 mm	26 slices 3 mm	26 slices 3 mm
Voxel size (mm)	0.6x0.6x3	0.7x0.7x3	0.5x0.5x3	2x2x3	0.9x0.9x3	0.9x0.9x3
NSA	1	1	1	4	1	1
Phase enc Dir	H>>F	R>>L	R>>L	R>>L	R>>L	R>>L
Fat suppres	None	None	None	SPAIR	None	None
WFS (pix) / BW (Hz)	1.991/218.2	1.963/221.3	1.987/218.5	minimum	0.6	0.6
b-values (sec/mm2) (Directions)	-	-	-	b 0, b 50, b 400, b 800, b 1400 (calculated)	-	-
Measurements	1	1	1	1	1	49
Contrast agent	-	-	-	-	-	15ml gadolinium
Acquisition time	4:26	3:13	4:59	6:12	0:15	5:06

APPENDIX 2: PIRADS v2 Assessment Categories

PIRADS 1	Very low: clinically significant cancer is highly unlikely to be present
PIRADS 2	Low: clinically significant cancer is unlikely to be present
PIRADS 3	Intermediate: the presence of clinically significant cancer is equivocal
PIRADS 4	High: clinically significant cancer is likely to be present
PIRADS 5	Very high: clinically significant cancer is highly likely to be present

APPENDIX 3: Biopsy outcomes using secondary definition of csPCa*

			FUS-TB (n=79)	COG-TB (n=78)	MRI-TB (n=77)	
Detection rate of csPCa [a], No. (%)			34 (43.0%)	31 (39.7%)	36 (46.8%)	p=0.7
			FUS-TB (n=23)	COG-TB (n=21)	MRI-TB (n=20)	
mpMRI outcome, No. (%)	PIRADS 3 (n=64)	csPCa [a]	4 (17.4%)	4 (19.0%)	4 (20.0%)	p>0.9
			FUS-TB (n=34)	COG-TB (n=32)	MRI-TB (n=35)	
	PIRADS 4 (n=101)	csPCa [a]	10 (29.4%)	6 (18.8%)	12 (34.3%)	p=0.4
			FUS-TB (n=22)	COG-TB (n=25)	MRI-TB (n=22)	
	PIRADS 5 (n=69)	csPCa [a]	20 (90.9%)	21 (84.0%)	20 (90.9%)	p=0.7
Small CSR (≤10mm), No. (%) (n=91)			FUS-TB (n=29)	COG-TB (n=31)	MRI-TB (n=31)	
		csPCa [a]	6 (20.7%)	6 (19.4%)	4 (12.9%)	p=0.7
Anterior located CSR, No. (%) (n=90)			FUS-TB (n=37)	COG-TB (n=25)	MRI-TB (n=28)	
		csPCa [a]	21 (56.8%)	13 (52.0%)	17 (60.7%)	p=0.8
Posterior located CSR, No. (%) (n=126)			FUS-TB (n=35)	COG-TB (n=46)	MRI-TB (n=45)	
		csPCa [a]	11 (31.4%)	12 (26.1%)	16 (35.6%)	p=0.6
Peripheral zone CSR, No. (%) (n=130)			FUS-TB (n=39)	COG-TB (n=44)	MRI-TB (n=47)	
		csPCa [a]	13 (33.3%)	13 (29.5%)	17 (36.2%)	p=0.8
Transition zone CSR, No. (%) (n=29)			FUS-TB (n=10)	COG-TB (n=14)	MRI-TB (n=5)	
		csPCa [a]	5 (50.0%)	10 (71.4%)	5 (100.0%)	p=0.14
Small prostate volume (<50 ml), No. (%) (n=100)			FUS-TB (n=38)	COG-TB (n=33)	MRI-TB (n=29)	
		csPCa [a]	16 (42.1%)	21 (63.6%)	21 (72.4%)	p=0.03
Small prostate volume (≥50 ml), No. (%) (n=134)			FUS-TB (n=41)	COG-TB (n=45)	MRI-TB (n=48)	
		csPCa [a]	18 (43.9%)	10 (22.2%)	15 (31.3%)	p=0.10

[a] = Gleason 3+3 + MCCL≥6mm or Gleason 3+4 + MCCL≥4mm or any Gleason≥4+3 or any PSA-density≥0.15 or any ≥cT3;

APPENDIX 4: Applied abbreviations in order of appearance in the text

PCa	Prostate Cancer
PSA	Prostate Specific Antigen
TRUS	Transrectal Ultrasound
SB	Systematic Biopsy
mpMRI	multiparametric Magnetic Resonance Imaging
TB	Targeted Biopsy
CSR	Cancer Suspicious Region
csPCa	clinically significant Prostate Cancer
MRI-TB	Magnetic Resonance Imaging – Target Biopsy
FUS-TB	MRI-TRUS fusion - Target Biopsy
COG-TB	Cognitive registration TRUS - Target Biopsy
IRB	Institutional Review Board
IC	Informed Consent
DRE	Digital Rectal Examination
UTI	Urinary Tract Infection
3-T	3 Tesla
PIRADS	Prostate Imaging Reporting and Data System
T2W	T2-Weighted
DWI	Diffusion Weighted Imaging
DCE	Dynamic Contrast Enhanced
ISUP	International Society of Urological Pathology
MCCL	Maximum Cancer Core Length

6

Chapter 6

Is there still a need for repeated systematic biopsy in patients with previous negative biopsies in the era of magnetic resonance imaging targeted biopsies of the prostate?

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European Urology Oncology 2019; in press

ABSTRACT

Background: The role of targeted prostate biopsies (TB) in patients with cancer suspicious lesions on multiparametric magnetic resonance imaging (mpMRI) following negative systematic biopsies (SB) is undebated. Whether they should be combined with repeated SB however remains unclear.

Objective: To evaluate the value of repeated SB in addition to TB in patients with prior negative SB and a persistent suspicion of prostate cancer (PCa).

Design, setting and participants: Prospective study as part of a multicenter randomized controlled trial conducted between 2014 and 2017, including 665 men with prior negative SB and a persistent suspicion of PCa (suspicious digital rectal examination and/or PSA>4.0 ng/ml).

Intervention: All patients underwent 3T mpMRI according to Prostate Imaging Reporting and Data System (PI-RADS) v2. Patients with PI-RADS≥3 were randomized 1:1:1 for three TB techniques: MRI-TRUS fusion (FUS-TB), cognitive registration fusion (COG-TB) or in-bore MRI (MRI-TB). FUS-TB and COG-TB were combined with repeat SB.

Outcome measurements and statistical analysis: Clinically significant prostate cancer (csPCa) was defined as Gleason≥3+4. Differences in detection rates of csPCa, clinically insignificant (cis)PCa and overall PCa between TB (FUS-TB and COG-TB) and repeat SB were compared using McNemar's test.

Results and limitations: In the 152 subjects who underwent both TB and SB, PCa was detected by TB in 47% and by SB in 32% ($p<0.001$, 95% CI: 6.0-22%). TB detected significantly more csPCa than SB (32% vs 16%; $p<0.001$, 95% CI: 11-25%). csPCa was missed by TB in 1.3% (2/152). Combining SB and TB resulted in detection rate differences of 6.0% for PCa, 5.0% for cisPCa and 1.0% for csPCa compared to TB alone.

Conclusions: In case of a persistent suspicion of PCa following negative SB, TB detected significantly more csPCa than SB. The additional value of SB was limited and only 1.3% of csPCa would have been missed when SB had been omitted.

Patient summary: We evaluated the role of systematic biopsies and MRI-targeted biopsies for the diagnosis of prostate cancer in patients with prior negative systematic biopsies. MRI-targeted biopsies perform better in detecting prostate cancer in these patients. The value of repeat systematic biopsies is limited.

INTRODUCTION

The most commonly used technique for PCa detection is transrectal ultrasound (TRUS) guided systematic biopsy (SB). SB is notorious for both underdiagnosing clinically significant prostate cancer (csPCa) due to undersampling of the anterior, midline and apical regions of the prostate and overdiagnosing clinically insignificant cancer (cisPCa) [1]. Many men undergo repeated SB due to a persistent suspicion of PCa, which is associated with pain, anxiety and a risk of infection [2-4].

Multiparametric MRI (mpMRI) offers increased sensitivity for csPCa and localization accuracy of cancer suspicious regions (CSR) [5]. Guidelines advise to perform mpMRI in patients with prior negative SB and a persistent clinical suspicion of PCa [6,7]. CSRs on mpMRI enable MR-targeted biopsies (TB). Systematic reviews of the literature have shown higher csPCa detection rates by TB than SB, and a lower yield of cisPCa while requiring less biopsy cores [8-11]. Therefore a combination of TB and SB is recommended. However, individual studies show heterogeneous results and are mainly focused on biopsy-naive men. Whether concurrent SB are also warranted in a repeat biopsy setting is still unclear [7].

To evaluate the value of SB in addition of TB in men with negative prior SB and a persisting clinical suspicion of PCa we compared detection rates of overall PCa, cisPCa and csPCa between SB and TB.

MATERIALS AND METHODS

Study design

We performed a prospective predefined analysis of participants of the FUTURE trial, which was designed as a multicenter randomized controlled trial comparing three techniques of TB in patients with a persistent suspicion of PCa following negative SB[12]. Detection difference between TB versus repeat SB was defined as a secondary endpoint in the study protocol. Institutional review board approval was granted. The protocol was registered in the Dutch Trial Registry (NTR4988). All patients provided written informed consent. Between December 2014 and November 2017 men with prior negative SB within the last 4 years (≥8 cores from the peripheral zone) and a persistent suspicion of PCa (PSA≥4.0 ng/mL and/or suspicious digital rectal examination (DRE)) were enrolled in two non-academic centers of excellence for prostate cancer diagnosis. Participants of the FUTURE trial who underwent both TB and SB were included in the current analysis.

Exclusion criteria for enrolment in the trial were prior diagnosed PCa, prior TB, proven urinary tract infection (UTI), contraindication for mpMRI or TB, imaging or TB or SB nog performed according to protocol, or withdrawal of consent.

Multiparametric MRI

All patients underwent 3T mpMRI according to Prostate Imaging Reporting and Data System (PI-RADS) v2 (**Supplementary table 1&2**) [13]. Sequences included: T2-weighted images (T2W), diffusion-weighted images (DWI) and dynamic contrast-enhanced images (DCE). Images were centrally evaluated by one of two expert radiologists (20 and 5 years' experience in prostate MRI, 1500 cases/year each). Radiologists were not blinded to clinical data. A written mpMRI report incorporating marked images was provided. If imaging showed no CSR patients entered biochemical follow-up.

Biopsy

Patients with PI-RADS≥3 lesions were randomized 1:1:1 to undergo TB using transperineal MRI-ultrasound fusion (FUS-TB) (Biopsee®, Medcom, Darmstadt, Germany), transrectal cognitive registration fusion (COG-TB) (BK Pro Focus®/Hitachi Hi-Vision Preirus®) or transrectal in-bore MRI (MRI-TB) (DynaTRIM, Invivo, Gainsville, USA) [12,14]. TB were performed by expert trained PhD candidates and urologists. TB cores were taken first and potted separately. A minimum of two TB cores per CSR was required for adequate sampling. SB were taken by the same operator that performed TB by transrectal approach, in cases of COG-TB, or transperineal approach, in case of FUS-TB. SB were performed using a standardized template irrespective of CSR location. For MRI-TB it was not feasible to perform concomitant SB since this would have meant an additional procedure [15]. Therefore, in these patients SB was omitted for ethical reasons and this group of patients was excluded from this analysis. The number of SB cores was based on common practice at the time of trial design and was dependent on prostate volume.Undersampling of the anterior/transition zone by prior negative SB was taken into account by including at least two anterior and two transition zone cores in the SB template, e.g. volume <40cc=8 biopsies (2 anterior, 2 transition zone and 4 peripheral zone); volume 40-60 cc=10 biopsies (2 anterior, 2 transition zone and 6 peripheral zone); volume >60 cc=12 biopsies (2 anterior, 4 transition zone and 6 peripheral zone). Specimens were processed in accordance to ISUP standards and evaluated by an experienced uro-pathologist per center (11, 17 and 10 years' experience in PCa diagnosis) [16]. Gleason scores and maximum cancer core length (MCCL) were reported. csPCa was defined as Gleason≥3+4. Analysis using an alternative threshold of csPCa was included in **Supplementary table 3**.

Statistical analysis

Primary outcome was cancer detection rates (CDR) by SB and TB. Secondary outcomes were csPCa and cisPCa detection rates. Sub-analyses on CDR per biopsy core, per approach (transperineal vs transrectal), and stratified per PI-RADS score were performed. Patient characteristics were summarized using mean±standard deviation (SD) or median and interquartile range (IQR) as appropriate. To assess comparability between paired continuous variables Wilcoxon signed-rank test was applied. McNemar's test was used to compare paired nominal data (CDR of SB and TB) by means of absolute rate differences. CDR of different TB techniques and different approaches were combined based on previously published data which have shown comparable detection rates for different SB and TB [12,17,18].

Since there is no gold standard for prostate biopsies we used (dis)concordance of results to calculate sensitivity and specificity as previously described [10]. A positive reference was defined as a positive test result on either test (SB or TB), so the number of concordant positive tests plus the number of discordant positive tests. Sensitivity of TB and SB was calculated as the number of positive results on either TB or SB divided by the total number of positive tests (TB and SB combined). Specificity was calculated as the number of negative results on either SB or TB divided by the total number of negative tests. Relative sensitivity and specificity is the sensitivity or specificity ratio between TB and SB.

Statistical analyses were performed using SPSS v24 (IBM) and 5% significance levels were adopted in all tests. The trial was not primarily powered for the comparison of TB and SB as it was a predefined secondary endpoint. For further details regarding sample size calculation of the trial we refer to our previously published work [12].

RESULTS

Patients

A total of 695 men were recruited in the trial and 665 men were included in the final analysis (**figure 1**). 234 (35%) patients with a PI-RADS≥3 lesion on mpMRI were randomized for TB: 79 for FUS-TB, 78 for COG-TB and 77 for MRI-TB. 152 patients underwent both TB (76 COG-TB and 76 FUS-TB) and SB. **Table 1** shows baseline characteristics of study populations. Of the analyzed cohort that underwent both TB and SB mean age was 66±6.7 years, mean pre-biopsy PSA was 11±7.9 ng/mL and mean PSA-density (PSAD) was 0.23±0.16 ng/mL/mL. By combining SB and TB overall CDR was 53% (81/152), csPCa was detected in 35% (53/152) and cisPCa in 18% (28/152).

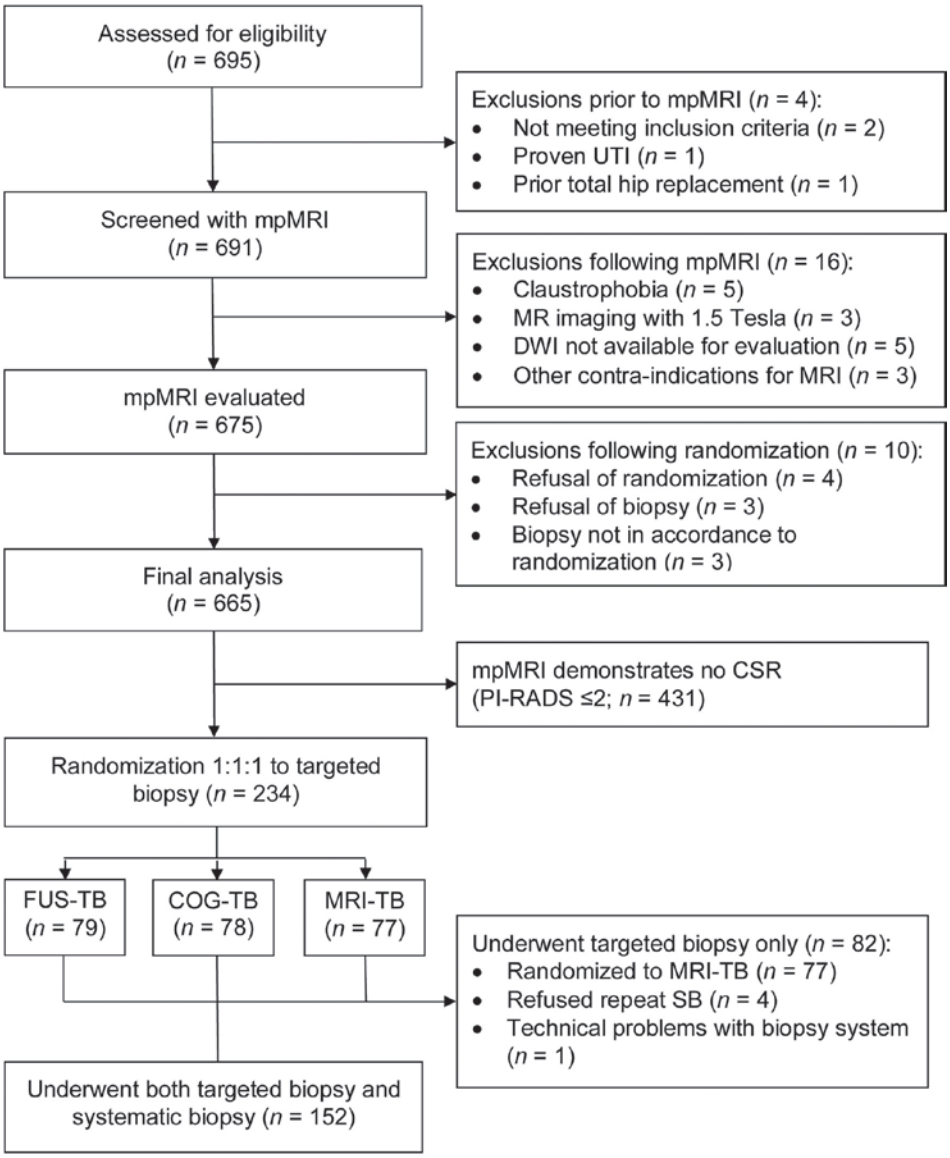

FIGURE 1. Flowchart of the study.

COG-TB = cognitive registration targeted biopsy; CSR = cancer suspicious region; DWI = diffusion weighted imaging; FUSTB = MRI-TRUS fusion targeted biopsy; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI targeted biopsy; PIRADS = Prostate Imaging Reporting and Data System; SB = systematic biopsy; TB = targeted biopsy; TRUS = transrectal ultrasound; UTI = urinary tract infection.

TABLE 1: Study population characteristics

	Cohort that underwent SB + TB (n=152)
Age (years), mean (SD)	66 (6.7)
PSA (ng/mL), mean (SD)	11 (7.9)
Volume TRUS (mL), mean (SD)	47 (16)
PSAD (ng/mL/mL), mean (SD)	0.23 (0.16)
Clinical stage (DRE), n (%)	
• cT1c	122 (80)
• cT2a/b	27 (18)
• cT2c	2 (1.3)
• cT3a	1 (0.66)
Number of prior negative biopsy procedures (n), median (IQR)	1 (1-2)
Time interval from previous biopsy to mpMRI (months), median (IQR)	8 (4-24)
Time interval from mpMRI to biopsies (days), median (IQR)	40 (26-56)
PI-RADS score, n (%)	
• 3	42 (28)
• 4	63 (41)
• 5	47 (31)
CSRs per patient (n), median (IQR)	1 (1-1)
CSR location, n (%)	
• Anterior	59 (40)
• Midline	14 (9.2)
• Posterior	79 (52)
Overall PCa detection rate, n (%)	81 (53)
Overall csPCa detection rate, n (%)	53 (35)

csPCa = clinically significant prostate cancer (Gleason≥3+4); CSR = cancer suspicious region; DRE = digital rectal examination; IQR = interquartile range; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PI-RADS = Prostate Imaging – Reporting and Data System; PSA = prostate specific antigen; PSAD = prostate specific antigen density; SB = systematic biopsy; SD = standard deviation; TB = targeted biopsy; TRUS = transrectal ultrasound.

Comparison of CDR by SB and TB

Crosstabs compare PCa detection rates of SB and TB (**table 2**). CDR for overall PCa by TB was 47% (71/152) and 32% (49/152) by SB. The 15% difference (95% CI: 6.0% to 22%) was significant (p<0.001). Overall CDR by combining SB and TB was 53%, representing a PCa detection rate difference of 6.0% compared to TB alone (CDR of 47%).

Sensitivity for overall PCa was 0.88 for TB and 0.60 for SB with a relative TB/SB sensitivity of 1.5. Specificity for overall PCa was 0.72 for TB and 0.91 for SB with a relative TB/SB specificity of 0.80.

TABLE 2: Biopsy outcomes

	Systematic biopsy (SB)			
	No PCa	**cisPCa**	**csPCa**	**Total**
Targeted biopsy (TB)				
• No PCa	71 (47%)	8 (5.3%)	2 (1.3%)	81
• cisPCa	12 (7.9%)	8 (5.3%)	0 (0.0%)	20
• csPCa	20 (13%)	9 (5.9%)	22 (14%)	51
Total	103	25	24	n=152

cisPCa = clinically insignificant prostate cancer (Gleason 3+3); csPCa = clinically significant prostate cancer (Gleason≥3+4); PCa = prostate cancer; SB = systematic biopsy; TB = targeted biopsy.

csPCa was detected by TB in 34% (51/152) and by SB in 16% (24/152). The 18% difference in detection (95% CI: 11% to 25%) was significant (p<0.001). Combining SB and TB detected csPCa in 35% (53/152) cases, representing a csPCa detection rate difference of 1.0% compared to TB alone (34% csPCa). Sensitivity of csPCa was 0.96 for TB and 0.45 for SB with a relative sensitivity of 2.1. Specificity of csPCa was 0.78 for TB and 0.98 for SB with a relative specificity of 0.80.

TB detected cisPCa in 13% (20/152) compared to 16% (25/152) by SB (p=0.4, 95% CI: -4.0% to10%). Combining SB and TB detected cisPCa in 18% (28/152) cases, representing a cisPCa detection rate difference of 5.0% compared to TB alone (13% cisPCa).

In patients in whom SB did not detect PCa, TB detected PCa in 21% and csPCa in 13%. Alternatively, in patients in whom TB did not detect PCa, SB detected PCa in 6.6% and csPCa in 1.3%. Overall, csPCa was missed by TB in 1.3% and by SB in 19%. This 18% difference (95% CI: 11% to 24%) was significant (p<0.001). Relative to the group of detected csPCa (n=53), TB missed 3.8% of csPCa and SB missed 55% csPCa. SB detected cisPCa in 5.3% of patients in whom TB detected no PCa and TB detected cisPCa in 7.9% of patients in whom SB detected no PCa. See Supplementary table 3 for outcomes for alternative csPCa thresholds.

A significantly higher number of TB cores were positive for PCa (34%; 201/593) than SB cores (17%; 100/1533) (p<0.001, 95% CI: 23% to 32%) resulting in a lower number of cores (median 3 vs. 10 cores per subject) needed to achieve a higher CDR (**table 3**). Sub-analysis of CDR stratified per PI-RADS score (**Supplementary table 4**) and per biopsy approach (transrectal vs transperineal) (**Supplementary table 5**) did not show significant differences.

TABLE 3: Biopsy cores

	TB cores	SB cores
Total cores	593	1533
Per subject, n (median, IQR)	3 (3-4)	10 (8-12)
PCa positive cores	201	100
Positivity rate	34%	6.5%

IQR = interquartile range; PCa = prostate cancer; SB = systematic biopsy; TB = targeted biopsy

Radical prostatectomy

A radical prostatectomy (RP) was performed in 40 patients with a CSR on mpMRI. Of these 40 patients 38 were diagnosed with PCa by at least one TB and 19 patients were diagnosed by at least one SB. Seventeen patients were diagnosed with PCa by both TB and SB. Gleason grading according to Epstein of TB cores and RP specimen was concordant in 17/38 (45%) patients, upgraded in 7/38 (18%) patients and downgraded in 14/38 (37%) patients. In 3/7 (43%) upgraded cases it concerned an upgrade from cisPCa to csPCa. Gleason grading of SB and RP specimen was concordant in 6/19 (32%) patients, upgraded in 6/19 (32%) patients and downgraded in 7/19 (37%) patients. In 6/6 (100%) upgraded cases it concerned an upgrade from cisPCa to csPCa

DISCUSSION

Main findings

To prevent cisPCa overdiagnosis and overtreatment without missing out on csPCa there is an obvious need for an optimal imaging and biopsy approach in men with prior negative SB and a persistent clinical suspicion of PCa. The aim of this analysis was to evaluate the value of SB in addition of TB in a homogeneous cohort of men with prior negative SB and a persistent suspicion of PCa.

In this prospective cohort, as part of a randomized controlled trial, TB significantly increased CDR of overall PCa as well as csPCa compared to SB. The number of biopsy cores needed to achieve a higher CDR was significantly lower for TB than for SB. The additional value of repeat SB was limited. Using TB only few csPCa were missed and less cisPCa was detected compared to SB.

Current knowledge

Recently a Cochrane review and meta-analysis and the updated EAU guideline recommend to perform TB only when mpMRI is positive in the repeated biopsy setting [19,20]. However, the evidence regarding this recommendation is still weak, as rated by the EAU guideline committee. Although the research question of our study might not be novel, the results are of clinical relevance. We performed an analysis of a predefined secondary endpoint within a randomized controlled trial. This has resulted in protocoled high-quality data collection and management of a homogeneous cohort of patients in centers of excellence regarding prostate cancer diagnosis. Therefore, our results contribute to increase the level of evidence for the guideline recommendation on TB and SB in the repeat biopsy setting.

So far, several studies have compared CDR of SB and TB in subjects with prior negative SB and found csPCa detection rates by TB ranging from 15-48% depending on patient selection, imaging quality, TB technique used and applied definition of csPCa [21-24]. In these studies repeated SB yields of csPCa ranged from 9.0-31%. The authors of these papers concluded that addition of SB may be needed to avoid missing csPCa. The results from this current paper seem to contradict these conclusion.

In accordance with our findings a systematic review and meta-analysis of Schoots et al. showed that TB detected significantly more (cs)PCa than SB (relative sensitivity of 1.54 (95% CI 1.05 to 2.57)) in a subgroup of men with prior negative SB [10]. The authors did not formulate a recommendation regarding the value of repeated SB in these men, possibly due to the heterogeneity of the study populations. On the contrary, Mischinger et al. recently evaluated the performance of transperineal robot-assisted TB compared to SB in primary and repeat biopsy setting and found that TB and SB showed similar csPCa detection rates. However, their patient selection was not restricted to fixed PI-RADS-thresholds, and more importantly a heterogeneous population was studied [15]. Despite the high sensitivity of TB for csPCa as presented by Filson et al. in a recent prospective trial, concerns regarding missing csPCa may arise when omitting SB in repeat biopsy setting [25]. In repeat biopsy setting studies show variable percentages of missed csPCa by TB ranging from 0.0-23% [23,24,26,27]. Filson et al showed in a mixed population (biopsy-naive, prior negative SB, and active surveillance) of men with PI-RADS≥3 that a combination of TB and SB (n=289) detected more csPCa in men than either modality alone (229 by TB and 199 by SB) [25]. Interestingly, a recent study showing frequent overlap of SB and TB cores further support our findings that SB adds limited diagnostic improvement in repeat biopsy setting [28].

In our study combining SB and TB resulted in similar csPCa detection compared to TB alone (35% vs. 34%, respectively). TB missed csPCa in only 1.3% of patients indicating that

SB could have been safely omitted in this group of patients. In one case it concerned a sampling error (positive SB in same quadrant as suspicious lesion on mpMRI), in the other the lesion was not diagnosed on mpMRI.

The correlation between TB and final RP specimen has not been widely studied. However, in concordance with our findings previous studies have shown that Gleason grading is often underestimated by SB (upgrading on prostatectomy between 30-43%) due to a large sampling error [29-32] Discrepancy may lead to undertreatment as an upgrade from cisPCa to csPCa is commonly seen. We found less upgrading from cisPCa to csPCa after TB than SB which may enhance therapeutic decision-making. Our relatively low concordance rate between TB and RP specimen (45%) compared to most literature may be explained by our relatively low number of cores per CSR (median 3-4) which might have resulted in a sampling error. Furthermore, while most studies report on (mixed) cohorts of biopsy naïve men, men with previous negative biopsy and men under active surveillance we analyzed a homogeneous cohort of men with previous negative biopsy. This repeated biopsy setting may have influenced our results by a higher incidence of smaller, harder to approach lesions resulting in a subsequent sampling error and lower concordance rate compared to other studies [33-38]

Nevertheless, some csPCa might fall below the threshold of mpMRI and therefore follow-up of men with negative mpMRI and TB, in whom clinical suspicion persists, is of great importance. Currently our follow-up is limited in duration and a more elaborate analysis on this issue will follow after completion of two to five years follow-up for all patients.

Limitations

This study has some limitations. First of all, the FUTURE trial was designed and powered to compare CDR of three different TB techniques and sample size calculations for our subgroup analyses are lacking. In this study he same operator performed TB and SB an therefor was not blinded to CSR on mpMRI while performing SB. We attempted to limit this bias by using a standardized SB template based on prostate volume. Also, CDRs for csPCa are dependent on the definition of csPCa. Therefore, CDR need to be interpreted with caution especially when tumor burden, PSA-value and clinical staging are not taken into account. We attempted to reduce this limitation by applying a secondary definition of csPCa incorporating tumor volume, PSAD and clinical staging (**Supplementary table 3**). Potentially TB samples CSR more thoroughly compared to SB resulting in higher Gleason scores. This study uses earlier published definitions of csPCa based on random sampling. Consensus on the definition of csPCa in the TB era is urgently needed to compare between series. Lastly, we are not informed on the actual PCa prevalence in our cohort as we used the combination of the two analyzed technique as our gold standard. In our study patients

were enrolled in two non-academic centers of excellence for prostate cancer diagnosis. All mpMRI studies were performed following PIRADS v2 standards and centrally reviewed in an academic center. Therefore, we believe that our results can be compared with other centers of excellence for prostate cancer diagnosis (either academic or non-academic) while on the other hand the generalizability of the presented outcomes to general practice may be limited. Nevertheless, this study shows how accurate mpMRI and consequent TB can be in an optimal situation. Therefore our results are in agreement with the statement of Rosenkrantz that omission of SB should only be considered when quality of mpMRI-acquisition and TB can be assured [7].

CONCLUSIONS

In men with prior negative SB and a persistent suspicion of PCa, TB have a 18% higher csPCa detection rate than SB. Combining SB and TB resulted in csPCa detection rate differences of 6.0% for PCa, 5.0% for cisPCa and 1.0% compared to TB alone. Only 1.3% csPCa would have been missed when SB would have been omitted. Therefore, the value of adding SB to TB in repeat biopsy setting is limited.

Acknowledgements

We would like to thank the following hospitals (in alphabetical order) for presenting eligible subjects for recruitment: Beatrix Rivas Hospital Gorinchem, Bernhoven Hospital Uden, Canisius Wilhelmina Hospital Nijmegen, Diakonessenhuis Hospital Utrecht, Gelderse Vallei Hospital Ede, Gelre Hospital Apeldoorn/Zutphen, Rivierenland Hospital Tiel, Slingeland Hospital Doetinchem, St. Antonius Hospital Nieuwegein/Utrecht, St. Jansdal Hospital Harderwijk, Streekziekenhuis Koningin Beatrix Winterswijk, Zuwe Hofpoort Hospital Woerden. Furthermore, we would like to thank the urology, pathology, radiology and research departments of our recruitment hospitals for their effort. We would also like to thank all men for their agreement and motivation to take part in this study. Statistical analysis was performed with help of dr. J.C. Kelder (Department of Epidemiology and Statistics, St. Antonius Hospital, Nieuwegein/Utrecht).

Funding

This investigation was sponsored by the St. Antonius Hospital Research and Innovation Funds, Foundation Urology 1973 and Astellas Pharma.

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APPENDICES

SUPPLEMENTARY TABLE 1: Specifications of applied mpMRI scan protocol

	Magnetom Skyra® Siemens, Magnetom Trio® Siemens					
Sequence	**T2 TSE**	**T2 TSE**	**T2 TSE**	**EPI DWI**	**PD T1 Twist or Vibe or fl3d**	**DCE dynamic T1 Twist or Vibe or fl3d**
Orientation	Sagittal	Coronal	Axial	Axial	Axial	Axial
TR (ms)	>5000	>5000	>5000	3200	40	3.62
TE (ms)	101	101	104	63	1.27	1.27
TI (ms)	-	-	-	-	-	-
Flip Angle (deg)	160	160	160	-	5	14
Freq FOV mm (Phase FOV)	180	192	192	256	192	192
Matrix size	320	320	384	128	224	224
# Slices/ Thickness(mm)	19 slices 3 mm	15 slices 3 mm	19 slices 3 mm	19 slices 3 mm	26 slices 3 mm	26 slices 3 mm
Gap	20%	0%	0%	0 %	-	-
Voxel size (mm)	0.6x0.6x3	0.6x0.6x3	0.5x0.5x3	2x2x3	0.9x0.9x3	0.9x0.9x3
Averages/NEX	2	2	4	8	-	-
Phase enc Dir	H>>F	R>>L	R>>L	R>>L	R>>L	R>>L
Fat suppres	None	None	None	Fat sat.	None	None
≅BW(Hz/Px)	200	200	200	1502	490	490
Flow Comp	-	-	-	-	-	-
≅ETL	13	13	11	-	-	-
b-values (sec/ mm2) (Directions)	-	-	-	b 50, b 400, b 800, b 1400 (calculated)	-	-
Measurements	1	1	1	1	1	45
Contrast agent	-	-	-	-		15ml gadolinium

SUPPLEMENTARY TABLE 1: Continued

	Ingenia® Philips					
Sequence	**T2 TSE**	**T2 TSE**	**T2 TSE**	**EPI DWI**	**PD THRIVE**	**DCE dynamic THRIVE**
Orientation	Sagittal	Coronal	Axial	Axial	Axial	Axial
TR (ms)	4169	4200	4996	4188	40	3.2
TE (ms)	110	90	100	82	1.43	1.51
Flip Angle (deg)	90	90	90	90	10	10
Freq FOV mm (Phase FOV)	180	300	200	256	200	200
Matrix size	320	432	432	144	224	224
SENSE	Yes	Yes	Yes	Yes	yes	Yes
# Slices/ Thickness(mm)	28 slices 3 mm	25 slices 3 mm	26 slices 3 mm	26 slices 3 mm	26 slices 3 mm	26 slices 3 mm
Voxel size (mm)	0.6x0.6x3	0.7x0.7x3	0.5x0.5x3	2x2x3	0.9x0.9x3	0.9x0.9x3
NSA	1	1	1	4	1	1
Phase enc Dir	H>>F	R>>L	R>>L	R>>L	R>>L	R>>L
Fat suppres	None	None	None	SPAIR	None	None
WFS (pix) / BW (Hz)	1.991/218.2	1.963/221.3	1.987/218.5	minimum	0.6	0.6
b-values (sec/mm2) (Directions)	-	-	-	b 0, b 50, b 400, b 800, b 1400 (calculated)	-	-
Measurements	1	1	1	1	1	49
Contrast agent	-	-	-	-	-	15 ml gadolinium
Acquisition time	4:26	3:13	4:59	6:12	0:15	5:06

SUPPLEMENTARY TABLE 2: PI-RADS v2 Assessment Categories

PI-RADS 1	Very low: clinically significant cancer is highly unlikely to be present
PI-RADS 2	Low: clinically significant cancer is unlikely to be present
PI-RADS 3	Intermediate: the presence of clinically significant cancer is equivocal
PI-RADS 4	High: clinically significant cancer is likely to be present
PI-RADS 5	Very high: clinically significant cancer is highly likely to be present

PI-RADS = Prostate Imaging – Reporting and Data System

SUPPLEMENTARY TABLE 3: Biopsy outcomes using secondary definitions of csPCa

	Systematic biopsy (SB)			
	No PCa	**cisPCa**	***csPCa**	**Total**
Targeted biopsy (TB)				
• No PCa	71 (47%)	3 (2.0%)	7 (4.6%)	81
• cisPCa	5 (3.3%)	2 (1.3%)	1 (0.66%)	8
• **csPCa	27 (18%)	1 (0.66%)	35 (23%)	63
Total	103	6	43	n=152

cisPCa = clinically insignificant prostate cancer (Gleason 3+3); *csPCa = clinically significant prostate cancer (Epstein's criteria); **csPCa = Gleason 3+3 and maximum cancer core length ≥6 mm or Gleason 3+4 and maximum cancer core length ≥4 mm or any Gleason 4+3 or any PSA-density≥0.15 or any cT3; PCa = prostate cancer; SB = systematic biopsy; TB = targeted biopsy.

SUPPLEMENTARY TABLE 4: Biopsy outcomes stratified per PI-RADS score

		Systematic biopsy (SB)			
		No PCa	**cisPCa**	**csPCa**	**Total**
Targeted biopsy (TB)					
• PI-RADS 3	No PCa	27 (64%)	4 (9.5%)	0 (0.0%)	31
	cisPCa	3 (7.1%)	1 (2.4%)	0 (0.0%)	4
	csPCa	5 (12%)	0 (0.0%)	2 (4.8%)	7
	Total	35	5	2	n=42
• PI-RADS 4	No PCa	42 (67%)	3 (4.8%)	1 (1.6%)	46
	cisPCa	4 (6.3%)	3 (4.8%)	0 (0.0%)	7
	csPCa	4 (6.3%)	3 (4.8%)	3 (4.8%)	10
	Total	50	9	4	n=63
• PI-RADS 5	No PCa	2 (4.3%)	1 (2.1%)	1 (2.1%)	4
	cisPCa	5 (11%)	4 (8.5%)	0 (0.0%)	9
	csPCa	11 (23%)	6 (13%)	17 (36%)	34
	Total	18	11	18	n=47

cisPCa = clinically insignificant prostate cancer (Gleason 3+3); csPCa = clinically significant prostate cancer (Gleason≥3+4); PCa = prostate cancer; PI-RADS = Prostate Imaging – Reporting and Data System; SB = systematic biopsy; TB = targeted biopsy.

SUPPLEMENTARY TABLE 5: Biopsy outcomes stratified per technique

		Transperineal systematic biopsy (SB)			
		No PCa	**cisPCa**	**csPCa**	**Total**
Targeted biopsy (TB)					
• FUS-TB	No PCa	34 (45%)	4 (5.3%)	1 (1.3%)	39
	cisPCa	9 (12%)	3 (3.9%)	0 (0.0%)	12
	csPCa	12 (16%)	4 (5.3%)	9 (12%)	25
	Total	55	11	10	n=76
		Transrectal systematic biopsy (SB)			
Targeted biopsy (TB)					
• COG-TB	No PCa	37 (49%)	4 (5.3%)	1 (1.3%)	42
	cisPCa	3 (3.9%)	5 (6.6%)	0 (0.0%)	8
	csPCa	8 (11%)	5 (6.6%)	13 (17%)	26
	Total	48	14	14	n=76

cisPCa = clinically insignificant prostate cancer (Gleason 3+3); COG-TB = cognitive registration targeted biopsy; csPCa = clinically significant prostate cancer (Gleason≥3+4); FUS-TB = MRI-TRUS fusion targeted biopsy; PCa = prostate cancer; SB = systematic biopsy; TB = targeted biopsy.

7

Chapter 7

Complications and adverse events of three MRI based target biopsy techniques in the diagnosis of prostate cancer among men with prior negative biopsies. Results from the FUTURE trial: a multicentre randomised controlled trial.

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European Urology Oncology 2019; 2 (6): 617-624

ABSTRACT

Background: 3 techniques of MRI based targeted biopsy (TB) of the prostate exist. There's no superiority regarding diagnostic efficacy of prostate cancer (PCa) detection.

Objective: To compare adverse events (AE) among three TB techniques and to evaluate the effect on urinary and erectile function.

Design, setting, participants: Post-hoc analysis of multicentre RCT among men with negative systematic biopsy (SB) and suspicion of PCa.

Intervention: In 234 subjects 3-T mpMRI demonstrated PIRADS≥ 3 lesions and subjects were randomised 1:1:1 for TB: transrectal in-bore MRI TB (MRI-TB), transperineal MRI-TRUS fusion TB (FUS-TB) or transrectal cognitive TRUS TB (COG-TB).

Outcomes measured, statistical analysis: AE's (Clavien-Dindo) were compared using Pearson Chi square test. Univariate logistic regression tests were performed for number of cores, biopsy approach and usage of anticoagulants. Subjects filled in baseline and 30-days post-biopsy IPSS and IIEF-5 questionnaires. The delta between measurements was compared using one-way ANOVA.

Results and limitations: There were significant differences in minor AE's; 53% in MRI-TB, 71% in FUS-TB and 85% in COG-TB ($p<0.001$). Number of cores was associated with AE's (OR 1.11 per extra biopsy (95%CI 1.06-1.17, $p<0.001$)). Anticoagulants were not associated with bleeding complications (OR 1.24 (95% CI 0.66-2.35, $p=0.5$)). Transrectal approach (MRI-TB + COG-TB) increased the risk of any AE (OR 2.54 (95%CI 1.16-5.77, $p<0.05$)), and non-significantly increased the risk of UTI's (OR 3.69 (95%CI 0.46-168.4, $p=0.3$)). Biopsy did not impact urinary (Δ IPSS 0.3, $p=0.1$) and erectile function (Δ IIEF-5 -0.4, $p=0.5$). Main limitation was that additional SB was performed in FUS-TB and COG-TB, and was omitted in MRI-TB, making comparison difficult.

Conclusion: There was a significant difference in minor AE's among groups. Increasing number of cores increased overall risk of AE's. Low AE occurrence in MRI-TB was likely caused by omission of SB. Prostate biopsy did not impact self-reported urinary and erectile function.

Patient summary: In this study, we compared the complication rates of three techniques of MRI based targeted biopsy of the prostate. We found a significant difference in the occurrence of minor complication rates among 3 groups in favour of MRI-TB, likely caused by the omission of additional systematic biopsy in this group.

INTRODUCTION

Until recently the standard procedure in PCa diagnosis was transrectal ultrasound (TRUS) systematic biopsy (SB). To increase clinically significant (cs)PCa detection rates guidelines advise to perform multiparametric (mp)MRI, enabling targeted biopsy (TB) of mpMRI identified cancer suspicious regions (CSR).[1] TB has been shown to detect more csPCa and less insignificant PCa compared to SB in repeat biopsy setting.[2-5] Recent evidence demonstrates that TB has an additional value in primary biopsy setting as well.[6-8] The updated European guidelines incorporate mpMRI and TB in the initial diagnostic work-up of PCa.[1] Three techniques of TB exist; 1) in-bore MRI target biopsy (MRI-TB), 2) MRI-TRUS fusion target biopsy (FUS-TB), and 3) cognitive registration TRUS target biopsy (COG-TB). A recent multicenter RCT could not demonstrate significant differences in the detection rates of (cs)PCa among the three techniques.[9] Consequently other factors than yield should be considered when determining the optimal technique, such as availability, associated costs, and adverse events (AE's).

In this post-hoc analysis we compared AE's among three mpMRI based TB techniques of the prostate in men with negative prior SB and a persisting suspicion of PCa, and evaluated the effect of TB on self-reported urinary and erectile function.

MATERIAL AND METHODS

Study design, setting and participants

This multicenter three-armed RCT was conducted between December 2014 and November 2017 in accordance with institutional review board requirements (Dutch Trial Registry NTR4988). All subject provided written informed consent. The methodology and results have been previously described, and the protocol was published online.[9,10]

665 men were included with prior negative TRUS-SB and a persistent suspicion of PCa (PSA≥4 (ng/ml) and/or suspicious DRE). Exclusion criteria were prior diagnosed PCa, prior TB procedures, a proven urinary tract infection (UTI), contra-indication for mpMRI and/or TB, imaging and/or TB not performed according to protocol. At inclusion screening for UTI took place using urinalysis, followed by urine culture if urinalysis tested positive.

Magnetic resonance imaging

All subjects underwent 3-T mpMRI in accordance to PIRADSv2 (Prostate Imaging Reporting and Data System) standards.[11,12] Images were evaluated using the PIRADSv2 by one of two

experienced urogenital radiologists. Up to three CSR (PIRADS≥3) were described in 234 subjects (35.2%). These 234 subjects were randomized 1:1:1 to undergo TB using either MRI-TB (n=77), FUS-TB (n=79) or COG-TB (n=78).

Biopsy

All subjects received prophylactic three-day oral regimen of Ciprofloxacin (500 mg twice/day). Anticoagulation therapy was continued unless subjects were treated with coumarines, direct oral anticoagulants (DOAC) or double antiplatelet therapy. All biopsies were performed using an 18 G biopsy gun with 17-22mm cores.

Transrectal MRI-TB was performed in the MRI-scanner (Magnetom Skyra® Siemens) under MR guidance without anaesthetics.[8,9] In MRI-TB it was not technically feasible to perform concomitant SB following TB. Therefore, in these patients SB was omitted.

Transperineal FUS-TB was performed in the operating room under general/spinal anaesthesia in lithotomy position using a MRI-TRUS fusion biopsy device (BiopSee® Medcom).[9] Initially TB cores were taken, followed by transperineal SB using a standardized template. The number of SB cores taken depended on prostate volume on MRI (≤40 mL= 8 cores; 40-60 mL= 10 cores; ≥60 mL = 12 cores).

Transrectal COG-TB was performed in the outpatient clinic using biplane TRUS guidance (Hitachi Hi Vision Preirus® or BK Pro Focus®).[9] Only upon patient request a peri-prostatic nerve block was performed with 10 cc 2% lidocaine. Initially TB cores were taken followed by transrectal SB as described above.

All biopsies were performed by a group of urologist and expert-trained PhD students (at least 6 months of experience) with similar experience levels between the groups.[9]

Outcomes measured

Prior to mpMRI and biopsy, baseline data was collected. Subjects filled-in questionnaires at baseline regarding Lower Urinary Tract Symptoms (LUTS) using the validated International Prostate Symptom Score (IPSS) and regarding Erectile Dysfunction (ED) using the validated International Index of Erectile Function (IIEF-5). Subjects underwent mpMRI and TB of PIRADS≥3 lesions. Data was collected regarding mpMRI, and TB procedure. At 30 days post-biopsy the occurrence of hematuria, hematospermia, rectal bleeding, fever, UTI, urinary retention, and perineal hematoma was recorded. UTI was defined as a positive urine culture with symptoms. Urine cultures were only performed in case a clinical suspicion on UTI arose. Using Clavien-Dindo classification the occurrence of AE's were graded (**table 1**).[13,14] Furthermore, subjects were requested to repeat IPSS and IIEF-5 questionnaires (**figure 1**).

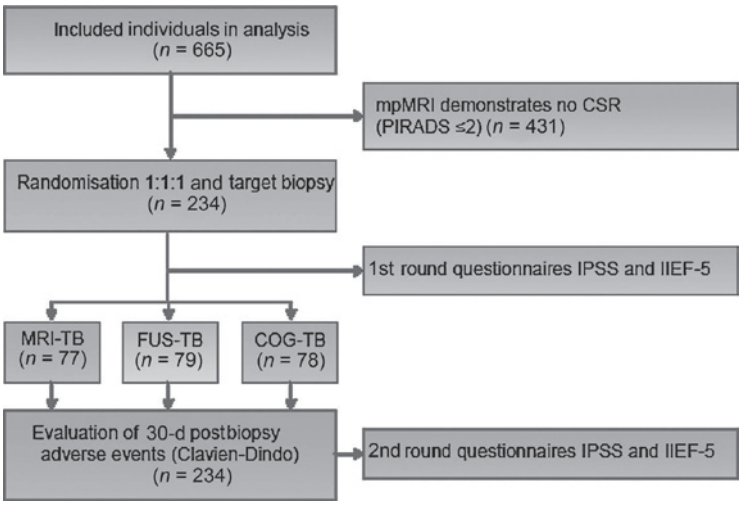

FIGURE 1. Flowchart of the study. CSR = cancer suspicious regions; IPSS = International Prostate Symptom Score; IIEF-5 = International Index of Erectile Function; MRI-TB = in-bore MRI targeted biopsy; FUS-TB = MRI-TRUS fusion targeted biopsy; COG-TB = cognitive registration TRUS targeted biopsy; TRUS = transrectal ultrasound.

TABLE 1. Clavien-Dindo classification of Surgical Complications

Grade 1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy.
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
Grade 3	Requiring surgical, endoscopic or radiological intervention
• **3a**	Intervention under local or spinal anaesthesia
• **3b**	Intervention under general anaesthesia
Grade 4	Life-threatening complication requiring medium/intensive care unit management
• **4a**	Single organ dysfunction
• **4b**	Multi-organ dysfunction
Grade 5	Death of a patient

Statistical analysis

All analyses were conducted with SPSS, 5% significance levels were adopted in all tests. Occurrences of AE's and Clavien-Dindo grade were compared among groups using Pearson

Chi square test. The effect of number of cores taken on occurrence of AE's was tested using a univariate logistic regression model. Exploratory analysis was performed correcting for biopsy approach (transrectal vs. transperineal) and usage of anticoagulants.

To evaluate the impact of biopsy on LUTS and ED we analysed respondents to both baseline and 30 days IPSS and IIEF-5 questionnaires. Overall effect was evaluated by subtracting the overall IPSS and IIEF-5 scores at 30 days measurement from the baseline measurement. Using one-way ANOVA test the overall effect of TB on ED and LUTS were compared among groups. Subsequently the delta per item on each questionnaire was compared among groups.

RESULTS

Population and biopsy outcomes

Among 234 men mean PSA was 11.2 ng/ml (SD 8.5), mean age was 65.7 (SD 6.4) and median prior biopsy sessions was 1 (IQR 1-2). Baseline characteristics were similar among groups (**table 2**). Median number of TB cores taken during MRI-TB was 2 (IQR 2-3), for FUS-TB 4 (IQR 3-5) and for COG-TB 3 (IQR 3-4) ($p<0.05$). Median number of concomitant SB cores taken during FUS-TB was 10 (IQR 8-12) and for COG-TB 10 (IQR 8-12) ($p=0.55$). Accordingly, the total (TB and SB) median number of cores taken during MRI-TB was 2 (IQR 2-3), for FUS-TB 14 (IQR 13-16), and for COG-TB 13 (IQR 12-15) ($p<0.001$) (**table 3**).

Adverse events

Overall 30.5% (71) had no AE's, 63.5% (148) had grade 1 AE's, and 6.0% (14) had grade 2 AE's (**table 4**). No grade 3, 4 or 5 AE's occurred. Among the 125 subjects experiencing hematuria, 3 (1.3%) required hospitalisation for catheterisation. Among the 8 subjects with a UTI, 4 (1.7%) required hospitalisation for intravenous antibiotics.

There were significant differences in occurrence of AE's (Clavien-Dindo grade 1 and 2) among groups; 52.6% in MRI-TB, 70.9% in FUS-TB and 84.7% in COG-TB ($p<0.001$, **table 4**). MRI-TB vs. FUS-TB OR 2.19 (95%CI 1.14-4.29, $p<0.05$), MRI-TB vs. COG-TB OR 4.95 (95%CI 2.36-10.96, $p<0.001$), and FUS-TB vs. COG-TB OR 2.27 (95%CI 1.04-5.00, $p<0.05$). There were significant differences in occurrence of hematuria (MRI-TB 35.5% vs. FUS-TB 50.6% vs. COG-TB 74.4%, $p<0.001$) and hematospermia (MRI-TB 26.3% vs. FUS-TB 35.4% vs. COG-TB 50.0%, $p<0.05$) among the groups. There were no significant differences among groups regarding rectal bleeding ($p=0.59$), UTI's ($p=0.21$), fever ($p=0.46$), urinary retention ($p=0.15$) or hematoma ($p=0.29$) (**table 4**).

TABLE 2. Baseline characteristics and mpMRI outcomes of three groups of TB

	Transrectal MRI-TB (n=77)	**Transperineal FUS-TB (n=79)**	**Transrectal COG-TB (n=78)**
Baseline data			
Age, mean (SD)	66.0 (SD 5.9)	64.6 (SD 6.9)	66.5 (SD 6.3)
PSA in ng/ml, mean (SD)	11.0 (SD 9.4)	11.6 (SD 9.0)	11.0 (SD 7.1)
Volume on TRUS in ml, mean (SD)	48.3 (SD 20.2)	45.4 (SD 14.4)	48.5 (SD 18.1)
Clinical stage (DRE), No. (%):			
• cT1c	62 (80.5%)	62 (78.5%)	64 (82.1%)
• cT2a/b	12 (15.6%)	16 (20.3%)	12 (15.4%)
• cT2c	1 (1.3%)	-	2 (2.6%)
• cT3a	2 (2.6%)	1 (1.3%)	-
Number of prior negative biopsies, median (IQR)	1 (IQR 1-2)	1 (IQR 1-1)	1 (IQR 1-2)
Months between mpMRI and previous biopsy, median (IQR)	9 (IQR 4-25)	8 (IQR 3-23)	7 (IQR 4-23)
Usage of anticoagulant therapy			
• Antiplatelet	14.3% (11)	20.3% (16)	24.4% (19)
• Coumarines	1.3% (1)	1.3% (1)	3.8% (3)
• DOAC	-	-	1.3% (1)
Usage of urological medication			
• α1- inhibitors	22.1% (17)	22.8% (18)	19.2% (15)
• 5α-reductase inhibitors	1.3% (1)	1.3% (1)	-
• M3-acetylcholine inhibitors	-	-	-
• β3-adrenergic agonist	-	-	-
• α1- inhibitors + 5α-reductase inhibitors	-	1.3% (1)	2.6% (2)
• α1- inhibitors + M3-acetylcholine inhibitors	1.3% (1)	1.3% (1)	1.3% (1)
MRI data			
PIRADS score, No. (%):			
• PIRADS 3	20 (26.0%)	23 (29.1%)	21 (26.9%)
• PIRADS 4	35 (45.5%)	34 (43.0%)	32 (41.0%)
• PIRADS 5	22 (28.6%)	22 (27.8%)	25 (32.1%)
CSR size in mm's, mean (SD)	13.6 (SD 7.1)	13.9 (SD 7.6)	12.9 (SD 6.1)
Number of CSR, mean (SD)	1.1 (SD 0.4)	1.1 (SD 0.3)	1.1 (SD 0.3)

MRI-TB = in-bore MRI targeted biopsy; FUS-TB = MRI-TRUS fusion targeted biopsy; COG-TB = cognitive registration TRUS targeted biopsy; TRUS = transrectal ultrasound; SD = standard deviation; DRE = digital rectal examination; IQR = interquartile range; DOAC = direct oral anticoagulants; PIRADS = Prostate Imaging Reporting and Data System; CSR = cancer suspicious regions.

TABLE 3. Biopsy outcome of three groups of TB

	Transrectal MRI-TB (n=77)	Transperineal FUS-TB (n=79)	Transrectal COG-TB (n=78)	
Procedural data				
Biopsy cores				
• Median TB cores, No. (IQR)	2 (IQR 2-3)	4 (IQR 3-5)	3 (IQR 3-4)	p<0.05
• Median SB cores, No. (IQR)	-	10 (IQR 8-12)	10 (IQR 8-12)	p=0.55
• Median total cores, No. (IQR)	2 (IQR 2-3)	14 (IQR 13-16)	13 (IQR 12-15)	p<0.001

MRI-TB = in-bore MRI targeted biopsy; FUS-TB = MRI-TRUS fusion targeted biopsy; COG-TB = cognitive registration TRUS targeted biopsy; TRUS = transrectal ultrasound; TB = targeted biopsy; SB = systematic biopsy; IQR = interquartile range.

TABLE 4. Adverse events of three groups of TB

	Overall (n=234)	Transrectal MRI-TB (n=77)	Transperineal FUS-TB (n=79)	Transrectal COG-TB (n=78)	
Clavien-Dindo grade					p<0.001
• No adverse events	30.3% (71)	47.4% (36)	29.1% (23)	15.4% (12)	
• Grade 1	63.2% (148)	50.0% (38)	65.8% (52)	74.4% (58)	
• Grade 2	6.0% (14)	2.6% (2)	5.1% (4)	10.3% (8)	
• Grade 3, 4, 5	-	-	-	-	
Hematuria	53.4% (125)	35.5% (27)	50.6% (40)	74.4% (58)	p<0.001
Hematospermia	37.2% (87)	26.3% (20)	35.4% (28)	50.0% (39)	p<0.01
Rectal bleeding	3.4% (8)	2.6% (2)	2.5% (2)	5.1% (4)	p=0.59
UTI	3.4% (8)	2.6% (2)	1.3% (1)	6.4% (5)	p=0.21
Fever	3% (7)	1.3% (1)	2.5% (2)	5.1% (4)	p=0.46
Urinary retention	3% (7)	-	3.8% (3)	5.1% (4)	p=0.15
Hematoma	1.3% (3)	-	3.8% (3)	-	p=0.29
Other					p=0.56
• Lower back pain	0.9% (2)	1.3% (1)	1.3% (1)	-	
• Atrial fibrillation	0.4% (1)	-	1.3% (1)	-	

MRI-TB = in-bore MRI targeted biopsy; FUS-TB = MRI-TRUS fusion targeted biopsy; COG-TB = cognitive registration TRUS targeted biopsy; TRUS = transrectal ultrasound; UTI = urinary tract infection.

In a univariable model the number of cores taken was significantly associated with the occurrence of any AE (OR 1.11 per additional core taken (95%CI 1.06-1.17, p<0.001)). Correcting for the number of cores taken, the advantage of MRI-TB compared to FUS-TB became statistically non-significant (OR 2.39 (95%CI 0.40-14.1, p=0.34)). When correcting for the number of cores taken the advantage of MRI-TB, compared to COG-TB, disappeared (OR 0.94 (95%CI 0.17-5.13, p=0.94)). FUS-TB remained advantageous compared to COG-TB when correcting for the number of biopsy cores taken (OR 2.56 (95%CI 1.14-5.56, p<0.05)).

In a univariable model anticoagulant usage wasn't associated with an increased risk of bleeding complications (hematuria, hematospermia, rectal bleeding and hematoma) (OR 1.24 (95%CI 0.66-2.35, p=0.51).

In a multivariable model (correcting for number of cores taken) transrectal biopsy (MRI-TB + COG-TB) demonstrated an increased risk for the occurrence of any AE compared to transperineal biopsy (FUS-TB) (OR 2.54 (95%CI 1.16-5.77, p<0.05)). Transrectal biopsy was associated with a non-significant increased risk of UTI's (OR 3.69 (95%CI 0.46-168.4, p=0.28).

Self-reported LUTS and ED

Response rate for both questionnaire rounds was 76.5% (n=179) for IPSS and 73.5% (n=172) for IIEF-5. Response rate to both questionnaire rounds was similar between groups for both IPSS (p=0.47) and IIEF-5 (p=0.72) (**table 5**).

TABLE 5. Self-reported lower urinary tract symptoms (IPSS) and erectile dysfunction (IIEF-5) outcomes at baseline and at 30-days post-biopsy of three groups of TB

	Transrectal MRI-TB (n=77)	**Transperineal FUS-TB (n=79)**	**Transrectal COG-TB (n=78)**	
IPSS				
Response rate IPSS questionnaires at baseline and 30 days	80.5% (62/77)	72.2% (57/79)	76.9% (60/78)	p=0.47
Overall (Q1-Q7) IPSS score at baseline, mean (SD)	9.64 (7.17)	10.6 (7.04)	10.6 (6.66)	p=0.61
Overall (Q1-Q7) IPSS score at 30 days post biopsy, mean (SD)	9.62 (8.13)	11.2 (6.71)	11.1 (7.42)	p=0.42
Overall (Q1-Q7) Δ in IPSS score between baseline and 30 days, mean (SD)	0.29 (5.06)	1.25 (5.23)	0.25 (4.92)	p=0.49
IIEF-5				
Response rate IIEF-5 questionnaires at baseline and 30 days	76.6% (59/77)	70.9% (56/79)	73.1% (57/78)	p=0.72
Overall (Q1-Q5) IIEF-5 score at baseline, mean (SD)	13.2 (9.02)	15.0 (8.38)	14.8 (8.40)	p=0.40
Overall (Q1-Q5) IIEF-5 score at 30 days post biopsy, mean (SD)	13.6 (8.93)	14.3 (8.47)	14.1 (8.51)	p=0.92
Overall (Q1-Q5) Δ in IIEF-5 score between baseline and 30 days, mean (SD)	0.9 (3.21)	-0.68 (4.23)	-0.95 (4.84)	p<0.05

MRI-TB = in-bore MRI targeted biopsy; FUS-TB = MRI-TRUS fusion targeted biopsy; COG-TB = cognitive registration TRUS targeted biopsy; TRUS = transrectal ultrasound; IPSS = International Prostate Symptom Score; IIEF-5 = International Index of Erectile Function; SD = standard deviation; Q = question.

Prostate biopsy did not significantly impact self-reported LUTS; baseline IPSS score 10.3 vs. 30 day post-biopsy IPSS score 10.6 (p=0.13). Baseline and 30 days post-biopsy IPSS scores were similar among groups of TB (p=0.61 and p=0.42 respectively). Accordingly, the delta of overall IPSS scores between baseline and 30 days post-biopsy were similar among groups (p=0.49) (**table 5**). Finally, no significant differences in delta per item of the IPSS questionnaire were found among groups (**table 1, supplementary data**).

Prostate biopsy did not significantly impact self-reported erectile function; baseline IIEF-5 score 14.4 vs. 30 days post-biopsy IIEF-5 score 14.0 (p=0.48). Baseline and 30 days post-biopsy IIEF-5 measurement were similar among groups (p=0.40 and p=0.92 respectively). We found a significant difference in the delta of overall IIEF-5scores between baseline and 30 days post-biopsy among groups; Δ 0.9 in MRI-TB, Δ -0.68 in FUS-TB, and Δ -0.95 in COG-TB (p<0.05) (**table 5**). There was a significant difference in the delta between baseline and 30 days post-biopsy for item 2 of the IIEF-5 (relating to erections being hard enough for penetration) among groups; Δ 0.32 in MRI-TB, Δ -0.16 in FUS-TB, and Δ -0.09 in COG-TB (p<0.05) (**table 1, supplementary data**). For the other 4 IIEF-5 questionnaire items no significant differences among groups occurred**.**

DISCUSSION

Adverse events

We found significant differences in occurrence of Clavien-Dindo grade 1 and 2 AE's among 3 groups; 52.6% in MRI-TB, 70.9% in FUS-TB and 84.7% in COG-TB (p<0.001).

Overall biopsy has a 69.2% rate of grade 1 and 2 complications, mainly consisting of hematuria (53.4%) and hematospermia (37.2%). The reported AE incidences are comparable with those reported in a meta-analysis on complications following prostate biopsy: hematuria 10-84%, hematospermia 1.1-93%, rectal bleeding 1.3-45%, UTI requiring hospitalization 0-6.3% and urinary retention 0.2-1.7%.[15]

The number of UTI's requiring hospitalisation in our cohort was 1.7%, which is relatively low. In a large multicentre study Wagenlehner demonstrated a hospitalization rate of 3.1% for febrile UTI following prostate biopsy.[16] Possibly this is due to low microbial fluocinolone resistance patterns in the Netherlands.[17]

The number of biopsy cores taken was significantly associated with the occurrence of AE's (OR 1.11 (95%CI 1.06-1.17, p<0.001)). Ghani et al reviewed the impact of 6, 8 and 12-core SB regimens on bleeding complications. The authors concluded that taking more than 6 cores

was associated with an increased risk of rectal bleeding, but the occurrence of hematuria and hematospermia were comparable between regimens.[18] Due to the introduction of mpMRI and TB, the number of cores can be reduced to 2-4 cores. The recently published PRECISION trial found significantly less AE's using 4 core TB compared to 12 core TRUS-SB. This was likely due to a lower percentage of men undergoing biopsy in the TB group (biopsy was omitted in case of negative mpMRI) and fewer biopsy cores obtained during biopsy (no SB was performed in the TB group). Surprisingly they found comparable occurrences of serious AE's between TB (1.6%) and TRUS-SB (2%).[7] In our study no serious AE's occurred, and the omission of SB in MRI-TB is reflected by significant reductions in hematuria ($p<0.001$) and hematospermia ($p<0.01$). Similarly, Eineluoto et al found that patients undergoing 3 core FUS-TB experienced less pain (20% vs. 34%) and hematuria (44% vs. 69%) compared to 12 core SB. The authors also concluded that patients experiencing less pain and discomfort would be more willing to undergo repeat biopsy.[19] When correcting for number of cores taken, we found that COG-TB significantly increased the risk of any AE compared with FUS-TB (OR 2.56 (95% CI 1.14-5.56, $p<0.05$)). This possibly relates to the increased risk of any AE associated with transrectal (MRI-TB + COG-TB) biopsy route within our cohort (OR 2.54 (95%CI 1.16-5.77, $p<0.05$)). However, the impact of transperineal vs. transrectal route on AE's remains controversial.[20] Two meta-analyses couldn't identify significant differences between transrectal and transperineal biopsy regarding AE's.[15,21] In this series there was non-significant advantage of transperineal biopsy compared to transrectal biopsy regarding UTI's, although the number of UTI's was limited and there was an increased incidence in transrectal biopsy.

In a previous study on FUTURE trial data, Exterkate at al demonstrated that the additional value of repeated SB was limited, and only 1.3% of csPCa would have been missed when SB had been omitted.[22] Simultaneously, this current study demonstrates that SB significantly increases the risk of AE's compared to TB alone. These two findings underline that SB should be omitted in patients with prior negative biopsies and CSR on mpMRI undergoing subsequent TB, as is recommended by the recently updated EAU guidelines.[1]

Self-reported LUTS and ED

Biopsy did not significantly impacted self-reported LUTS at 30-days post-biopsy for the entire cohort (Δ IPSS 0.3, $p=0.13$), nor for each technique of TB (Δ IPSS ranging 0.25-1.25, $p=0.49$). This is comparable with the literature, summarized in the review by Glaser et al. The authors state that biopsy may cause a transient increase in IPSS, unlikely to last more than 1–3 months.[23] Similarly Klein et al found a non-significant increase in IPSS following 10-core prostate biopsy at 1, 4 and 10 weeks post-biopsy.[24]

For the entire cohort, biopsy did not significantly impact self-reported ED at 30-days post-biopsy (Δ IIEF-5 -0.4, p=0.48). Comparably Chrisofos et al found no significant differences in IIEF-5 score between baseline, 1 and 3 months post-biopsy following TRUS-SB.[25] In their review Loeb et al conclude that if biopsy impacts ED, its effect is minimal and transient.[15] Surprisingly we found a significant difference ($p<0.05$) of biopsy on ED between groups; MRI-TB positively influenced ED (Δ IIEF-5 +0.9) compared with the negative impact of FUS-TB (Δ IIEF-5 -0.68) and COG-TB (Δ IIEF-5 -0.95). Possibly this can be explained by the non-significantly (p=0.40) decreased baseline IIEF-5 in the MRI-TB group (IIEF-5 13.2) compared with FUS-TB (IIEF-5 15.0) and COG-TB (IIEF-5 14.8). Furthermore, the clinical relevance is debatable.

Limitations

The main limitation of this study is that in both FUS-TB and COG-TB additional SB were taken during the TB procedure, whereas no SB cores were taken in MRI-TB. This makes comparison difficult since it cannot be deduced whether TB cores or SB cores caused AE's. Especially considering the association between the number cores taken and the occurrence of AE's.

Furthermore, all three techniques were performed using various methods of anaesthesia. Consequently, pain experience could not meaningfully be compared between groups. Also, 2 measurements were used for the evaluation of self-reported LUTS and ED; at baseline and at 30-days post-biopsy. Though no differences in IPSS and IIEF-5 between those intervals could be demonstrated, it cannot be ruled out that differences occurred within this interval (i.e. 1 week post-biopsy). Although potential differences seem to be of no clinical importance since none persist at 30-days post-biopsy.

Finally, the FUTURE trial was powered to compare detection rates of PCa among three techniques of TB, and not to detect differences in AE's. Therefore potential significant differences in occurrence of AE's between the three techniques cannot be ruled out. This is especially true for UTI's for which we found a non-significant advantage of transperineal biopsy compared to transrectal biopsy.

CONCLUSION

There was a significant difference in Clavien-Dindo grade 1 and 2 AE's among 3 groups; 53% in MRI-TB, 71% in FUS-TB and 85% in COG-TB. AE's consisted mainly of self-limiting hematuria and hematospermia. There was an association between the number of biopsy cores and the occurrence of AE's. The low occurrence of AE's in the MRI-TB group is likely

caused by the omission of additional SB in this group. Decreased AE rates could be an argument to omit additional SB when performing TB procedures in repeat biopsy setting. In our cohort transrectal (MRI-TB + COG-TB) biopsy demonstrated an increased risk for the occurrence of any AE compared to transperineal (FUS-TB) biopsy, though this advantage could not be demonstrated for UTI's. Overall prostate biopsy did not significantly impact self-reported LUTS and ED at 30 days post-biopsy.

Take home message

There is a significant difference in minor AE's among 3 techniques of TB. Increasing number of biopsy cores, increases the risk of AE's. Low occurrence of AE's in MRI-TB is likely caused by the omission of additional SB.

Funding/Support and role of the sponsor

This investigation was sponsored by the St. Antonius Hospital Research and Innovation Funds, Foundation Urology 1973, and Astellas Pharma.

Acknowledgements

We would like to thank the urologists in the reference hospitals for presenting eligible patients for recruitment in our recruitment centres: Beatrix Rivas Hospital Gorinchem, Bernhoven Hospital Uden, Canisius Wilhelmina Hospital Nijmegen, Diakonessenhuis Hospital Utrecht, Gelderse Vallei Hospital Ede, Gelre Hospital Apeldoorn/Zutphen, Rivierenland Hospital Tiel, Slingeland Hospital Doetinchem, St. Antonius Hospital Nieuwegein/Utrecht, St. Jansdal Hospital Harderwijk, Streekziekenhuis Koningin Beatrix Winterswijk, and Zuwe Hofpoort Hospital Woerden. Furthermore, we would like to thank all the men recruited in the trial.

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APPENDICES

TABLE 1 SUPPLEMENTARY DATA. Delta of self-reported lower urinary tract symptoms (IPSS) and erectile dysfunction (IIEF-5) between baseline and at 30-days post-biopsy per item on questionnaire of three groups of TB

	Transrectal MRI-TB (n=77)	**Transperineal FUS-TB (n=79)**	**Transrectal COG-TB (n=78)**	
IPSS				
Q1 Δ in IPSS score between baseline and 30 days, mean (SD)	0.16 (1.04)	0.26 (1.09)	0.30 (1.21)	p=0.79
Q2 Δ in IPSS score between baseline and 30 days, mean (SD)	-0.10 (1.26)	0.28 (1.13)	-0.03 (1.35)	p=0.22
Q3 Δ in IPSS score between baseline and 30 days, mean (SD)	0.03 (1.25)	0.23 (1.48)	-0.18 (1.24)	p=0.25
Q4 Δ in IPSS score between baseline and 30 days, mean (SD)	0.28 (1.21)	0.12 (1.44)	-0.07 (1.57)	p=0.41
Q5 Δ in IPSS score between baseline and 30 days, mean (SD)	-0.11 (1.27)	0.23 (1.76)	0.32 (1.36)	p=0.24
Q6 Δ in IPSS score between baseline and 30 days, mean (SD)	0.20 (1.11)	0.05 (1.09)	0.12 (0.94)	p=0.76
Q7 Δ in IPSS score between baseline and 30 days, mean (SD)	-0.16 (1.32)	0.05 (1.25)	-0.20 (1.48)	p=0.56
Q8 Δ in IPSS score between baseline and 30 days, mean (SD)	0.00 (0.83)	0.21 (1.08)	0.00 (0.85)	p=0.36
IIEF-5				
Q1 Δ IIEF-5 between baseline and 30 days, mean (SD)	0.20 (0.71)	0.05 (0.64)	0.00 (0.68)	p=0.25
Q2 Δ IIEF-5 between baseline and 30 days, mean (SD)	0.32 (0.86)	-0.16 (0.93)	-0.09 (1.12)	p<0.05
Q3 Δ IIEF-5 between baseline and 30 days, mean (SD)	0.10 (0.99)	-0.07 (1.32)	-0.28 (1.46)	p=0.27
Q4 Δ IIEF-5 between baseline and 30 days, mean (SD)	0.19 (0.94)	-0.21 (1.44)	-0.21 (1.50)	p=0.17
Q5 Δ IIEF-5 between baseline and 30 days, mean (SD)	0.10 (0.99)	-0.29 (1.41)	-0.37 (1.43)	p=0.11

MRI-TB = in-bore MRI targeted biopsy; FUS-TB = MRI-TRUS fusion targeted biopsy; COG-TB = cognitive registration TRUS targeted biopsy; TRUS = transrectal ultrasound; IPSS = International Prostate Symptom Score; IIEF-5 = International Index of Erectile Function; SD = standard deviation; Q = question.

8

Chapter 8

General discussion of this thesis

Prostate cancer (PCa) is the second most common malignancy in men worldwide, with increasing reported incidence due to aging of the general public and PSA testing.[1] The ideal diagnostic tool would have a high detection rate of clinically significant (cs)PCa while limiting the detection rate of insignificant (i)PCa. As described in the introductory chapter of this thesis, the long-standing gold standard for PCa diagnosis, transrectal ultrasound (TRUS) guided systematic biopsy (SB), often misses csPCa and has a high rate of overdiagnosis of iPCa.[2-6] Consequently, much research effort has gone into developing additional diagnostic tools to increase sensitivity and specificity of the diagnostic pathway for csPCa.

A game changer in PCa diagnosis has been the introduction of multiparametric (mp)MRI and subsequent target biopsy (TB). mpMRI alone is not reliable enough to predict the presence of (cs)PCa; not all lesions identified by mpMRI turn out to be cancerous on biopsy, and vice versa some csPCa is missed by mpMRI. Therefore, TB of mpMRI-identified lesions should always be performed to verify the nature of these lesions. Since the conception of mpMRI and subsequent TB, clinicians have struggled with how best to perform TB.

Currently three techniques of mpMRI based TB exist; in-bore MRI TB (MRI-TB); MRI-TRUS fusion TB (FUS-TB); and cognitive TRUS TB (COG-TB). As previously stated, the main objective of this thesis is to gain insight into which method of biopsy should be preferred in men with a persistent clinical suspicion on PCa and cancer suspicious regions (CSR) on mpMRI, following negative TRUS-SB.

In this chapter, the main findings of this thesis are discussed, along with their strengths and limitations. Furthermore, recent research developments are summarized along with a discussion of how these impact on the findings of this thesis. Finally, future perspectives in the field of prostate cancer diagnosis and management are discussed.

mpMRI BASED TARGET BIOPSY

Systematic review and meta-analysis of the literature

At the time commencing work on this thesis in 2014, the literature on mpMRI based TB of the prostate consisted mainly of cohort studies describing the yield of (cs)PCa of one technique of TB (either MRI-TB, FUS-TB or COG-TB), occasionally comparing it with the yield of TRUS-SB.

In the systematic review and meta-analysis of the literature presented in chapter 2, it was concluded that the pooled yield of CSR on mpMRI in patients at risk of PCa was 73% (2225/3053), but 79% (567/716) in patients with prior negative biopsies and a persistent

suspicion of PCa. Furthermore, it was demonstrated that in men at risk for PCa, mpMRI based TB has a higher sensitivity for csPCa (relative sensitivity of 1.16 (95% CI: 1.02–1.32) and a lower sensitivity for iPCa (relative sensitivity of 0.47 (95% CI: 0.35–0.63) than TRUS-SB. Regarding csPCa detection rates, there was no significant advantage of any one technique of TB (MRI-TB vs. FUS-TB (p=0.60), MRI-TB vs. COG-TB (p=0.42), FUS-TB vs. COG-TB (p=0.62)).

As described in chapter 2, the comparison of diagnostic efficacy of the three techniques of TB based on the available literature is complex due to several factors. Primarily, the number of studies directly comparing two techniques of mpMRI based TB was limited to only four studies.[7-10] Furthermore, there is significant heterogeneity in the literature in terms of the population investigated, the quality of MRI acquisition, the method of image evaluation, the applied threshold for TB, and the applied definition of csPCa.

In order to minimize the effect of these described differences, stringent inclusion criteria were applied for the meta-analysis. Inclusion criteria mandated that studies report on (cs)PCa detection rates among patients at risk of PCa (i.e. excluding patients with prior diagnosed PCa). In addition, mpMRI acquisition should be in accordance to the latest imaging guidelines.[11-13] Finally, only studies were included which presented paired data of any mpMRI based TB and TRUS-SB results separately, within the same population. This made it possible to carry out a meaningful comparison of the three TB techniques even though the number of head-to-head comparisons was limited, by using a common reference test (the results of TRUS-SB).

Nonetheless, for a truly meaningful comparison of the three mpMRI based TB techniques essential components are targeted lesion characteristics, such as PIRADS assessment, lesion size and lesion localisation. Since lesion specific components are missing in the majority of the studies included in the meta-analysis presented in chapter 2, the results are indicative at best.

FUTURE trial – comparison of three mpMRI based TB techniques

A sounder method to compare techniques is through making a head-to-head comparison within one specific population. To that end, the FUTURE trial protocol was drafted and published in 2015 (described in chapter 4). In the FUTURE trial men were enrolled with prior negative SB and persistent suspicion of PCa. At the time of protocol drafting, clinical guidelines advised performing mpMRI diagnostics in that setting; pre-biopsy mpMRI was still experimental at that time.[14] Participants primarily underwent 3-T mpMRI diagnostics according to imaging guidelines and images were centrally evaluated using PIRADSv2.[12,13] If imaging demonstrated PIRADS≥3 lesions, participants were randomised 1:1:1 to undergo

TB using FUS-TB, COG-TB, or MRI-TB. The primary outcome was the overall detection rate of PCa for each TB technique and the detection rate of csPCa comprised an important secondary outcome. Methodology is described in detail in chapter 4.

The main finding of the FUTURE trial is that there are no statistically significant differences in the detection rates of overall PCa between the three techniques (FUS-TB 49.4%, COG-TB 43.6%, and MRI-TB 54.5%, p=0.4). Similarly, there were no significant differences in the detection rate of csPCa among the techniques (FUS-TB 34.2%, COG-TB 33.3%, and MRI-TB 32.5%, p>0.9). Although the differences in detection rates of (cs)PCa are statistically non-significant, the range for overall PCa detection is 10.9% and for csPCa detection 1.7%. From these figures, it can be deduced that MRI-TB has the highest detection rate of iPCa within this cohort as compared to FUS-TB and COG-TB. This seems to be in contrast to current dogma that MRI-TB detects significantly more csPCa and significantly less iPCa[5,6,15], although this prevailing notion is based on the comparison of MRI-TB with TRUS-SB, and not with alternate techniques of mpMRI based TB. Alternatively, this non-significant increased detection rate of PCa and similar detection rate of csPCa in MRI-TB might be an expression of increased accuracy of MRI-TB. PCa lesions are heterogeneous regarding differentiation grade, meaning that tumorous lesions often contain high Gleason grades along with lower Gleason grades within the same foci. Potentially the described findings indicate that MRI-TB more accurately targets the periphery of a CSR containing lower Gleason grades, instead of hitting the 'hot spot' of a CSR containing higher disease grades, as compared to FUS-TB and COG-TB which potentially miss the smaller lesion altogether. Finally, the demonstrated differences in detection of iPCa can be a result of variations in applied biopsy techniques, such as applied anaesthesia and applied route of biopsy (transrectal/transperineal) (see chapter 5).

The strength of the FUTURE trial lie in several factors. Primarily the comparison of mpMRI based TB techniques was performed in a homogenous population, by applying stringent inclusion criteria and by performing randomisation for technique allocation. Regardless of the randomised design of the FUTURE trial, a comparative analysis of baseline characteristics and mpMRI outcomes was performed among techniques of TB, which demonstrated that there were no statistically significant differences between groups, indicating that randomisation successfully eliminated confounding factors. The resulting homogeneous population makes the comparison of techniques within this population highly reliable, but potentially makes extrapolation of the main findings of the trial to other populations more difficult (such as in biopsy naïve patients or patients with histologically proven PCa enrolled in active surveillance programs).

Analysis of procedural outcomes revealed significant differences in the number of cores taken per technique: the median number of cores was four for FUS-TB (IQR 3–5), three for COG-TB (IQR 3–4), and two for MRI-TB (IQR 2–3; $p<0.05$). This resulted is significantly different core positivity rates among the groups (FUS-TB 31.3%, COG-TB 33.3%, and MRI-TB 47.7%, $p<0.05$). Potentially this is a confounding factor for (cs)PCa detection rates. In the research protocol described in chapter 4, it has been stipulated that at least two biopsy cores should be taken per CSR for each technique of TB, but no upper limit of allowed biopsy cores was defined.

mpMRI acquisition was performed using state of the art MRI-scanners and scanning protocols. Prior to enrolment in the study, uniformity of mpMRI acquisition was mandated in all three recruiting centres. Although, minor differences in mpMRI acquisition could not be eliminated because of usage of various MRI-scanners in the various recruiting centres (Magnetom Skyra® Siemens, Magnetom Trio® Siemens, Ingenia® Philips). Furthermore, a high standard of image evaluation was a prerequisite, which was ensured by performing central reading of all mpMRI imaging by an expert urogenital radiologist using PIRADSv2. These factors further contributed to homogeneity the imaging protocols and evaluation, but simultaneously potentially limited the applicability of the trial findings to general urological practice. Inter-observer variability is a known factor in both the evaluation of imaging and histology.[16,17] Unfortunately, the trial design did not incorporate double reading of mpMRI imaging and histopathology of the biopsy cores, primarily due to limitations in trial funding and available logistics.

Moreover, accuracy of mpMRI based TB is operator dependent. Accurate targeting of lesions increases if an operator has more experience in performing target biopsy procedures. The number of operators was quite large in the trial; ten operators performed MRI-TB, and five operators performed both FUS-TB and COG-TB. Differences in operators' experience can potentially confound to the differences in observed detection rates of (cs)PCa. However, the experience levels were more or less equal for all three techniques of TB, since all operators were expert-trained prior to commencement of the trial.

The prospective trial design allowed for collection of CSR specific data such as PIRADS assessment, dimensions of CSR, and location of CSR. The collection of this data enabled lesion specific sub-group analysis of outcomes among techniques (per PIRADS grade, in small CSR's (≤10 mm), anterior/posteriorly located CSR's, peripheral/transition zone CSR's, in small/large (<50 ml or ≥50 ml) prostate volumes). The sub-group analysis could not demonstrate statistically significant advantages of any technique of TB regarding the

detection rates of (cs)PCa. However, all sub-group analyses were limited by the fact that no powering calculation was performed, and group sample size for each analysis was relatively small.

Before trial commencement, it was hypothesised that MRI-TB might be advantageous in small lesions, since it was assumed that accuracy for mpMRI identified CSR's would be optimal due to direct real-time visualisation of the CSR by MRI. However, in 91 patients with small CSR's (≤10 mm), overall detection rate of PCa (FUS-TB 24.1%, COG-TB 19.4%, and MRI-TB 29.0%, p=0.7) and of csPCa (FUS-TB 10.3%, COG-TB 19.4%, and MRI-TB 16.1%, p=0.6) was similar among the groups. Unfortunately, the small number of patients limited this sub-analysis. Furthermore, the measurement of lesions was performed in three dimensions on mpMRI (axial, sagittal and coronal planes). The largest dimension was recorded for this sub-analysis. However, this does not necessarily indicate the most relevant dimension, since the perpendicular dimension (respectively of biopsy needle tract) is probably most important in determining the chance of accurate sampling.

Additionally, it was hypothesised that, due to the applied biopsy route, transperineal FUS-TB would more accurately sample anteriorly located lesions compared to transrectal COG-TB and MRI-TB. However, this potential advantage could not be demonstrated in the 90 patients with anteriorly located CSR's, neither for the overall detection of PCa (FUS-TB 62.2%, COG-TB 60.0%, and MRI-TB 64.3%, p>0.9), nor for the detection of csPCa (FUS-TB 48.6%, COG-TB 44.0%, and MRI-TB 35.7%, p=0.6).

Finally, the applied definition of csPCa (and as such of iPCa) in the FUTURE trial was solely based on Gleason sum score of ≥3+4 (ISUP grade ≥2), in accordance to the applied definition of csPCa in recent literature on TB.[9,18-20] The systematic review and meta-analysis of the literature presented in chapter 2, demonstrates heterogeneous usage of definitions for csPCa in the current literature on TB. Current clinical guidelines define risk groups for biochemical recurrence of localized prostate cancer based on PSA, Gleason sum score (and/or ISUP grade) and clinical stage.[21] Definition of csPCa have not yet been defined in the era of mpMRI based TB. For that reason, a more conservative, secondary definition of csPCa (derived from the Epstein criteria) was defined in the FUTURE trial based on Gleason sum score, tumour volume on biopsy (maximum cancer core length (MCCL)), PSA density and clinical staging. Using this alternate definition of csPCa there were also no significant differences in detection rates among groups (FUS-TB 43.0%, COG-TB 39.7%, and MRI-TB 46.8%, p=0.7).

Beside the minor limitations described above, a major limitation of the FUTURE trial is the unexpected low yield of PIRADS≥3 lesions on mpMRI. At the time of protocol formulation

and powering of the FUTURE trial, the yield of PIRADS≥3 lesions on mpMRI was based on a published systematic review and meta-analysis dating from 2013.[6] In a pooled analysis of men with an initial negative biopsy (i.e. a similar population as in the FUTURE trial), the authors found that 69% (328/479) had a suspicious MRI. Based on assumed detection rates of the various mpMRI based TB techniques derived from the literature, 152 patients with PIRADS≥3 lesions on mpMRI per group were required, resulting in 456 patients for all three groups combined. An additional 10 patients were included to correct for loss to follow-up, resulting in 466 required patients with PIRADS≥3 lesions on mpMRI. Based on a yield of 69% of suspicious lesions on mpMRI among men with an initial negative biopsy, 675 patients needed to be recruited. Among the 665 men included in the final analysis of the FUTURE trial, only 234 (35.2%) had PIRADS≥3 lesions on mpMRI. The reason for the low percentage of PIRADS≥3, may be the expert reading, as high level and high volume centres have a higher percentage of normal mpMRI.[18-20] This resulted in approximately half the necessary randomised patients per technique of TB (range 77-79 per group), and subsequently an under-powering for the primary endpoint of the trial. This is partially counterbalanced by higher PCa detection rates (44–55%) than the anticipated yields (25–40%). Consequently, a larger trial might have been able to demonstrate statistically significant differences in PCa detection rates amongst techniques TB (especially considering the broad 95% confidence intervals in these analyses, as reported in chapter 5). However, a post-hoc power analysis (based on the established yield of mpMRI for PIRADS≥3 lesions and yields of PCa of the three TB techniques) demonstrated that an overwhelmingly high number of 9.886 individuals would have had to undergo mpMRI using the current study design. This is clearly an unattainable figure for any RCT.

Retrospectively, a more relevant primary endpoint of the FUTURE trial would have been csPCa detection rates of the three TB techniques (despite being hampered by the absence of a widely accepted definition of csPCa). The detection rates of csPCa (based on Gleason sum score of ≥3+4 or ISUP grade ≥2) in the FUTURE trial ranged between 32.5%-34.2% and differences in csPCa detection rates ranged between 0.8-1.7%. Seeing this moderate detection rate difference of csPCa among TB techniques, a much larger sample size would possibly not have led to statistically significant differences among techniques. Therefore, even a much larger trial, may not have led to meaningfully different findings from the ones found with the current design.

To conclude, based on this RCT there are neither significant differences in the overall detection rate of PCa nor for csPCa among the three techniques of mpMRI based TB in patients with prior negative SB and persistent suspicion of PCa. Consequently, other factors (such as local experience, availability, and costs) should be evaluated when determining which technique to implement.

REPEATED SYSTEMATIC BIOPSY IN PATIENTS WITH mpMRI LESIONS AND NEGATIVE SYSTEMATIC BIOPSY

FUTURE trial – comparison of detection rates of (cs)PCa of TB and repeated SB

A secondary endpoint of the FUTURE trial is the comparison of outcomes of repeated TRUS-SB and TB within the FUTURE trial cohort. The primary question of this analysis is whether repeated SB should be included when performing TB. To that end, subjects with PIRADS≥3 lesions on mpMRI who were randomised to either COG-TB of FUS-TB, underwent repeated SB.

The main finding of this analysis was that TB detected significantly more PCa than SB (47% vs. 32%, p<0.001), and TB detected significantly more csPCa than SB (34% vs. 16%, p<0.001). By combining TB and SB, the detection rate of PCa was 53% and csPCa 35%, representing a detection rate difference of 6% and 1% respectively, compared to TB alone. Furthermore, TB detected less iPCa compared to SB (13% vs 16%, p=0.4) Finally, the Gleason score concordance between TB, SB and radical prostatectomy (RP) was evaluated, in a sub-group of 40 patients who underwent both TB, SB and RP. The Gleason score concordance between TB and RP was 45% (upgrading occurred in 18% and downgrading in 37%). The Gleason score concordance between SB and RP was 32% (upgrading occurred in 32% and downgrading in 37%).

The main strength of this secondary analysis lies in the fact that it was performed in a homogenous population using prospectively collected, high quality data. Nonetheless, several methodological limitations apply to this secondary analysis.

In the FUTURE trial TB was performed initially, followed by SB by the same operator. Potentially this could have led to sampling bias of SB, since the operator was not blinded for the mpMRI results. Whether introducing a second, blinded operator to perform SB completely eliminates this bias is questionable since one could potentially visualise the previous biopsy tract on TRUS due to minor haemorrhage occurring following biopsy. Consequently, one could aim SB cores onto previous TB biopsy tracts. Alternatively, one could perform SB prior to TB, instead of the other way around. When drafting the FUTURE trial protocol this was considered and dismissed, because SB induced haemorrhage could cause tissue deformation of the prostate, potentially compromising the accuracy of TB (being the primary endpoint of the trial). Instead, the impact of sampling bias was limited by performing SB using a standardised template based on prostate volume but irrespective of CSR location.

Moreover, the FUTURE trial was powered to detect PCa differences between three techniques of mpMRI based TB, and not to detect differences between TB and repeated SB. This is underlined by the broad 95% confidence intervals presented in the main findings of chapter 6.

The analysis on Gleason score concordance is hampered by the fact that Gleason score is evaluated differently between biopsy specimens and RP specimens. In biopsy specimens, the Gleason score consists of the most commonly found Gleason pattern and the highest found Gleason pattern. In RP specimens, the Gleason score consists of the most commonly found Gleason pattern and the second most commonly found Gleason pattern (incidentally combined with a tertiary component consisting of the highest found Gleason pattern).[21] An alternative method to compare concordance between biopsy and RP specimens is by comparing highest Gleason grade (HGG). HGG was used by Hambrock et al to compare concordance of MRI-TB, SB and RP. The authors found that MRI-TB has a higher HGG concordance with RP (88%) compared with concordance between SB and RP (55%).[22] However, the meaning of HGG is limited because HGG is not routinely used in clinical practice, where differentiation grade is always expressed in Gleason sum score or ISUP grade.

Finally, the previously mentioned limitation referring to the applicability of the outcomes for general urological clinicians and heterogeneous usage of definition of csPCa, also apply to this secondary analysis.

Based on the literature, dating from the time when repeated SB was common practise (i.e. without mpMRI and/or TB), it is known that the PCa yield drops for each repeated SB performed. PCa detection rates drop from 22% on primary biopsy, to 10% on first repeat SB, to 5% on second repeat SB, to 4% on third repeat SB.[23] Simultaneously the cancers detected during second and third repeated SB are lower in grade, stage and volume, than the cancers detected during primary and first repeated SB. Based on these findings, first repeated SB seems justified[23], although the introduction of mpMRI diagnostics and subsequent TB shed a different light on that. In the era of preselection with mpMRI diagnostics, a distinction can be made between patient with no CSR (PIRADS≤2) and with CSR (PIRADS≥3). Subsequent SB reveals csPCa in only 3-6% in biopsy naïve patients with PIRADS≤2, and between 42-52% in biopsy naïve patients with PIRADS≥3.[20,24] As described in chapter 5 and 6, the patients in the FUTURE trial have a median of one prior negative SB (IQR 1-2). Furthermore, repeated SB was only performed in patients with PIRADS≥3 who were randomised to either COG-TB or FUS-TB. Based on these facts the expected (cs)PCa detection rates of repeated SB should have been significant. Consequently, the established PCa detection rate of repeated SB of 32% from the FUTURE trial cohort is significantly higher than the reported detection rates

of 10% on first repeat SB by Djavan et al.[23] From these data, it can be concluded that mpMRI appears to be an adequate tool to select patients for repeat biopsy.[24,25] In repeat biopsy setting in patients with PIRADS≥3, TB significantly increases the csPCa detection rates as compared with SB, as described in chapter 6 and literature.[5,6]

The principle conclusion from the comparative analysis presented in chapter 6, is that the omission of SB in patients undergoing TB due to PIRADS≥3 lesions on mpMRI, would lead to missing only 1% of the csPCa as compared to TB alone. Secondly, adding SB to TB in repeat biopsy setting increases the detection rates of iPCa by 5% compared to TB alone. Thirdly, the Gleason score (or ISUP grade) in RP is more accurately predicted by TB than by SB. Based on these findings repeated SB should be omitted in patients in repeat biopsy setting and PIRADS≥3 lesions on mpMRI, when performing TB. These findings support the statements in the 2019 updated EAU guidelines on PCa, which state that in patients with prior negative biopsy, only TB should be performed in mpMRI positive patients (PIRADS≥3).[21]

FUTURE trial – comparison of adverse events

Another potential downside to the application of concomitant SB when performing TB in repeat biopsy setting, might be the increased risk of adverse events, as the number of biopsies taken is significantly higher due to the addition of SB. In another secondary endpoint of the FUTURE trial, presented in chapter 7, the adverse events (AE) among three TB techniques were compared and the effect of biopsy on urinary and erectile function was evaluated. Details of the research methodology are described in chapter 7.

The main finding of this analysis was that there were significant differences in occurrence of Clavien-Dindo grade 1 and 2 AE's among groups (MRI-TB 52.6%, FUS-TB 70.9%, and COG-TB 84.7%, $p<0.001$). No grade 3, 4 or 5 AE's occurred. There were significant differences in occurrence of self-limiting hematuria ($p<0.001$) and hematospermia ($p<0.05$) (being the two most commonly reported AE's) among the groups, with the lowest rates occurring in MRI-TB. There were no significant differences between groups with regard to the occurrence of urinary tract infections (UTI's) ($p=0.21$) or fever ($p=0.46$). There was a significant association between the number of biopsy cores taken and the occurrence of any AE (OR 1.11 per additional core taken (95%CI 1.06-1.17, $p<0.001$)). When correcting for the number of cores taken, the advantage of MRI-TB compared to FUS-TB and COG-TB became statistically non-significant ($p=0.34$ and $p=0.94$ respectively). Anticoagulant (principally platelet aggregation inhibitors) usage was not associated with an increased risk of bleeding complications (OR 1.24 (95%CI 0.66-2.35, $p=0.51$)) following biopsy. Transrectal biopsy (MRI-TB and COG-TB) was associated with an increased risk on the occurrence of any AE compared to transperineal biopsy (FUS-TB) (OR 2.54 (95%CI 1.16-5.77, $p<0.05$)), but

not associated with an increased risk of UTI's (OR 3.69 (95%CI 0.46-168.4, p=0.28)). Finally, prostate biopsy did not significantly affect self-reported LUTS (p=0.13) or self-reported erectile function (p=0.48) (based on serial IPSS and IIEF-5 questionnaires respectively).

Similar to the previous secondary endpoint analysis, the main strength of this secondary endpoint analysis is its high quality, prospectively collection, and randomisation of data from a homogenous population. Nevertheless, several remarks can be made on the applied methodology.

Primarily there is a significant variability in the applied biopsy methodology; the number of biopsy cores taken, the biopsy route, and the applied anaesthesia. This limits the validity of the comparison of AE outcomes. Comparing subjects who had a median of 2 needle insertions (MRI-TB, where no SB were taken) versus 13 or 14 core sampling (FUS-TB and COG-TB, where concomitant SB was applied), is likely to comprise a major cause of bias. By correcting for the number of biopsy cores taken, the effect of the limitation was reduced. From this multivariate model (correcting for number of cores) the statically significant advantage of MRI-TB compared to FUS-TB and COG-TB disappeared. This suggests that the found advantage of MRI-TB in the (uncorrected) univariate model was principally caused by the difference in number of biopsy cores taken. This seems intuitive since applying more biopsy cores, results in more tissue damage and thus more AE's.[19,26,27] Another conclusion drawn from this finding is that adding SB cores to a TB procedure, significantly increases the post-procedural AE's. This can be another argument to omit SB, when performing TB of mpMRI identified CSR's in repeat biopsy setting. This supports the recommendation of the 2019 updated EAU guidelines on PCa, which state that in patients with prior negative biopsy, only TB should be performed when mpMRI is positive (PIRADS≥3).[21]

The second main cause of variation is the applied biopsy route. In a multivariate model (correcting for the number of cores) transrectal biopsy demonstrated an increased risk of the occurrence of any AE compared to transperineal biopsy, but transrectal biopsy was not associated with an increased risk of UTI's. This seems counter-intiutive, since in transrectal biopsy the rectal wall is punctured, potentially inoculating the prostate with pathogens coming from the rectum. Whereas in transperineal biopsy, the skin of the perineum is disinfected, limiting the risk of introducing pathogens. Surprisingly, no statically significant difference was found in occurrence of UTI's between transrectal and transperineal biopsy (1.3% vs. 4.5%). Although, this finding is hampered by the overall low occurrence of UTI's in this cohort (3.4%), which is reflected by the very broad 95% confidence interval for this comparison, suggesting that the sample size was too small for this secondary analysis to lead to meaningful conclusions. As described earlier, the FUTURE trial was powered to detect PCa differences between three techniques of mpMRI based TB, and not to detect

differences in AE's between techniques. Therefore, potential significant differences in occurrence of AE's between the three techniques cannot be ruled out, which seems especially true for UTI's.

To summarize, several conclusions can be drawn from this analysis. TB procedures are relatively safe since no grade 3, 4 or 5 AE's occurred. There are significant differences in Clavien-Dindo grade 1 and 2 AE's between the three groups, predominantly consisting of self-limiting hematuria and hematospermia. An association was found between the number of biopsy cores and the occurrence of AE's. The low occurrence of AE's in the MRI-TB group is likely caused by the omission of additional SB in this group, which is an argument to omit SB, when performing TB in repeat biopsy setting. Finally, prostate biopsy did not significantly impact self-reported urinary and erectile function at 30 days post-biopsy.

RECENT DEVELOPMENTS

Recent evidence on mpMRI and TB in biopsy naïve men

At the time of designing the FUTURE trial protocol in 2014, the 2013 European Urology Guidelines on PCa advised to perform mpMRI if clinical suspicion of PCa persists despite a negative TRUS-SB.[14] mpMRI can be used to investigate the possibility of an anteriorly located PCa, followed by TRUS or MRI-guided biopsies of the CSR. The 2013 European Urology Guidelines on PCa did not recommended pre-biopsy mpMRI. Since then four key studies have been published comparing the yield of mpMRI (and subsequent TB) with the yield of TRUS-SB in primary biopsy setting.

In the PROMIS study, published by Ahmed in 2017, 576 biopsy naïve men with a suspicion of PCa, underwent mpMRI, TRUS-SB (10-12 cores) and subsequently template prostate mapping biopsy (TMP), which samples the entire prostate using a grid and biopsy cores every 5 mm. The primary outcome was the detection rate of csPCa (Gleason≥4+3 or a MCCL ≥6mm). The objective of the study was to evaluate whether mpMRI used as a triage test might allow men to avoid unnecessary TRUS-SB and improve diagnostic accuracy. Overall TMP detected PCa in 71% (408/576) and csPCa in 40% (230/576). Using the results of TMP as a reference test, the diagnostic results for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were compared for mpMRI and TRUS-SB. For csPCa mpMRI was more accurate than TRUS-SB in terms of both sensitivity (93% *vs* 48%; test ratio 0.52, p<0.0001) and NPV (89% *vs* 74%, test ratio 0.34, p<0.0001). However, TRUS-SB showed better specificity (41% *vs* 96%; test ratio 2.34, p<0.0001) and PPV (51% *vs* 90%;

test ratio 8.2, p<0.0001). Based on these figures the authors concluded that using mpMRI as a triage test in biopsy naïve men could identify a quarter of men who might safely avoid an unnecessary biopsy and might improve the detection of csPCa compared to TRUS-SB alone.[18]

In 2018, Kasivisvanathan et al published the results of the PRECISION trial. The PRECISION trial randomised 500 biopsy naïve men with a clinical suspicion of PCa to undergo either standard TRUS-SB, or mpMRI and (if mpMRI demonstrated a CSR (i.e. PIRADS≥3)) subsequent TB (without concomitant TRUS-SB) using either COG-TB or FUS-TB. Participants in the TB group without CSR (PIRADS≤2) did not undergo biopsy. The primary outcome was detection rate of csPCa (ISUP grade≥2 (Gleason≥3+4)) and the secondary outcome was detection rate of iPCa. In the TB group 175 (69%) of the 252 men had a PIRADS≥3 lesion and underwent TB. 77 (31%) men had PIRADS≤2 on mpMRI and biopsy was omitted. csPCa was detected in 38% (95/252) in the TB group, and in 26% (64/248) in the SB group (p=0.005). iPCa was detected in 9% (23/252) in the TB group, and in 22% (55/248) in the SB group (p<0.001). The authors concluded that in the MRI (and subsequent TB) group fewer men under-went biopsy, whilst detecting more csPCa and less iPCa than in the SB group. Consequently, mpMRI and subsequent TB is considered superior than SB.[19]

In the MRI-FIRST trial, published in 2018 by Rouvière et al, 251 biopsy naïve men with a clinical suspicion of PCa underwent mpMRI. Subsequently one operator (blinded for the mpMRI results) performed TRUS-SB, followed by a second (un-blinded) operator performing TB of any mpMRI identified CSR (i.e. Likert≥3) using either COG-TB or FUS-TB. Men without CSR on mpMRI (Likert≤2) underwent SB only. The primary outcome was detection rate of csPCa defined as ISUP grade≥2 (Gleason≥3+4). Secondary outcomes included detection rate of csPCa using alternative definitions of csPCa and detection rate of iPCa. mpMRI demonstrated CSR's in 215 men, who underwent TB and SB. Alternatively in 36 patients no lesions were found, and these men underwent only SB.

csPCa (ISUP≥2 (Gleason≥3+4)) was detected in 37% (94/251). Of these 94 cases, 13 (14%) were detected by SB only, 19 (20%) by TB only, and 62 (66%) by both techniques. Separately the detection rates of csPCa were not significantly different between TB (32%) and SB (30%) (p=0.38). The detection rate of iPCa was 6% (14/251) using TB, whilst SB detected 20% (49/251) (p<0.0001). Based on these finding the authors concluded that there was no significant difference in the detection rate of csPCa (ISUP≥2 (Gleason≥3+4)) between TB and SB. Although a combined approach yielded the highest detection rate of csPCa, and thus the addition of mpMRI improves detection of csPCa in biopsy naïve men.[28]

In the 4M study published in 2019 by van der Leest et al, 626 biopsy naïve men with a clinical suspicion of PCa underwent mpMRI. In 317 (51%) men with a CSR on mpMRI (PIRADS≥3) MRI-TB was performed. Subsequently all men underwent TRUS-SB by a second operator (blinded for the mpMRI results). Consequently, men without CSR on mpMRI (PIRADS≤2) underwent SB only. The primary outcome was detection rate of csPCa (ISUP grade≥2 (Gleason≥3+4)) and the secondary outcome was detection rate of iPCa. csPCa was detected in 25% (159/626) in the TB group, and in 23% (146/626) in the SB group (p=0.17). iPCa was detected in 14% (88/626) in the TB group, and in 25% (155/626) in the SB group (p<0.0001). By combining TB and SB csPCa was detected in 30% (190/626) and iPCa 23% (144/626). In men without a CSR on mpMRI (PIRADS≤2), SB detected iPCa in 20% (63/309) and csPCa in 3% (10/309). In men with a CSR on mpMRI (PIRADS≥3) a combined approach of TB and SB resulted in an increased detection rate of csPCa of 7% (21/317), compared to TB alone. Based on these results the authors concluded that in biopsy-naïve men, TB and SB have similar detection rates of csPCa. Simultaneously, TB detects significantly less iPCa compared to SB. Furthermore, by omitting immediate SB following a negative mpMRI, 49% of men did not need to undergo biopsy, at the cost of missing 4% of csPCa.[20]

Shifting role of mpMRI and TB in diagnostic pathway of PCa

Based on these studies the updated 2019 European Urology Guidelines on PCa, advises to perform mpMRI in biopsy naïve patients prior to biopsy. If imaging demonstrates PIRADS≥3 lesions, TB and TRUS-SB should be combined. If imaging demonstrates PIRADS≤2 and suspicion on PCa is low, SB should be omitted based on shared decision making with the patient.[21] This is a significant alteration compared to the 2013 European Urology Guidelines on PCa, where mpMRI diagnostics was reserved for men with a persistent clinical suspicion of PCa in spite of negative TRUS-SB.[14]

The implications of this change in the guidelines on this current thesis should be considered. Would the outcomes of the FUTURE trial, comparing techniques of mpMRI based TB among patients with a prior negative SB, have been different if it had been performed among biopsy naïve patients instead? Probably the shifting of setting between secondary (i.e. following negative SB) to primary biopsy procedure, would significantly alter the yield of mpMRI diagnostics itself (i.e. relatively more dorsally and less ventrally located lesions, an overall increased yield of PIRADS≥3 lesions, and increased size of lesions), since patient with large, dorsally located tumour foci, are likely to have been diagnosed with PCa using standard TRUS-SB. In contrast, TB procedures are directed towards mpMRI identified lesions. Once a lesion is identified on mpMRI, the yield of subsequent TB procedures is unlikely to be significantly altered by a shift of setting, since mpMRI is used as a triage test preceding TB. In other words, the outcomes of the FUTURE trial on the comparison of three

techniques of mpMRI based TB, are unlikely to have changed if it had been performed among biopsy naïve patients. It is unlikely that this setting change would benefit any particular technique more than another. Furthermore, although the aforementioned studies indicate an advantage of pre-biopsy mpMRI and subsequent TB, it remains unclear which sub-population benefits most of earlier mpMRI usage. Perhaps selective implementation of mpMRI, based on decision-making tools such as the ERSPC risk calculator or serum/urinary molecular tests, could further boost the sensitivity of mpMRI and subsequent TB in biopsy naïve patients.

FUTURE PERSPECTIVE

Biparametric MRI

A major barrier to widespread implementation of mpMRI diagnostics in patients at risk of PCa are availability, expertise, associated costs, and capacity burden on MRI devices. In order to reduce these drawbacks recent research has focussed on reducing the number of necessary imaging parameters.[29-31] The introduction of PIRADS v1 in 2012 and v2 in 2015 caused a shift in evaluation of mpMRI imaging.[12,13] A major alteration compared to PIRADS v1 was that lesion location (peripheral or transition zone) determines which imaging modality should be dominant in the overall PIRADS score. If a lesion is located in the peripheral zone diffusion weighted imaging (DWI) is the dominant imaging modality, and if a lesion is located in the transition zone T2 weighted imaging (T2W) is dominant.[12,13] A side effect of this alteration is that the third modality in mpMRI, dynamic contrast enhanced imaging (DCE), plays a minor role in overall PIRADS grade. The outcomes of DCE imaging (positive or negative) can upgrade a PIRADS 3 lesion to a PIRADS 4 lesion in the peripheral zone only. For all other lesions, the outcome of DCE imaging does not influence overall PIRADS v2 grade.

Consequently, a new imaging protocol has been suggested. Biparametric (bp)MRI consists of DWI and T2W but does not incorporate DCE imaging. Consequently, the required MR imaging time and associated costs are reduced. A further advantage is that administration of contrast agent can be avoided. Recent research has investigated whether the diagnostic yield of bpMRI is comparable with mpMRI. The results of these studies are summarised in a recent systematic review and meta-analysis on 31 original studies published in 2019.[30] The authors concluded that there is no significant difference in diagnostic test accuracy for csPCa between mpMRI and bpMRI in treatment naïve patients at risk for PCa. However,

individual heterogeneity in these studies warrants caution in the interpretation of the results of this meta-analysis. Nonetheless, bpMRI is a faster, cheaper, and contrast free alternative to mpMRI, and consequently the implications of this development are significant.

MRI in a therapeutic setting of focal therapy

Current curative interventions for PCa such as RP, external beam radiation, or interstitial radiation (brachy) are whole gland therapies. This implies that healthy prostatic tissue is treated along with tumour foci. Focal therapy is directed onto tumour foci selectively and consequently limits therapy related toxicity by sparing the neurovascular bundles, sphincter and urethra.[21]

Currently various ablative techniques exist for focal treatment of localized PCa. Focal treatment modalities include high-intensity focused ultrasound (HIFU), cryotherapy, photodynamic therapy (PDT), laser-induced thermotherapy, brachytherapy, irreversible electroporation (IRE), and radiofrequency (RF) ablation. A systematic review dating from 2017 summarises the evidence of 37 studies on focal treatment modalities for PCa.[32] The authors found that HIFU, cryotherapy, PDT and brachytherapy have been most extensively investigated, and that their outcomes have been reported in larger cohorts. Other treatment modalities have been less extensively reported on, and papers are limited to proof of principle studies and smaller development studies. Currently there are no studies comparing outcomes of focal treatment modalities with outcomes of standard of care. Nonetheless, focal therapy seems safe and offers good preservation of genito-urinary function. The small number of papers reporting on oncological outcomes following focal therapy are encouraging, although they are limited by short follow-up and lack of comparison with accepted treatment modalities.[32] Consequently, current clinical guidelines state that focal treatment should only be considered for treatment of localised PCa in the setting of clinical trials.

Since the introduction of imaging modalities such as mpMRI and imaging-based TB procedures, tumour foci can be more accurately diagnosed, and distinguished from benign prostatic tissue.

The implications of more accurate diagnostics of tumour index lesions and exclusion of multifocal csPCa on image directed focal ablative therapy are significant, since this could potentially enhance oncological outcomes following treatment.[33,34] Nonetheless, negative MRI diagnostics do not completely eliminate the possibility of csPCa presence contralateral of index lesions in patients eligible for focal treatment.[35] Consequently, stricter eligibility criteria for focal treatment are needed, and active surveillance of the untreated prostate half is mandatory following focal treatment of index lesions.[35-37] With increasing reliability

of diagnostic imaging, focal therapy could become a more attractive treatment option for patients with intermediate risk PCa. Whether SB or template prostate mapping are necessary in the setting of focal therapy remains to be determined.

PSMA PET-CT

A novel imaging modality for PCa diagnostics is the Prostate Specific Membrane Antigen (PSMA) PET-CT. PSMA has a relatively specific expression in prostatic tissue, and PCa cells have an increased expression of PSMA on their membranes. Consequently, PSMA labelled imaging (such as ^{68}Ga- or ^{18}F-labelled PSMA PET-CT) has an excellent contrast-to-noise ratio, and improves detectability of PCa lesions.[21] Initial investigation using PSMA PET-CT have focussed on its reliability of imaging of nodal involvement, bone or visceral metastasis, especially in patients with biochemical recurrence following curative treatment.[38] The results of these studies are encouraging and have led to a growing interest of the usage of PSMA PET-CT in initial staging. Guidelines state that PSMA PET-CT has higher sensitivity for lymph nodal metastases as compared to abdominal contrast-enhanced CT or choline PET-CT.[21] Furthermore, PSMA PET-CT outperforms conventional imaging (i.e. technetium bone scan) for bone metastasis.[39] Potentially PSMA PET-CT could also enhance local PCa detection. This is especially interesting in patients at high risk of PCa due to elevated and progressive serum PSA and no visible lesions on mpMRI. Nonetheless, the accuracy of PSMA PET-CT in localization of PCa in the prostate remains unclear and it is currently unknown whether PSMA PET-CT might be used as a tool for targeting prostate biopsies. Overall, the impact of PSMA PET-CT on management and treatment outcomes in PCa remains unclear, which at this point forms a barrier to widespread application of PSMA PET-CT diagnostics in patients with an elevated PSA of diagnosed with primary PCa.

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9

Chapter 9

Summary

SUMMARY

Chapter 1 (general introduction) provides an overview of the epidemiology, diagnosis and grading of prostate cancer. Prostate cancer is the most common malignancy among Dutch men. Nonetheless, cancer specific mortality of prostate cancer is relatively low in the Netherlands compared to other types of cancer. This suggests an indolent natural history of (localised) prostate cancer in many men. Prostate cancer can be classified as clinically significant or insignificant cancer. Clinically significant prostate cancer is a likely cause of death in men with a life expectancy of >10 years when left untreated, whereas insignificant prostate cancer is unlikely to lead to clinical symptoms and cancer related death during their lifetime.

Prostate biopsy has been the cornerstone in the diagnosis of prostate cancer and has undergone significant improvement over the years. Imaging modalities, such as transrectal ultrasonography (TRUS) and magnetic resonance imaging (MRI), have been developed to improve prostate cancer detection rates. The long-time standard of systematic biopsy (SB) of the prostate has a low reliability to rule out clinically significant prostate cancer and carries a risk of over-diagnosis of clinically insignificant prostate cancer. More recently, multiparametric MRI (mpMRI) and subsequent mpMRI based targeted biopsy (TB) of tumour suspicious lesions have become the mainstay of prostate cancer diagnosis. Three co-existing techniques of mpMRI based biopsy are MRI-TRUS fusion targeted biopsy (FUS-TB), cognitive TRUS targeted biopsy (COG-TB), and in-bore MRI targeted biopsy (MRI-TB). There is no consensus on the preferred technique. The primary objective of this thesis is to gain insight into which technique of mpMRI based TB of the prostate should be preferred in men with a persistent clinical suspicion of PCa following negative SB. The thesis consists of five parts, including the appendices in part V.

Part I: Overview of current literature

Chapter 2 presents a systematic review and meta-analysis of the contemporary literature on three techniques of mpMRI based TB. The meta-analysis demonstrates that in men at risk for prostate cancer, mpMRI based TB (any technique) has an increased sensitivity for clinically significant prostate cancer and a decreased sensitivity for clinically insignificant prostate cancer when compared with SB. Regarding overall prostate cancer detection rates, the sensitivity of mpMRI based TB and SB are similar. Based on the studied literature MRI-TB has an advantage in overall prostate cancer detection when compared to COG-TB. No significant differences were found in overall prostate cancer detection rates when

comparing FUS-TB with MRI-TB, and when comparing FUS-TB with COG-TB. Perhaps more importantly, there is no significant advantage of any specific technique of mpMRI based TB over another for the detection of clinically significant prostate cancer.

The meta-analysis of the literature is limited by significant heterogeneity among studies on mpMRI based TB with regard to a) the investigated population, b) the quality of MRI acquisition, c) the applied threshold for subsequent TB, and d) the definition of clinically significant prostate cancer used. Furthermore, the number of head-to-head comparisons of various techniques of mpMRI based TB is limited. Finally, in the majority of studies, the absence of lesion specific descriptive characteristics (such as size, PIRADS assessment and location) limits the ability to accurately compare the various TB techniques. Consequently, the results of the meta-analysis presented in chapter 2 are indicative at best. Robust RCT's comparing the three techniques of mpMRI based TB are needed.

Part II: Principle of MRI-TRUS-fusion and design of FUTURE trial

Chapter 3 presents an ex-vivo study evaluating the accuracy of an MRI-TRUS fusion device for FUS-TB. The various origins of errors during the procedural steps of FUS-TB are introduced. The concepts of planning error (PE), targeting error (TE), and overall error (OE) are defined and applied. In this ex-vivo experiment, the mean PE, TE, and OE in the transversal plane were 1.18, 0.39, and 2.33 mm respectively. The OE is predominantly determined by the PE, whereas the TE has a moderate impact on OE. The likelihood that a single biopsy core can accurately sample a lesion is dependent on the size of the lesion, ranging from 26% for lesions with a diameter of 2 mm to 99% for lesions with a diameter of 6 mm. Furthermore, the likelihood of accurate sampling increases if more targeted biopsy cores are taken. These ex-vivo results cannot be extrapolated to the in-vivo situation without caution, due to the fact that several additional factors that cannot be simulated ex-vivo (e.g., tissue deformation, inhomogeneous tissue resistance, needle deflection and reduced precision of contouring) negatively influence the in-vivo accuracy. Therefore, the results of this ex-vivo experiment on accuracy of FUS-TB should be considered to be the lower limit of in-vivo accuracy. This implies, than during an optimal FUS-TB procedure, at least 2.3 mm error in targeting will occur.

In **chapter 4** the research protocol of a three-armed multicentre randomised controlled trial comparing three techniques of mpMRI based TB amongst patients at risk of prostate cancer is presented. In the FUTURE trial patients with at least one prior negative TRUS-SB and a persisting clinical suspicion of prostate cancer (PSA >4.0 ng/ml and/or suspicious digital rectal examination) are recruited. Primarily, all included patients undergo 3-T mpMRI. All images are centrally evaluated by an expert prostate radiologist using the Prostate Imaging Reporting And Data System version 2 (PIRADS v2). If imaging demonstrates

PIRADS≥3 lesions, patients are randomised 1:1:1 for one TB technique: FUS-TB, COG-TB or MRI-TB. If imaging demonstrates PIRADS≤2 lesions, patients undergo biochemical follow-up. The primary outcome of the FUTURE trial is the comparison of prostate cancer detection rates among three techniques of TB. Secondary objectives comprise the comparison of clinically significant prostate cancer detection rates, adverse events (AE) and self-reported functional outcomes among techniques, and the comparison of (clinically significant) prostate cancer detection rates of mpMRI based TB and repeated TRUS-SB. The sample size calculation indicates that 675 patients are required for inclusion. The research protocol has been approved by the regional medical ethical research committee and institutional review board approval was granted for each participating centre. The research protocol has been registered in the Dutch National Trial Register. All patients provided written informed consent. Trial recruitment started in December 2014.

Part III: Outcomes of the FUTURE trial

In **chapter 5** the primary outcomes of the FUTURE trial are presented. Among the 665 recruited patients, 234 (35%) had PIRADS≥3 lesions on mpMRI and were randomised for subsequent mpMRI based TB (79 for FUS-TB, 78 for COG-TB, and 77 for MRI-TB). There were no significant differences in baseline characteristics or mpMRI outcomes among the groups. Overall 115 cases of prostate cancer (49%) and 78 cases of clinically significant prostate cancer (33%) (Gleason score ≥3+4 (ISUP grade ≥2)) cases were detected using TB. We demonstrated that there are no statistically significant differences in the overall detection rates of prostate cancer among three techniques of mpMRI based TB (FUS-TB 49%, COG-TB 44%, MRI-TB 55%, p=0.4). Furthermore, no significant differences have been found in the detection rates of clinically significant prostate cancer among the techniques (FUS-TB 34%, COG-TB 33%, MRI-TB 33%, p>0.9). Finally, pre-specified sub-analysis did not demonstrate statistically significant differences in (clinically significant) prostate cancer detection rates between the techniques in various subgroups of patients. The study was, however, hampered by a lower yield of PIRADS≥3 on mpMRI than predicted and thus low availability of TB, causing under-powering for the primary endpoint. Thus, these results should be considered with caution.

Chapter 6 presents a secondary analysis of the FUTURE trial, in which the yield of mpMRI based TB was compared with the yield of repeated TRUS-SB. In a FUTURE trial cohort of 152 patients that underwent both TB and SB, we demonstrated that TB detected significantly more prostate cancer than SB (47% vs 32%, p<0.001). The combination of TB and SB detected prostate cancer in 53% cases, representing a prostate cancer detection rate difference of 6% compared with TB alone. Furthermore, TB detected significantly more clinically significant prostate cancer (34% vs 16%, p<0.001) and less clinically insignificant

prostate cancer (13% vs 16%, p=0.4) than SB. The combination of TB and SB detected clinically significant prostate cancer in 35% cases (representing a detection rate difference of 1% compared with TB alone) and detected clinically insignificant prostate cancer in 18% cases (representing a detection rate difference of 5% compared with TB alone). In other words, had repeated TRUS-SB been omitted in these patients, only 1% of clinically significant prostate cancer would have been missed. Simultaneously, omitting TRUS-SB in these patients would have resulted in 5% less detected clinically insignificant prostate cancer. Finally, the Gleason score concordance of radical prostatectomy (RP) and TB was higher than the Gleason score concordance of RP and SB. Therefore, the additional value of repeated TRUS-SB in patients undergoing TB in a repeat biopsy setting is limited, and should not be performed.

Chapter 7 presents another secondary analysis of the FUTURE trial, in which adverse events (AE) among three TB techniques are compared and the effect on urinary and erectile function is evaluated. We demonstrated that there are significant differences in minor (grade 1 and 2) AE's between techniques (FUS-TB 71%, COG-TB 85%, MRI-TB 53%, p<0.001). There are significant differences in occurrence of self-limiting hematuria (p<0.001) and hematospermia (p<0.05) among the groups, being the two most common AE's. No significant difference in occurrence of UTI's (p=0.21) have been found between the groups. Significant differences in the median number of biopsy cores obtained during biopsy have been found between the techniques (FUS-TB 14, COG-TB 13, MRI-TB 2, p<0.001) due to the omission of repeated SB in the MRI-TB group. The number of biopsy cores taken, was significantly associated with the occurrence of AE's (OR 1.11 per extra biopsy, p<0.001). When correcting for the number of cores taken, the advantage of MRI-TB as compared to FUS-TB and COG-TB became statistically non-significant (p=0.34 and p=0.94, respectively), regarding the occurrence of AE's. The low occurrence of AE's in the MRI-TB group has likely been caused by the omission of additional SB in this group. Decreased AE rates could be an additional argument to omit repeated SB when performing TB procedures in repeat biopsy setting and to reduce the number of TB cores during biopsy. Overall prostate biopsy did not significantly impact self-reported urinary and erectile functions at 30 days post-biopsy.

Part IV: General discussion and future perspectives

In **chapter 8** a general discussion on the various studies of the previous chapters is presented.

Furthermore, a recent adaptation in the clinical guideline and its impact on the outcomes of this thesis is discussed. Based on several discussed key papers, the updated 2019 European Urology Guidelines on prostate cancer advises to perform mpMRI in biopsy naïve patients (that is prior to initial biopsy). This is a significant alteration compared to the 2013 European

Urology Guidelines on prostate cancer, where mpMRI diagnostics was reserved for men with a persistent clinical suspicion of prostate cancer in spite of negative TRUS-SB. Probably, the shift from secondary (following negative SB) to primary (prior to initial biopsy) setting would significantly alter the yield of mpMRI diagnostics itself. However, once a lesion is identified on mpMRI, the detection yield of subsequent TB procedures is unlikely to be significantly affected by a shift of setting, since mpMRI is used as a triage test preceding TB. In other words, the outcomes of the FUTURE trial on the comparison of three techniques of mpMRI based TB, are unlikely to change if it had been performed among biopsy naïve patients.

Although this thesis demonstrates that SB has limited value in when performing TB procedures in repeat biopsy setting, are we ready to abandon SB completely, including in primary setting? Several studies present paired data of TB and SB in primary setting. The outcomes of these studies demonstrate that TB and SB have equivalent detection rates of clinically significant prostate cancer. However, the clinically significant prostate cancer yield SB in patients with PIRADS≤2 is limited to 3-6%. This suggest that mpMRI can be used as triage test to select patients in whom to perform biopsy. If imaging demonstrates PIRADS≥3 TB and SB should be combined, since a combined approach yields the highest detection rate of csPCa. If imaging demonstrates PIRADS≤2 the need for biopsy should be discussed, since the estimated yield of clinically significant prostate cancer is limited but not nihil. As the accuracy of mpMRI for clinically significant prostate cancer continues to increase the role of SB as a reference test will be reduced. With new MR imaging protocols being proposed this will be a question for future research.

A barrier for wide-spread implementation of MRI diagnostics in prostate cancer is the capacity burden on MRI devices and associated costs. Novel imaging protocol have been proposed including biparametric (bp)MRI. bpMRI consists of diffusion weighted imaging and T2 weighted imaging, without additional dynamic contrast enhanced imaging. This reduces the required time on the MRI device and associated costs. A further advantage of bpMRI is that administration of contrast agent can be avoided. Studies have shown that bpMRI and mpMRI have a similar diagnostic test accuracy for significant prostate cancer when performed by an expert reader. The development of bpMRI can further increase the usage of MR imaging in the diagnostic work-up of prostate cancer.

Traditionally, the studies investigating the value of screening for prostate cancer have employed PSA-testing as triage test, and consequently screening for prostate cancer is not routinely performed. As MR imaging protocol continue to develop, the combination of PSA testing and MR imaging could enhance the diagnostic yield of clinically significant prostate cancer, whilst reducing the yield of clinically insignificant prostate cancer associated with

PSA testing. Potentially the combination of PSA testing and MR imaging could be a useful tool for screening for clinically significant prostate cancer, and this should be a subject for future research.

Due to the introduction of mpMRI and TB procedures, tumour foci can be more accurately diagnosed. With increasing reliability of diagnostic imaging, focal therapy could become a more attractive treatment option for patients with intermediate risk PCa. However, negative MRI diagnostics do not completely eliminate the possibility of csPCa presence contralateral of index lesions in patients eligible for focal treatment. Whether SB or template prostate mapping are necessary in the setting of focal therapy remains to be determined.

The novel imaging modality of PSMA PET-CT is traditionally employed to evaluate nodal involvement, bone or visceral metastasis. However, PSMA PET-CT can potentially enhance localised prostate cancer detection. This is especially true for patients at high risk of prostate cancer due a progressive and elevated serum PSA and no visible lesions on mpMRI. The role of TB of PSMA PET-CT identified lesions remains unclear, and is a question which future research should answer.

SAMENVATTING

Inleiding

Hoofdstuk 1 beschrijft dat prostaatkanker de meest voorkomende kankersoort onder Nederlandse mannen is, met in 2018 een absolute incidentie van 12.646. Hoewel deze vorm van kanker zoveel voorkomt is de kanker-specifieke mortaliteit van prostaatkanker relatief laag vergeleken met andere vormen van kanker. In 2017 overleden 2.862 Nederlandse mannen aan prostaatkanker, terwijl er in datzelfde jaar 10.391 mannen overleden aan longkanker. Dit suggereert een mild en indolent natuurlijk beloop van sommige vormen van prostaatkanker.

Er kan onderscheid gemaakt worden tussen klinisch significante prostaatkanker en klinisch insignificante prostaatkanker. Onbehandelde klinisch significante prostaatkanker is een belangrijke oorzaak van sterfte onder mannen met een levensverwachting van meer dan 10 jaar. Daarentegen leidt klinisch insignificante prostaatkanker zelden tot symptomen of sterfte als de kanker onbehandeld blijft. Het ideale diagnostische hulpmiddel heeft een hoge betrouwbaarheid voor het opsporen van klinisch significante prostaatkanker, terwijl het weinig klinisch insignificante prostaatkanker identificeert.

Prostaatbiopten vormden decennialang de hoeksteen van de diagnostiek van prostaatkanker. Ontwikkelingen in beeldvormende technieken, zoals transrectale echografie (TRUS) en magnetic resonance imaging (MRI), hebben het diagnostisch traject bij prostaatkanker sterk beïnvloed. Tot voor kort waren TRUS geleide systematische prostaatbiopten (SB) het belangrijkste diagnostische hulpmiddel van de uroloog voor het vaststellen van prostaatkanker. Onderzoek heeft echter aangetoond dat SB een beperkte betrouwbaarheid heeft om klinisch significante prostaatkanker vast te stellen: indien geen prostaatkanker wordt aangetoond, sluit dat de aanwezigheid ervan niet goed uit. Tevens heeft SB een hoog risico van over-diagnostiek van klinisch insignificante prostaatkanker.

Sinds een paar jaar speelt de multiparametrische (mp)MRI een grote rol in het diagnostische traject van prostaatkanker. De parameters van een mpMRI bestaan uit anatomische beelden gecombineerd met twee functionele beelden op basis van weefseldichtheid en doorbloeding. Met mpMRI kan klinisch significante prostaatkanker beter worden ontdekt. De diagnose moet echter altijd bevestigd worden door (bij voorkeur gerichte "targeted") prostaatbiopten (TB). Tot voor kort adviseerden de richtlijnen om een mpMRI uit te voeren bij patiënten met een aanhoudende verdenking van prostaatkanker ondanks eerdere negatieve SB (waarbij geen kanker werd gevonden). Thans zijn er drie TB-technieken op basis van mpMRI beelden beschikbaar:

MRI-TRUS-fusie gerichte biopten (FUS-TB) waarbij een softwarematige beeldfusie wordt gemaakt van mpMRI beelden en 'live' TRUS beelden. Hierdoor kan zowel gebruik worden gemaakt van de betrouwbaarheid van mpMRI voor het vaststellen van klinisch significante prostaatkanker, als van de eenvoudige toepasbaarheid van TRUS bij het uitvoeren van een biopsie.

Cognitieve TRUS gerichte biopten (COG-TB) waarbij de uroloog vlak voor het afnemen van TRUS prostaatbiopten de beelden van de mpMRI bekijkt. De uroloog onthoudt waar in de prostaat de van prostaatkanker verdachte laesie op de mpMRI zit, om deze laesie vervolgens met TRUS te biopteren. Hierbij wordt geen softwarematige beeldfusie toegepast.

In-bore MRI gerichte biopten (MRI-TB) waarbij de biopten in de MRI-scanner zelf worden afgenomen. De procedure wordt door 'live' MRI-beelden begeleid zodat de eerder vastgestelde laesie kan worden gebiopteerd.

Het is nog niet voldoende duidelijk welke van de drie technieken de voorkeur zou moeten hebben. Het doel van dit proefschrift is daarom om te onderzoeken welke van de drie beschreven TB-technieken op basis van mpMRI bij voorkeur zou moeten worden toegepast bij mannen met een aanhoudende verdenking van prostaatkanker ondanks eerdere negatieve SB. Het proefschrift is onderverdeeld in vijf delen, waarvan deel V bestaand uit bijlagen.

Deel I: Samenvatting van relevante literatuur

Hoofdstuk 2 beschrijft een systematisch review en meta-analyse van de relevante literatuur over de drie TB-technieken. Met deze meta-analyse wordt aangetoond dat TB (alle technieken gecombineerd) een verhoogde sensitiviteit heeft om klinisch significante prostaatkanker vast te stellen vergeleken met SB, en dat TB een lagere sensitiviteit heeft voor klinisch insignificante prostaatkanker dan SB. Voor de totale (significante én insignificante) prostaatkanker detectie is de sensitiviteit van TB vergelijkbaar met die van SB. Met betrekking tot totale prostaatkanker detectie heeft MRI-TB heeft een significant betere sensitiviteit dan COG-TB. Voor totale prostaatkanker detectie lijken er geen significante verschillen te bestaan tussen de sensitiviteit van FUS-TB en MRI-TB óf van FUS-TB en COG-TB. Op basis van het literatuuronderzoek lijkt er geen significant voordeel te zijn om één specifieke techniek van TB te gebruiken om klinisch significante prostaatkanker vast te stellen. De beperkingen van deze systematische review en meta-analyse komen voort uit de heterogeniteit van de studies met betrekking tot a) de onderzochte populatie, b) de manier van vervaardigen en beoordelen van de mpMRI beelden, c) de gebruikte drempel om TB uit te voeren, en d) de toegepaste definitie van klinisch significante prostaatkanker. Tevens waren er maar een paar studies die meerdere technieken van TB rechtstreeks met

elkaar vergeleken. Tot slot, ontbraken laesie-specifieke gegevens in het merendeel van de studies uit deze meta-analyse. Vanwege de bovenstaande beperkingen kunnen de uitkomsten van deze systematische review en meta-analyse slechts richtinggevend zijn. Gerandomiseerde klinische trials zijn nodig om uitsluitsel te geven over welke TB-techniek op basis van mpMRI beelden de voorkeur verdient.

Deel II: MRI-TRUS fusie principe en opzet FUTURE trial

In **hoofdstuk 3** wordt een ex-vivo studie gepresenteerd die de nauwkeurigheid van een MRI-TRUS fusie apparaat evalueert. De onnauwkeurigheden gedurende het proces van FUS-TB worden geanalyseerd aan de hand van de concepten van planning error (PE), targeting error (TE), en overall error (OE). PE wordt gevormd door onnauwkeurigheden die optreden voorafgaande aan de biopsie. Voorbeelden hiervan zijn beperkte resolutie van MRI en TRUS-beeldvorming, beperkingen ten gevolge van het coördinatenstelsel van het biopsie-rooster, onnauwkeurige fusie van MRI en TRUS-beelden, en onnauwkeurige virtuele biopsie naald planning. De TE bestaat uit onnauwkeurigheden die optreden ten tijde van de biopsie. Bijvoorbeeld als gevolg van naald afbuiging op (inhomogeen) weefsel, weefsel-deformatie als gevolg van de biopsie, onnauwkeurigheden van de operateur, en het onnauwkeurig vastleggen van de fysieke biopsie-naald direct na de biopsie. De OE is de optelsom van de PE en TE, in combinatie met niet-meetbare onnauwkeurigheden in dit experiment (zoals het verschuiven van verificatie voerdraden voorafgaand aan de post-interventie MRI en onnauwkeurige fusie van pre- en post-interventie MRI beelden). Aangetoond wordt dat de gemiddelde PE, TE en OE in het transversale vlak 1.18, 0.39, en 2.33 mm zijn. De OE wordt voornamelijk bepaald door de PE, de TE draagt slechts beperkt bij aan de OE. De kans dat men een laesie met één enkele naald accuraat kan aanprikken is afhankelijk van de grootte van de laesie. Hoe groter de diameter van de laesie, hoe hoger de trefkans; 26% voor laesies met een diameter van 2 mm tot 99% voor laesies met een diameter van 6 mm. Daarnaast neemt de trefkans toe indien er meerdere biopsie-naalden worden gebruikt. De uitkomsten van dit ex-vivo experiment zijn niet direct vertaalbaar naar de in-vivo situatie aangezien er enkele factoren met negatieve invloed op de nauwkeurigheid niet gesimuleerd kunnen worden (zoals weefsel-deformatie als gevolg van manipulatie/beweging, inhomogene weefselstructuren, naald afbuiging als gevolg van weefsel weerstand, en onnauwkeurige contourbouw op beeldvorming). De uitkomsten van dit ex-vivo experiment geven daarom slechts een indicatie voor de minimale marge van de in-vivo nauwkeurigheid van FUS-TB.

Hoofdstuk 4 presenteert het onderzoeksprotocol van een driearmige, multicenter, gerandomiseerde klinische trial, waarbij de drie TB-technieken op basis van mpMRI beelden met elkaar zijn vergeleken. In deze FUTURE-trial zijn mannen met eerdere negatieve SB (geen kanker) en een aanhoudende verdenking van prostaatkanker (op basis van een PSA

>4.0 ng/ml en/of een afwijkend rectaal toucher) geïncludeerd. Alle patiënten werden om te beginnen onderworpen aan een 3-T mpMRI. Alle mpMRI beelden zijn vervolgens centraal beoordeeld door een expert prostaat radioloog middels de 'Prostate Imaging Reporting And Data System' versie 2 (PIRADS v2). Indien er een tumor verdachte laesie (PIRADS≥3) op de mpMRI werd gevonden, werden patiënten gerandomiseerd (1:1:1) om TB te ondergaan middels één van de drie eerder beschreven technieken: FUS-TB, COG-TB of MRI-TB. Indien er geen tumor verdachte laesie (PIRADS≤2) werd gevonden op de mpMRI, werden de patiënten biochemisch vervolgd.

De primaire uitkomst van de FUTURE-trial is de vergelijking van detectie ratio's van prostaatkanker tussen de drie TB-technieken. Secundaire uitkomsten bestaan uit de vergelijking van detectie ratio's van klinisch significante prostaatkanker, het optreden van complicaties (adverse events (AE)) en zelf-gerapporteerde functionele uitkomsten en de vergelijking van de detectie ratio's van TB en herhaalde SB. De poweranalyse liet zien dat er 675 patiënten geïncludeerd moesten worden. Het onderzoeksprotocol is goedgekeurd door de regionale medische ethische toetsingscommissie en er is lokale goedkeuring verkregen in elk deelnemend medisch centrum. Het protocol is geregistreerd bij het Nederlands trial register. Alle deelnemende patiënten hebben een schriftelijk verklaring van toestemming voor deelname aan de studie ondertekend. Het rekruteren van patiënten is in december 2014 gestart.

Deel III: Uitkomsten van de FUTURE trial

In **hoofdstuk 5** worden de primaire uitkomsten van de FUTURE-trial gepresenteerd. In totaal hadden 234 (35%) van de 665 geïncludeerde patiënten een voor tumor verdachte laesie (PIRADS≥3) op de mpMRI. Deze patiënten werden vervolgens gerandomiseerd voor FUS-TB (n=79), COG-TB (n=78) of MRI-TB (n=77). Er waren geen significante verschillen in de patiënt karakteristieken of de mpMRI uitkomsten tussen de patiënten van de verschillende groepen. In totaal (de drie groepen gecombineerd) werd bij 115 (49%) patiënten prostaatkanker vastgesteld en bij 78 (33%) patiënten klinisch significante prostaatkanker (Gleason score ≥3+4 (ISUP grade ≥2)) vastgesteld. Er werd aangetoond dat bij het vaststellen van (totaal) prostaatkanker er geen significante verschillen bestaan tussen de drie technieken van TB (FUS-TB 49%, COG-TB 44%, MRI-TB 55%, p=0.4). Bij het vaststellen van klinisch significante prostaatkanker werd eveneens geen significant voordeel voor één specifieke TB-techniek aangetoond (FUS-TB 34%, COG-TB 33%, MRI-TB 33%, p>0.9).

Tenslotte kon ook geen significant voordeel voor één specifieke TB-techniek worden aangetoond in diverse vooraf gedefinieerde subgroepen. De belangrijkste beperking van

deze studie is dat het aantal patiënten met PIRADS≥3 laesies aanzienlijk lager was dan verwacht. Hierdoor ontstond under-powering van de primaire uitkomst, waardoor de uitkomsten met enige voorzichtigheid geïnterpreteerd moeten worden.

In **hoofdstuk 6** wordt een analyse van een secundaire uitkomsten van de FUTURE-trial gepresenteerd waarin de uitkomsten van TB en herhaalde SB zijn vergeleken. In het FUTURE-trial cohort ondergingen 152 patiënten zowel TB (FUS-TB en COG-TB) als herhaalde SB. Met behulp van TB werd meer (totale) prostaatkanker vastgesteld dan met SB (47% vs 32%, p<0.001). Gecombineerd laten TB en SB prostaatkanker bij 53% van de patiënten zien, dus 6% hoger dan TB alleen. Daarnaast werd met TB vaker significante prostaatkanker vastgesteld dan met SB (34% vs 16%, p<0.001), en minder vaak insignificante prostaatkanker (13% vs 16%, p=0.4). Gecombineerd toonden TB en SB significante prostaatkanker bij 35% van de patiënten, dus slechts 1% meer dan TB alleen. Tegelijkertijd zou er door het achterwege laten van SB, 5% minder klinisch insignificante prostaatkankers zijn vastgesteld. Tot slot is aangetoond dat TB de uiteindelijke Gleason score bij een radicale prostatectomie (RP) beter voorspelt dan SB. Concluderend heeft herhaalde SB een zeer beperkte toevoegde waarde bij patiënten met eerdere negatieve SB die TB van een afwijking op de mpMRI ondergaan, en dienen daarom achterwege gelaten te worden.

In **hoofdstuk 7** worden de complicaties ('adverse events': AE's) van de drie TB-technieken met elkaar vergeleken. Tevens wordt de impact van TB op erectiele-functie en plasklachten beoordeeld. Er waren significante verschillen in het vóórkomen van (graad 1 en 2) AE's tussen de drie technieken (FUS-TB 71%, COG-TB 85%, MRI-TB 53%, p<0.001). De verschillen tussen de drie groepen werden voornamelijk veroorzaakt door verschillen in het optreden van bloed in de urine (hematurie) (p<0.001) en bloed in het semen (hematospermie) (p<0.05). Er waren geen significante verschillen in het vóórkomen van urineweginfecties (p=0.21) tussen de groepen. Er waren significante verschillen in het totaal (TB en SB) aantal afgenomen biopten tussen de drie groepen (FUS-TB 14, COG-TB 13, MRI-TB 2, p<0.001). Dit werd veroorzaakt door het achterwege laten van SB in de MRI-TB groep. Er is een significante correlatie tussen het vóórkomen van AE's en het aantal afgenomen biopten (OR 1.11 per extra afgenomen biopt, p<0.001). Bij een multivariaat analyse werd nadien gecorrigeerd voor het aantal afgenomen biopten. In deze multivariaat analyse bleek het voordeel van MRI-TB, ten aanzien van het aantal AE's, ten opzichte van FUS-TB en COG-TB statistisch niet-significant (p=0.34 en p=0.94, respectievelijk). Het lage aantal AE's in de MRI-TB groep is waarschijnlijk veroorzaakt door het achterwege laten van SB in deze groep. Het lagere risico op het optreden van AE's kan een extra argument zijn om herhaalde SB achterwege te laten, bij patiënten met eerdere negatieve SB die TB van een afwijking op de mpMRI ondergaan. Biopsie had geen significante invloed op erectiele functie en plasklachten.

Deel IV: Algemene discussie en toekomstperspectieven

Hoofdstuk 8 vormt de algemene discussie van dit proefschrift. Op basis van onder andere enkele in dit proefschrift besproken studies, wordt in de Europese Urologie richtlijn prostaatkanker van 2019 geadviseerd een mpMRI uit te voeren vóórafgaand aan het initiële biopt (biopsie-naïeve patiënten). Dit is een belangrijke verandering ten opzichte van het advies in de richtlijn van 2013, waarin een mpMRI gereserveerd bleef voor patiënten met een aanhoudende verdenking van prostaatkanker ondanks eerdere negatieve prostaatbiopten (waarbij geen kanker werd gevonden). De wijziging van het moment waarop de mpMRI in het diagnostisch traject bij prostaatkanker wordt ingezet, heeft vanwege een andere kanker incidentie, zeer waarschijnlijk invloed op de opbrengst van de mpMRI zelf. Echter wanneer een afwijking eenmaal met mpMRI is vastgesteld, zal een wijziging van setting van primair (voorafgaan aan initieel biopt) naar secundair (na eerder negatief biopt) waarschijnlijk geen invloed hebben op de uitkomsten van daaropvolgende TB-procedures, omdat de mpMRI als triage test fungeert. Met andere woorden: de uitkomsten van de FUTURE-trial, over welke TB-techniek de voorkeur verdient, zullen waarschijnlijk niet anders zijn als de studie was uitgevoerd bij patiënten die nog geen biopsie hebben gehad.

Hoewel deze thesis aantoont dat de toegevoegde waarde van SB in herhaal biopsie setting zeer beperkt is en achterwege gelaten moet worden, is het de vraag of SB ook veilig achterwege gelaten kan worden onder biopsie-naïeve patiënten. Een aantal studies waarin zowel TB als SB zijn uitgevoerd bij biopsie-naïeve patiënten, toonden dat TB en SB een vergelijkbare detectie van klinisch significante prostaatkanker hebben. Echter is de detectie van klinisch significante prostaatkanker bij mannen zonder een voor tumor verdachte laesie (PIRADS≤2) op de mpMRI slechts beperkt tot 3-6%. Dit suggereert dat de mpMRI goed gebruikt kan worden als triage test om patiënten te selecteren die een biopt moeten ondergaan. Als de mpMRI een voor tumor verdachte laesie (PIRADS≥3) toont, dienen zowel TB als SB uitgevoerd te worden. Indien de mpMRI geen voor tumor verdachte laesie (PIRADS≤2) toont, is de noodzaak om een biopsie uit te voeren minder uitgesproken. In dat geval is de kans dat er sprake is van een klinisch significante prostaatkanker beperkt maar niet geheel afwezig. Bij verdere toename van de accuratesse van MRI voor klinisch significante prostaatkanker, zal de rol van SB als referentie test verder afnemen en dient deze opnieuw kritisch geëvalueerd te worden bij biopsie-naïeve patiënten.

De capaciteitsbelasting op MRI-scanners en geassocieerde kosten zijn een belangrijke drempel voor routinematig gebruik van MRI in het diagnostische traject naar prostaatkanker. Een nieuwe ontwikkeling is de biparametische (bp)MRI. Een bpMRI bestaat uit anatomische beelden gecombineerd met functionele beelden op basis van weefseldichtheid. De functionele beelden op basis van doorbloeding van de prostaat worden bij bpMRI achterwege gelaten. Vergeleken met mpMRI kan met bpMRI de benodigde tijd op een

MRI-scanner (en de geassocieerde kosten) hierdoor beperkt worden zonder dat dit de diagnostische accuratesse nadelig beïnvloedt (mits de beelden door een expert worden beoordeeld). Een ander voordeel van bpMRI is, dat er geen contrast wordt gebruikt. Door de ontwikkeling van bpMRI kan MRI-diagnostiek makkelijk routinematig gebruikt worden bij een verdenking op prostaatkanker.

Studies naar de rol van screening bij prostaatkanker maken traditioneel gebruik van de PSA test als triage test. De PSA test heeft een matige betrouwbaarheid bij het aantonen van klinisch significante prostaatkanker en daarnaast is er een risico op de over-diagnostiek van klinisch insignificante tumoren. Bij verdere ontwikkeling van de betrouwbaarheid en beschikbaarheid van MRI-diagnostiek, kan de combinatie van MRI-beeldvorming en PSA de diagnostische accuratesse voor klinisch significante prostaatkanker verbeteren, terwijl het risico op over-diagnostiek van klinisch insignificante tumoren gereduceerd wordt. Potentieel is de combinatie van de PSA test en MRI-beeldvorming een meer betrouwbaar hulpmiddel bij het screenen naar prostaatkanker ten opzichte van de PSA test afzonderlijk. Er is aanvullend onderzoek nodig om hier meer duidelijkheid over te krijgen.

Door de introductie van MRI en TB-procedures kunnen tumor foci nauwkeuriger worden vastgesteld. De implicaties van deze ontwikkelingen op bijvoorbeeld active surveillance en beeldvorming gestuurde focale behandelingen zijn aanzienlijk. Bij focale behandelingen wordt alleen de kanker in de prostaat behandeld in plaats van de gehele prostaat. Door nauwkeurigere beeldvorming kunnen focale behandeltechnieken mogelijk betere behandeluitkomsten krijgen bij patiënten met gelokaliseerd prostaatkanker. Bij patiënten met prostaatkanker die geschikt zijn voor focale therapie, sluit een negatieve MRI de aanwezigheid van een contralaterale significante tumor echter niet geheel uit. Het blijft daarom de vraag of bij deze patiënten verificatie SB of saturatie biopsie nodig is voorafgaande aan een focale ablatieve behandeling.

Een nieuwe beeldvormingsmodaliteit bij prostaatkanker is de prostaat specifieke membraan antigeen (PSMA) PET-CT. De PSMA PET-CT wordt tegenwoorden ingezet om de aanwezigheid van klier-, bot- of afstandsmetastasen aan te tonen. De PSMA PET-CT kan echter ook de diagnostiek naar gelokaliseerd prostaatkanker verbeteren, in het bijzonder bij patiënten met een hoog risico op prostaatkanker en geen zichtbare afwijking op de mpMRI. Toekomstig onderzoek moet duidelijkheid verschaffen over de rol van TB van PSMA PET-CT geïdentificeerde laesies bij de diagnostiek naar gelokaliseerd prostaatkanker.


A

Appendices

- **List of abbreviations**
- **List of publications**
- **List of presentations**
- **Dankwoord**
- **Curriculum Vitae**

LIST OF ABBREVIATIONS

US	ultrasound
TRUS	transrectal ultrasound
MRI	magnetic resonance imaging
mpMRI	multiparametric MRI
bpMRI	biparametric MRI
T2W	T2 weighted imaging
DWI	diffusion weighted imaging
DCE	dynamic contrast enhanced imaging
MRSI	magnetic resonance spectroscopic imaging
PIRADS	prostate imaging reporting and data system
3-T	3 tesla
PCa	prostate cancer
csPCa	clinically significant prostate cancer
iPCa/cisPCa	clinically insignificant prostate cancer
TB	targeted biopsy
SB	systematic biopsy
MRI-GB	MRI guided biopsies
TRUS-GB	TRUS guided biopsy
COG-TB	cognitive TRUS targeted biopsy
MRI-TB	in-bore MRI targeted biopsy
FUS-TB	MRI-TRUS fusion targeted biopsy
CSR	cancer suspicious region
PSA	prostate specific antigen
PSAD	PSA density
DRE	digital rectal examination
CDR	cancer detection rate
IPSS	international prostate symptom score
SHIM	sexual health inventory for men
IIEF	International Index of Erectile Function
AE	adverse event
UTI	urinary tract infection
LUTS	lower urinary tract symptoms

ED	erectile dysfunction
RP	radical prostatectomy
HGG	highest Gleason grade
AS	active surveillance
ERSPC	European randomized study of screening for prostate cancer
EAU	European association of urology
ESUR	European society of urogenital radiology
ACR	American college of radiology
ISUP	international society of urological pathology
PRISMA	preferred reporting items for systematic reviews and mete-analysis
QUADAS	quality assessment of diagnostic accuracy studies
CONSORT	consolidated standards of reporting trials
SPIRIT	standard protocol items: recommendations for interventional trials
CRF	case report form
IC	informed consent
RCT	randomized controlled trial
START	standards of reporting for MRI-targeted biopsy studies
CI	confidence interval
SD	standard deviation
IQR	interquartile range
ANOVA	analysis of variance
OR	odds ratio
PE	planning error
TE	targeting error
OE	overall error
FoV	field of view
DOAC	direct oral anticoagulants
HIFU	high-intensity focused ultrasound
PDT	photodynamic therapy
IRE	irreversible electroporation
RF	radiofrequency
PSMA	prostate specific membrane antigen
PET	positron emission tomography
CT	computed tomography

LIST OF PUBLICATIONS

Thesis publications

- **Wegelin O**, van Melick HHE, Hooft L, Bosch JLHR, Reitsma HB, Barentsz JO, Somford DM. Comparing three different techniques for magnetic resonance imaging-targeted prostate biopsies: A systematic review of in-bore versus magnetic resonance imaging-transrectal ultrasound fusion versus cognitive registration. is there a preferred technique? Eur Urol. 2017;71(4):517-531

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LIST OF PRESENTATIONS

- **Voorjaarsvergadering Nederlandse Vereniging voor Urologie, 2019, Rotterdam, Netherlands**
  Wegelin O, Exterkate L, an der Leest MG, Kelder JC, Bosch JLHR, Barentsz JO, Somford DM, van Melick HHE.
  Vergelijking van complicaties van 3 technieken van MRI gerichte prostaatbiopten (FUTURE trial)
  Tijdschr Urol (2019) DOI: 10.1007/s13629-019-0255-6
  Award: top 5 abstract

- **Voorjaarsvergadering Nederlandse Vereniging voor Urologie, 2018, Nijmegen, Netherlands**
  Wegelin O, Exterkate L, Barentsz JO, van der Leest MG, Kelder JC, Kummer JA, Vreuls W, de Bruin PC, de Vocht TF, Nuininga JE, Bosch JLHR, Somford DM, van Melick HHE.
  De FUTURE trial; een multicenter RCT naar MRI-geleide prostaatbiopten. Vergelijking van drie technieken van target biopten en vergelijking met systematische biopten.
  Tijdschr Urol (2018) DOI: 10.1007/s13629-019-0252-9
  Award: top 5 abstract

- **European Association of Urology, 2018, Kopenhagen, Denmark**
  Wegelin O, Exterkate L, Somford DM, Barentsz JO, van der Leest MG, Kummer JA, Vreuls W, de Bruin PC, Bosch JLHR, van Melick HHE.
  The FUTURE trial; a multicenter RCT on three techniques of MRI targeted prostate biopsy
  Eur Urol Suppl 2018 17(2):e699-e700 · DOI: 10.1016/S1569-9056(18)31321-6
  Award: 2nd best abstract in oncology

- Exterkate L, Wegelin O, van Melick HHE, Barentsz JO, van der Leest MG, Kummer JA, Vreuls W, de Bruin PC, Bosch JLHR, Somford DM.
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- **American Urological Association, 2018, San Francisco, USA**
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  Wegelin O, van Melick HHE, Somford DM, Bosch JLHR, Kummer JA, Vreuls W, Barentsz JO
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  Award: top 5 abstract

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CURRICULUM VITAE

Olivier Wegelin was born on the 28th of January 1986 in Jakarta, Indonesia. He lived in Indonesia till aged 3 when the family moved back to the Netherlands. He grew up in Rotterdam where he attended primary school. At the age of 7 the family moved to Kenya, where they resided in Nairobi for several years. At the age of 11his family moved back to Rotterdam. In 1998 he attended a bilingual secondary school in Rotterdam, the Wolfert van Borselen, from which he graduated 2004. In 2005 he spent his gap year doing voluntary work in Ghana and traveling in South-East Asia.

After returning to the Netherlands in 2005, he enrolled in the medical faculty of the University of Maastricht. During his medical studies he was initially oriented towards the tropics, spending internships in Kampala (Uganda), Oranjestad (Aruba) and Semarang (Indonesia). Towards the end of his student time he gradually became focused on surgical specialties and decided to pursue a carrier in the Netherlands.

In 2011 he graduated from medical school and started his first job in the urology department of the Catharina hospital in Eindhoven. Gaining interest in urology, his second job brought him to the department of urology of the St. Antonius hospital in Nieuwegein in 2012. There he further explored his interest in medical research and published his first paper in 2015. By that time he had received a financial grant which allowed him to initiate his PhD project in 2014. The research focused on the role of multiparametric MRI and image-based targeted biopsy of the prostate in patients at risk of prostate cancer. The project was conducted in collaboration with the urology department of the St. Antonius hospital in Nieuwegein, the urology department of the Canisius Wilhelmina hospital in Nijmegen and the radiology department of the Radboud University Medical Centre in Nijmegen.

He continued his research in Utrecht and Nijmegen until 2017, when he started his urological residency training program at the department of general surgery of the Diakonessenhuis hospital in Utrecht (tutor dr. van Dalen). In 2019 he continued his urological residency training program at the department of urology of the St. Antonius hospital in Nieuwegein (tutor dr. van Melick). At that time all the papers for his thesis had been published, and he was able to finish his PhD (this thesis) at the University of Utrecht. In 2021 he will continue and finish his urological residency training program in the University Medical Centre of Utrecht. Olivier is married to Marieke Groen. Together they have two children; Thomas and Ella. The family lives happily in Utrecht.

DANKWOORD

Dit proefschrift is tot stand gekomen dankzij hulp en steun van vele kanten. Ik wil iedereen die hier een bijdrage aan heeft geleverd ontzettend bedanken en een aantal personen in het bijzonder.

Allereerst Harm, samen hebben wij de initiële voorzet gedaan van een project wat later uitgroeide tot de FUTURE-trial. Dankzij jouw onuitputtelijke steun heeft dit project uiteindelijk geleid tot dit proefschrift. Dank voor het vertrouwen en alle kansen die je me hebt geven. Met veel trots ben ik de eerste in een reeks van promovendi die jij als copromotor begeleidt. Ik heb veel bewondering voor de manier waarop je alle verschillende balletjes in de lucht houdt. Een ware duizendpoot. Je hebt me gedurende belangrijke fasen in mijn leven begeleid; ANIOS-tijd, promotieonderzoek, vaderschap, het 'in opleiding komen', en nu gedurende mijn opleiding tot uroloog. Dank voor alle tips en trucs die je me onderweg hebt bijgebracht.

Beste Rik, eveneens partner in crime vanaf het eerste moment. Dankzij jouw hulp heeft de FUTURE-trial zijn uiteindelijke vorm aangenomen en zonder jouw steun was dit project nooit zover gekomen. Onderweg waren er vele beren op de weg waardoor ik zo nu en dan het vertrouwen verloor. Dankzij jouw enthousiasme en optimisme wist ik echter altijd hernieuwde energie te vinden om door te gaan. Ik heb dan ook veel respect voor de manier waarop jij moeilijke problemen out-of-the-box benadert, altijd optimistisch blijft en de dosis humor die je inbrengt. Dank voor je de fijne begeleiding als copromotor.

Beste Jelle, dank voor het vervullen van de rol van promotor en 3e hoofdonderzoeker van de FUTURE-trial. Mede dankzij uw voortdurende inspanningen is het diagnostisch pad bij een verdenking op prostaatkanker radicaal veranderd. "Yes, we scan!" Door de implementatie van de mpMRI wordt bij menig man een 3/4/5/etc serie prostaatbiopten vermeden. Dank voor de begeleiding bij het opstellen van het onderzoeksprotocol, de implementatie daarvan en het uitwerken van de resultaten. Dank voor het beoordelen van die vele honderden MRI-beelden van mannen uit de FUTURE-trial, zelfs vanaf de andere kant van de wereld.

Beste Ruud, dank dat u mijn promotor wilde zijn. Dank voor de begeleiding bij het opstellen en uitvoeren van dit grote project. Dank voor de brainstormsessies, vele overleg momenten, vlotte reacties op mijn e-mails en feedback op al mijn stukken.

Geachte prof. van Diest, prof. Lam, prof. Horenblas, prof. van Moorselaar en prof. Incrocci, dank voor het plaatsnemen in de beoordelingscommissie van mijn manuscript.

Beste Leonie, ontzettend bedankt voor de fijne samenwerking. Het is best spannend om een zelf-geïnitieerd onderzoeksproject over te dragen aan een ander. Gelukkig ben jij net zo'n control freak als ik met betrekking tot wetenschappelijke systematiek en integriteit (zo niet nog een grotere). Ondanks de korte inwerktijd had je de logistiek rondom de FUTURE-trial snel in de smiezen. Dank voor alle steun die ik van je heb gekregen gedurende ons gezamenlijke onderzoek. Dank voor de vele gezellige overleg momenten, duizelingwekkende statistische brainstormsessies en leuke tijden op congressen. Ik ben vereerd dat je mijn paranimf wil zijn.

Beste Roos, dank voor het aanhoren van mijn gemopper en uitingen van mijn onderzoek frustraties. Sinds die eerste naaldprik in Maastricht een goede vriendin. Ondanks dat we al jarenlang ver uit elkaar wonen (voor Nederlandse begrippen dan), zijn we nog altijd erg close. Dank voor de vele etentjes en borrels. Ik ben vereerd dat je mijn paranimf wil zijn.

Beste Marloes, dank voor de fijne samenwerking. Ik heb veel bewondering voor de manier waarop jij naast het coördineren van je eigen 4-M studie, tijd wist te vinden om de vele MRI-beelden van mannen uit de FUTURE-trial te beoordelen. Dank voor je kritische blik op de MRI-beelden en op mijn stukken.

Beste Alain, Willem en Peter, dank voor de fijne samenwerking. Dank voor het beoordelen van de vele prostaatbiopten van mannen uit de FUTURE-trial. Dank voor jullie kritische blik door de microscoop en dank voor het meelezen van mijn stukken.

Beste Hans (Kelder) en Ellen, dank voor jullie hulp bij het opstellen van het onderzoeksprotocol en uitvoeren van de statistische analyses.

Beste Kirsten en Christiaan, dank voor jullie fysische expertise bij het uitvoeren en opschrijven van het ex-vivo experiment.

Beste Lotty en Hans (Reitsma), dank voor jullie hulp bij het uitvoeren en opschrijven van de uitgebreide systematische review van de literatuur en meta-analyse. Dank voor de uitleg die moeilijke materie helder heeft gemaakt.

Beste urologen van het St. Antonius ziekenhuis, dank voor de begeleiding, het vertrouwen en de mogelijkheid om mijn wetenschappelijke ambities te ontplooien. In 2012 begon ik als ANIOS in jullie kliniek en na 1.5 jaar ben ik mij vrijwel volledig gaan richten op de wetenschap. Ik heb in mijn Antonius tijd altijd veel steun aan jullie als groep ervaren. Altijd geïnteresseerd in hoe de vorderingen van het onderzoek gingen. Met heel veel plezier ben ik nu weer terug onder jullie vleugels als uroloog in opleiding.

Beste urologen van het Canisius Wilhelmina ziekenhuis, dank dat ik als vreemde eend in jullie keuken mocht rondneuzen. Ik heb me altijd heel welkom gevoeld op de vele dinsdagen die ik in jullie kliniek heb doorgebracht. Dank voor de steun en interesse bij de vorderingen van het onderzoek. Dank voor de leuke etentjes op congressen.

Beste Antoinette en Noortje, dank voor jullie rol als hoeders vanuit de urologie en Antonius academie. Zonder jullie hulp was dit grootschalige onderzoeksproject niet tot stand gekomen. Ik ben heel trots op de professionaliseringsslag die er heeft plaatsgevonden binnen de research en development van het St. Antonius ziekenhuis en de afdeling urologie in het bijzonder, mede gefaciliteerd door jullie.

Beste Marije, Cynthia en Nicole uit het St. Antonius en beste Joost, Monique en Sandra uit het Canisius, dank voor jullie hulp bij het uitvoeren van de logistiek rondom de FUTURE-trial. Gezamenlijk hebben jullie heel wat vragenlijsten en MRI-verslagen rondgezonden. Ontzettend bedankt.

Beste Karin en Annette, dank voor het plannen van de wetenschapspoli. Dank voor jullie gezellige geklets, onuitputtelijke interesse in van alles en nog wat, en al vele jaren fijne samenwerking.

Beste poli medewerkers van de urologie uit het St. Antonius en Canisius, dank voor de hulp bij het afnemen van de vele prostaatbiopten en het scannen van al die formulieren.

Beste mannen die deelnamen aan de FUTURE-trial, dank voor het vertrouwen wat jullie in dit onderzoek en onze onderzoeksgroep hebben gehad. Ik heb gedurende het onderzoek mijn best gedaan jullie allen zo goed mogelijk te begeleiden. Ik hoop dat dit gelukt is.

Beste urologen van de verwijzingsklinieken, dank voor het verwijzen van patiënten vanuit 14 verschillende centra in Nederland.

Beste (oud) collega's uit het St. Antonius, Diakonessenhuis en Canisius, dank voor het vele werkplezier gedurende de afgelopen jaren. Dank voor de gezellige sfeer op de werkvloer, het vele lachen en de mooie borrels.

Beste vrienden, dank voor het aanhoren van mijn gemopper over mijn promotie en voor de benodigde afleiding zo nu en dan. Beste Govert dank voor de vele ritjes naar Nijmegen op en neer. Dank dat ik niet de enige ben bij wie het lijkt alsof het afronden van het op proefschrift eeuwig duurt.

Lieve familie, papa, mama, Anneke en Sjaak, dank voor jullie onuitputtelijke steun gedurende dit langdurige project en aanhoudende interesse in de voortgang van mijn promotie. De spreekwoordelijke marathon is eindelijk ten einde. Lieve papa dank voor het meelezen van de laatste stukken en je kritische taalkundige blik.

Allerliefste Marieke, mijn rots in de branding. Dank voor je onvoorwaardelijke steun van begin tot eind van dit project, je onuitputtelijke geduld bij het aanhoren van mijn gemopper en je begrip als ik weer eens iets moest doen voor mijn proefschrift. Dank voor het stimuleren van mijn ambities en voor het trappen op de rem als dat nodig was. Ik ben heel trots dat ik jouw man mag zijn. We zijn een hecht team, genieten van ons leven samen en hebben een mooi gezin gesticht. Ik hoop dat dat nog vele jaren zo mag zijn.

Lieve kleine Thomas, dank dat je mij laat inzien wat er nou écht belangrijk is in het leven. Zonder jou was dit proefschrift waarschijnlijk sneller afgerond maar ik ben dolgelukkig dat je in ons leven bent gekomen. Je bent recent grote broer geworden en ik ben ontzettend trots op je. Lieve Ella, welkom in onze familie. We zijn dolblij met je komst. Ik ben heel blij ik dit proefschrift net heb afgerond rondom je geboorte zodat ik meer knuffel tijd met jou heb.