

Extending multiparametric magnetic resonance imaging of prostate cancer

Spectroscopic and lymph node imaging

Carlijn Tenbergen

**RADBOD
UNIVERSITY
PRESS**

Radboud
Dissertation
Series

**Extending multiparametric magnetic resonance
imaging of prostate cancer
spectroscopic and lymph node imaging**

Carlijn Tenbergen

**Extending multiparametric magnetic resonance imaging of prostate cancer -
spectroscopic and lymph node imaging**

Carlijn Tenbergen

Radboud Dissertation Series

ISSN: 2950-2772 (Online); 2950-2780 (Print)

Published by RADBOUD UNIVERSITY PRESS

Postbus 9100, 6500 HA Nijmegen, The Netherlands

www.radbouduniversitypress.nl

Design: Proefschrift AIO | Guus Gijben

Cover: Jorieke Tenbergen

Printing: DPN Rikken/Pumbo

ISBN: 9789465151021

DOI: 10.54195/9789465151021

Free download at: <https://doi.org/10.54195/9789465151021>

© 2025 Carlijn Tenbergen

**RADBOUD
UNIVERSITY
PRESS**

This is an Open Access book published under the terms of Creative Commons Attribution-Noncommercial-NoDerivatives International license (CC BY-NC-ND 4.0). This license allows reusers to copy and distribute the material in any medium or format in unadapted form only, for noncommercial purposes only, and only so long as attribution is given to the creator, see <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

**Extending multiparametric magnetic resonance imaging
of prostate cancer
spectroscopic and lymph node imaging**

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 1 juli 2025
om 14.30 uur precies

door

Carlijn Josine Andrea Tenbergen
geboren op 8 februari 1992
te Zevenaar

Promotoren:

Prof. dr. ir. T.W.J. Scheenen

Prof. dr. J.P.M. Sedelaar

Manuscriptcommissie:

Prof. dr. J.A. Schalken

dr. E.C. Wiegiers (UMC Utrecht)

Prof. dr. P.J.L. De Visschere (Universitair Ziekenhuis Gent, België)

Table of contents

Chapter 1

Introduction	7
--------------	---

Section I: MRSI and DWI of the prostate at 3 T

Chapter 2

Evaluation of prostate DOT Engine and slaser sequence	33
---	----

Chapter 3

Improving magnetic field homogeneity in prostate MR imaging and spectroscopy using an add-on local external shim array coil	47
---	----

Chapter 4

Improving the Effective Spatial Resolution in 1H-MRSI of the Prostate with Three-Dimensional Overdiscretized Reconstructions	75
--	----

Section II: MR imaging of the prostate and lymph nodes at 7 T

Chapter 5

Ultra-high-field MR in Prostate cancer: Feasibility and Potential	101
---	-----

Chapter 6

The Potential of Iron Oxide Nanoparticle–Enhanced MRI at 7 T Compared With 3 T for Detecting Small Suspicious Lymph Nodes in Patients With Prostate Cancer	129
--	-----

Chapter 7

Discussion and future perspectives	151
------------------------------------	-----

Chapter 8

Summary	167
---------	-----

Chapter 9

Nederlandse samenvatting	173
--------------------------	-----

Appendices	181
------------	-----

Chapter 1

Introduction



General Introduction

The Prostate gland

The prostate is part of the male reproductive system. It consists of glandular tissue, structurally composed of lumina lined with epithelial cells, which are surrounded and supported by stroma with smooth muscle cells and connective tissue (Fig. 1b). The prostate gland produces and stores prostatic fluid, containing compounds such as enzymes, citrate, spermine, and prostate-specific antigen (PSA), and constituting around 20-30% of the semen^{1,2}. The seminal vesicles produce the bulk of the seminal fluid (65-75%). Together with spermatozoa, which make up about 2-5% of the volume of the whole ejaculate, prostatic fluid and seminal fluid are combined in the ejaculatory duct to form the complete semen, ready for ejaculation via the urethra. The prostate ensures male fertility as it controls the ejaculation process and supplies an energy source for sperm motility^{1,2}.

The prostate is anatomically divided into three glandular zones, with the central zone surrounding the ejaculatory ducts, the transition zone surrounding the proximal urethra, and the peripheral zone constituting the bulk of the prostatic glandular tissue covering the posterior and lateral aspects of the prostate (Fig. 1a). The anterior fibromuscular stroma covers the anterior of the prostate with muscle fibers and connective tissue. It is in the transition zone where a benign enlargement of the prostate (benign prostatic hyperplasia BPH) often occurs in men at an older age and leads to symptoms due to increased pressure on the urethra. Another common disease of the prostate, inflammation of prostate tissue called prostatitis, occurs in both transition and peripheral zone. Prostate cancer (PCa), on the other hand, most commonly arises from the peripheral zone (70% of cases, 30% in transition zone) and with its location posteriorly in the prostate, gives symptoms in a later stage, usually not until a stage of ingrowth in the surrounding tissues, such as bladder or rectum, or when the disease has metastasized to the lymph nodes and bones.

Prostate cancer

Prostate cancer is classified as an adenocarcinoma, developing primarily from the glandular part of the organ, and is currently the second most frequent cancer and the fifth leading cause of cancer death among men⁴, accountable for more than 14000 new cases and 3000 deaths in the Netherlands in 2022⁵. With older age as a known risk factor for prostate cancer and increasing population age, the incidence of PCa increased over the last years and is expected to rise further in coming years. The incidence shows also trends that can be related to the use of PSA as a screening tool, which allowed the detection of pre-symptomatic cancers⁶. PSA is produced by the

glandular epithelial cells and secreted into the lumen and subsequently glandular ducts. The disruption in the architecture of the glands in prostate cancer, however, causes secretion into the circulation with increased levels of PSA in the blood as a consequence⁷. With PSA not specific to PCa but also increased in BPH, PSA testing can lead to overdiagnosis and overtreatment of clinically insignificant cases and is therefore used with a bit more caution in the Netherlands from around 2010⁶. Over the last years, the incidence of PCa in the Netherlands has been rising again.

A tumor classification system is used to group PCa patients before treatment with a likely similar outcome. This is helpful in discussing prognosis and treatment recommendations and comparing data of, and designing trials on relatively homogeneous populations. For staging of PCa the Tumor, Node, Metastasis (TNM) classification is used, a schematic representation of anatomic tumor extent. Initial PCa assessment relies on a digital rectal examination to determine the T-stage (Fig. 2A). Traditionally, a CT or bone scan is used for N- and M-stage⁸. With developments in imaging modalities, discussed in the next sections, additional staging information is nowadays available and in clinical practice is incorporated for classification.

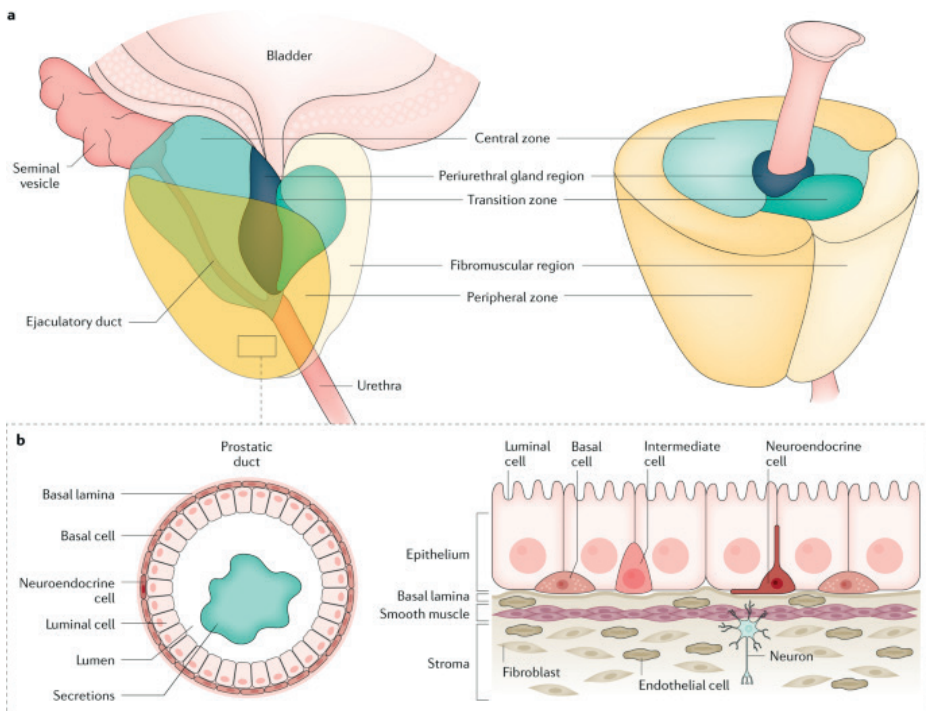


Figure 1: Anatomy and histological structure of the human prostate gland. **a)** The anatomical regions, so called zones, of the prostate. **b)** The structural composition of prostatic tissue. Figure adapted from Rebello et al.³

Histopathological examination of biopsy tissues is needed to confirm the presence of prostate cancer with the accompanying Gleason score based on histological tumor architecture and de-differentiation of tumor cells. Normal healthy tissue (the lowest score) represents small uniform and well-differentiated glands, while the highest pattern grade is given in the case of poorly differentiated structures with only occasional gland formation (Fig. 2B). The Gleason score (GS) of biopsy-detected PCa comprises the Gleason grade of the most extensive (primary) pattern, plus the second most common (secondary) pattern⁹. This pathological tumor grade is reflective of tumor aggressiveness. The most recent version, the 2019 ISUP-endorsed grading system, assigns the different Gleason scores to 5 Grade Groups (Fig. 2C) with each grade group representing a different prognosis¹⁰.

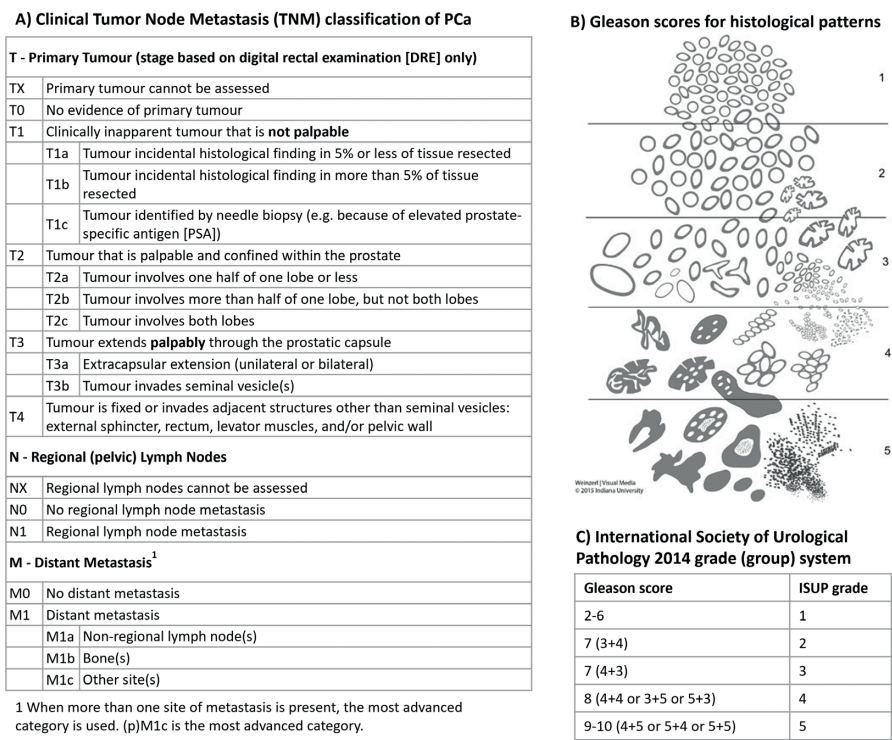


Figure 2: Classification systems for prostate cancer: **A)** TNM classification, **B)** Gleason scores for histological patterns and **C)** ISUP grading system of Gleason scores.

The pathological grading is combined with clinical information on tumor extent and PSA level to define PCa risk groups (Table 1). This risk group classification by the European Association of Urology (EAU) groups patients with a similar risk of

biochemical recurrence after local treatment, aimed to adapt PCa management according to that risk¹¹. Next to these risk groups, the term ‘clinically significant’ is widely used to differentiate PCa that may cause morbidity or death in a specific patient from types of PCa that do not. This distinction is important, as insignificant PCa has a high incidence and high risk of over-treating, with the treatment itself possibly causing side effects and thereby more harm to patients than the tumor itself. The definition though is not unambiguous, as the distinction between significant and insignificant is a balance between tumor and patient factors. Low-risk PCa is insignificant in almost all men and high-risk PCa is significant in almost all men, except when life expectancy is limited. The intermediate risk group, though, shows heterogeneous outcomes¹².

Table 1: Risk stratification of prostate cancer based on PSA testing, histopathological and DRE examination, and conventional imaging for lymph nodes.

EAU risk groups for biochemical recurrence of localized and locally-advanced prostate cancer			
Definition			
Low-risk	Intermediate-risk	High-risk	
PSA < 10 ng/ml and GS < 7 (ISUP grade 1) and cT1-2a*	PSA 10-20 ng/ml or GS 7 (ISUP grade 2/3) or cT2b*	PSA > 20 ng/ml or GS > 7 (ISUP grade 4/5) or cT2c*	any PSA any GS (any ISUP grade) cT3-4* or cN+**
Localised			Locally advanced

* based on DRE

** based on CT/bone scan

mpMRI

Over the last decades, the clinical utility of magnetic resonance imaging (MRI) of the prostate has increased. With the use of scanners at high magnetic field strengths (3 Tesla), and the development of functional imaging sequences, the role of MRI in prostate cancer management has rapidly expanded. Based on an expert consensus in 2012, the European Society of Urogenital Radiology (ESUR) published the Prostate Imaging Reporting and Data System (PI-RADS), to standardize the evaluation and reporting of prostate MRI. Nowadays MRI provides detailed visualization of the prostate after first indications of prostate disease with elevated PSA levels and positive digital rectal exam.

Both anatomical and functional information about the prostate can be derived with multiparametric MR imaging (mpMRI)¹³, with a clinical mpMRI examination consisting of the acquisition of T2-weighted (T2w), diffusion-weighted (DWI) and

gadolinium-based dynamic contrast-enhanced images (DCE) (Fig. 3). A detailed description of underlying MR physics can be found by, for instance, Bottomley¹⁴ and Levitt¹⁵.

T2w-MRI

T2-weighted imaging depicts anatomy because of the variety in transverse relaxation times (T2) of the different tissues in the prostate. This pulse sequence is ideal for distinguishing the different prostate zones: the peripheral zone often appears with high signal intensity due to its high glandular ductal tissue content opposed to the transitional- and central zones that often have lower signal intensity. Lesions, with high cellularity and therefore decreased intensity, can be localized and morphologically assessed on their shape and size. T2w imaging is the dominant MR series in the overall assessment for abnormalities in the transition zone in PI-RADS. PCa is characterized by features such as a homogenous moderately hypointense signal, non-circumscribed or ill-defined margins, and lenticular or fusiform shape, in contrast to a circumscribed hypointense or heterogenous encapsulated nodule in BPH¹⁶. T2w imaging of clinically significant cancer in the peripheral zone shows round or ill-defined hypointense focal lesions, however not specific as these can also indicate prostatitis or hemorrhage. To determine whether an abnormal region is suspicious for clinically significant PCa, T2w imaging should be used in combination with the other two functional imaging techniques in the mpMRI exam to improve sensitivity and specificity. T2w imaging is also the dominant MRI modality to assess the extent of the tumor, with possible growth outside the prostatic capsule or invasion of the seminal vesicles.

DWI-MRI

Diffusion reflects the motion of water molecules through tissue. Water molecules are in constant motion, with free random diffusion when this is in an unrestricted environment. In the body the intra- and extracellular movement of molecules is restricted by interaction with boundaries; tissue compartments, cell membranes, or intracellular compartments that form barriers to diffusion. The more barriers water molecules encounter in a certain time interval, the smaller the mean movement (diffusion) distance. The degree of restriction to water diffusion in biological tissue is inversely correlated to tissue cellularity and the integrity of cell membranes.

Diffusion-weighting in MR images is acquired by applying a pair of diffusion-sensitizing gradients, at a certain strength, with a certain duration and with a certain spacing, together referred to by the term b-value. By varying the b-value,

the sensitivity of the diffusion sequence is adjusted determining what type of diffusion is visible. With low b-values, a large diffusion distance is needed to cause signal loss, which is the case in blood vessels, highlighting tissue perfusion. With high b-values, the sequence is sensitive to water molecules that move slower or are more restricted, representing water movement in the extra- and intracellular compartments. The use of DWI at different b values provides qualitative information on tissue cellularity and structure and can be used for lesion detection or characterization. Diffusion restriction can also be assessed quantitatively by the apparent diffusion coefficient (ADC). The ADC is calculated based on the signal intensity changes of at least two b-values and can be displayed as a parametric map. The higher the ADC value, the more freely the water molecules can move.

In PI-RADS, DWI is the dominant mpMRI series for assessing peripheral zone lesions. Scores are assigned based on the lesion's appearance on ADC maps and DWI images at (calculated) high b values ($\geq 1400 \text{ s/mm}^2$). PCa exhibits a reduced diffusion of water compared to normal prostate tissue due to the loss of glandular tissue and relative increase in cell density. PCa lesions, as a result, show a low signal on the ADC map and preservation of signal in the high b-value image. In the transition zone, BPH can also show restricted diffusion; therefore DWI is less accurate for PCa detection in the transition zone. ADC values have been reported to correspond to histopathological findings: decreasing ADC values correlate with increasing Gleason scores. While there is considerable overlap between healthy tissue, low-grade cancers, and high-grade cancers, ADC values might assist the differentiation of lesions¹⁶⁻¹⁸. Quantification results may vary though with scan protocols and DWI quality is sensitive for artifacts caused by bowel peristalsis, rectal gas, or hip prosthesis.

DCE-MRI

DCE MRI is acquired with a sequential series of fast T1w scans before, during, and after the intravenous administration of gadolinium contrast agent, showing tissue vascularity and microvessel permeability. PCa often induces angiogenesis and increased vascular permeability compared to normal prostatic tissue resulting in an early and increased enhancement followed by a rapid washout of the contrast. Next to low-grade and clinically significant PCa, also BPH and inflammation show this earlier and more pronounced signal enhancement on T1w images compared to healthy prostate tissue. Therefore the value of this sequence in the differentiation of lesions is limited, and in PI-RADS guidelines DCE is included in the mpMRI exam to not overlook small significant PCa lesions or in the case of failing quality of DWI or T2w series¹⁶. DCE-MRI remains essential in the assessment of local recurrent disease following prior treatments that change prostate morphology¹⁶. As some

gadolinium-based contrast agents lead to adverse events and require an IV infusion line, MRI protocols with only the dominant sequences T2w and DWI are also studied for diagnostic performance¹⁹. These bi-parametric protocols could have the additional potential benefits of shortened examination time, and reduced costs¹⁶.

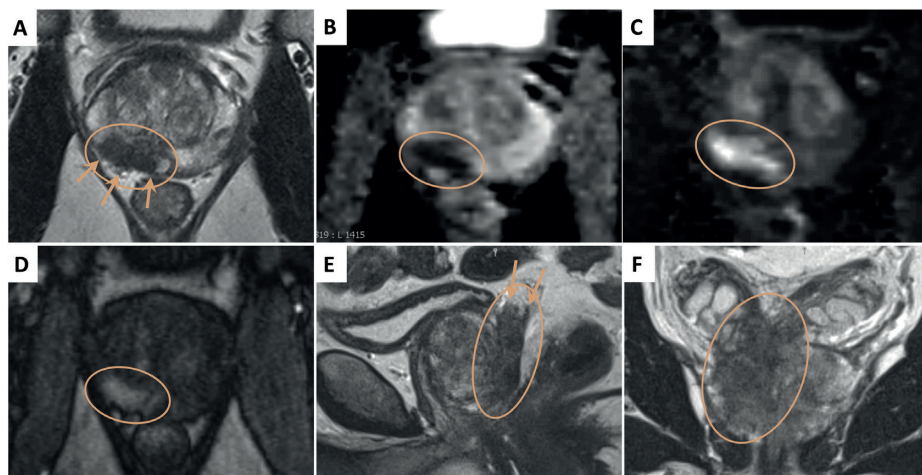


Figure 3: mpMRI of a lesion, scored PI-RADS 5. **A)** Axial, **E)** sagittal, and **F)** coronal T2W Images, show a low-signal lesion midprostate, PZ (orange circles). DWI shows a **B)** focal “black” area on the ADC map with a low ADC value ($600 \text{ mm}^2/\text{s}$) and **C)** focal “white” area on the high b-value image (1400 s/mm^2). **D)** On the DCE image, this lesion shows early focal enhancement. **A)** Axial T2W image shows extracapsular extension (arrows) MRI stage T3a. **E)** Sagittal T2W image shows seminal vesicle infiltration (arrows) MRI stage T3b. Figure adapted from Israël et al.²⁰

MRI in localized prostate cancer

With the standardized PI-RADS analysis of mpMRI acquisitions, lesions get a score from 1 to 5 which indicates the likelihood of clinically significant cancer. MRI shows a good sensitivity for the detection of PCA with ISUP grade >2 when correlated with prostatectomy specimens, especially for lesions with a diameter $>1 \text{ cm}$ or size $>0.5 \text{ cc}$ and with increasing detection rates for higher grade tumors²¹⁻²³. However, mpMRI is less sensitive in identifying ISUP grade 1 PCa as it could identify less than 30% of ISUP grade 1 PCa lesions $<0.5 \text{ cc}$ that were identified on prostatectomy specimens²¹. Extracted from recent studies using PI-RADS v2.1, the average positive predictive value for clinically significant cancer of lesions was 20% (13–27%) for lesions with PI-RADS 3 score, 52% (43–61%) for PI-RADS 4, and 89% (76–97%) for PI-RADS 5²⁴.

The PI-RADS score is used to decide on the need for biopsies. While previously systemic biopsies were performed using trans-rectal ultrasound (TRUS), which is

prone to biopsy sampling errors, MRI is taking over the role of the first diagnostic method and enables selective sampling of high-risk regions with MRI-informed targeted prostate biopsies (MRI/US fusion biopsies or occasional MRI-in bore biopsies). Targeted biopsy improves the detection of clinically significant PCa compared to systematic biopsy, at a detection ratio of 1.12²⁵. Less insignificant PCa is found with targeted biopsies compared to systematic biopsies (detection ratio of 0.61)²⁵. Thereby, acquiring a pre-biopsy MRI scan can reduce overdiagnosis of insignificant PCa as biopsy can be avoided after negative MRI results in a pooled 33% of the patients at a risk of a patient having csPCa and a negative mpMRI scan result at a pooled 3%²⁶.

Besides the identification of clinically significant PCa lesions, it is also possible to identify extra-prostatic extension of the lesion and seminal vesicle invasion on mpMRI. Being able to identify the extent of the tumor improves localized disease staging which is essential for personalized treatment planning¹¹. mpMRI parameters, such as tumor extent and lesion size, and Gleason grade from a targeted biopsy are being incorporated into risk classification systems. By adding a fourth category of very high risk and reclassifying patients, with considerable upgrading of patients to higher risk groups, recurrence prediction is significantly improved²⁷⁻²⁹.

Next to this localization and characterization of PCa, mpMRI enables focal minimally invasive treatment options. Whereas currently radical prostatectomy and high-dose conformal radiotherapy are the curative treatment options for localized disease, high-intensity focused ultrasound, cryoablation, and focal laser ablation may become an alternative to reduce treatment-related morbidity³⁰. mpMRI may also play a crucial role in the evaluation of recurrent prostate cancer after any whole gland or focal treatment.

The qualitative interpretation of mpMRI in the assessment of prostate cancer, however, remains challenging and is prone to inter-reader variability. The PI-RADS reading standard was started with the intention of reducing this interpretation variation and has been updated since its introduction in 2012, along with improvements in mpMRI acquisition, to the current version 2.1 in 2019. The PI-RADS v2.1 shows a pooled sensitivity of 0.90 (95% CI: 0.87–0.92) and specificity of 0.62 (95% CI: 0.59–0.64) for the detection of clinically significant prostate cancer in the whole gland. A moderate-to-substantial inter-reader agreement for PI-RADS v2.1 was found (reported k-statistics ranging from 0.42 to 0.70)³¹. This inter-reader variability and the range in values found remains an unsolved problem despite training, particularly when mpMRI is used in centers with little experience¹³. This

dependence on radiologists' interpretation is unfavorable and demands, especially in an active surveillance setting, the use of quantitative measures for correct follow-up on lesions.

Spectroscopic imaging of the prostate

Besides the sequences used in clinical mpMRI, MR spectroscopic imaging (MRSI) can offer additional functional information on prostatic lesions based on the presence of certain metabolites.

While MR imaging uses the signal of water and lipids to image tissues, a multitude of molecules can be visualized by MRSI. This modality exploits the specific resonance frequencies (chemical shifts) that MR-sensitive nuclei, like ^1H , in a molecule possess, and which are influenced by their chemical and physiological environment. MRSI combines spectroscopic techniques with phase encoding to acquire MR spectroscopic data in multiple voxels over a 3D volume of interest. The Fourier transform of an MRSI signal (time domain) obtained from a location in the body results in a spectrum (frequency domain) with signal peaks at specific frequencies from which the identity and metabolite levels present at that location can be deduced. As tissue concentration of biochemicals is much lower than water, their detection at sufficient signal-to-noise ratios is only possible at a relatively low spatial resolution compared to MRI and only with accurate lipid and water suppression.

Malignant prostate tissue shows lowered levels of citrate, likely from a lower secretion of citrate in the lumen and reduced luminal space in PCa and increased choline levels, as a sign of increased cell membrane synthesis and degradation, compared to healthy tissue (Fig. 4)^{32,33}. Ratios including these metabolites measured by MRSI in combination with anatomical T2w MRI can identify and localize prostate cancer^{34,35}. Moreover, previous work in a multi-center setting has also shown a correlation between these quantitative metabolite ratios and Gleason Grade groups³⁶, indicating a role for ^1H -MRSI in characterizing PCa. While these results promote the use of MRSI as an imaging biomarker in PCa and therefore was included in the original PI-RADS, the technique comes with challenges in implementation and interpretation and limited robustness³⁷. The demand for specific expertise and relatively long acquisition times (of 5-10 min) have excluded this technique from the latest PI-RADS version for routine mpMRI examinations¹⁶.

Essential for the acquisition of high-quality MRSI data is the optimization of the main magnetic field (B_0 field) homogeneity, a process called shimming. Inhomogeneous

fields lead to faster decay of the apparent transverse magnetization in a voxel. As a result, the center frequency varies over the field of view (FOV), causing spectra in different voxels to lack alignment. These off-resonance effects can affect water suppression and cause lipid contamination of spectra within the prostate³⁷. B0 field inhomogeneity within a voxel can cause spectral line broadening, resulting in an overlap of signals. For the prostate, this effect will complicate the separation of choline from spermine and creatine, as their resonant frequencies are close to each other, and affect the reliability of their quantification. With the prostate located within the pelvis, the motion of gas through the bowel or in the rectum can influence the B0 field and therefore image quality, mostly at the posterior part of the prostate³⁸.

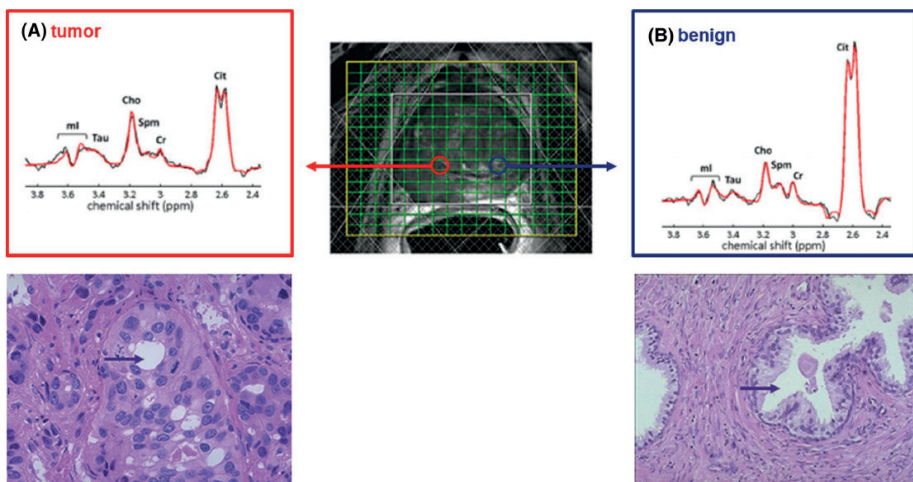


Figure 4: 3D MRSI of a patient with histopathology-confirmed prostate cancer. The T2w MR image is overlaid with the MRSI voxel grid, with the field of view indicated with the yellow box. The location of a tumor voxel **A**) and a benign voxel **B**) are indicated with circles to better represent their actual shape. Representative MR spectra illustrate decreased citrate and spermine and increased choline signals in the tumor lesion. Histopathology slides illustrate the corresponding reduced luminal space in a cancer lesion in comparison with healthy prostate tissue (purple arrow). Figure adapted from Stamatelatos³⁷

In localized MRSI acquisitions, a standard Cartesian grid is sampled in k-space, spatially encoded by phase encoding in 3 directions, similar to phase-encoding in MR imaging³¹. With a finite number of phase-encoding steps, the spatial origin of the signal does not coincide with the rectangular voxel representation in the MRSI grid. Better represented, from the limited number of k-space steps in MRSI and the properties of the Fourier transform, the signal in a voxel after FT is described by the spatial response function (SRF) (Fig. 5). The SRF is a spatial weighting function, indicating the distribution of signal contributions to the reconstructed signal of a particular voxel³⁹. The SRF has the shape of a sinc-function with a broadened main

lobe, which extends somewhat beyond the boundaries of the nominal voxel and with a full width at half maximum which corresponds to the enlarged effective voxel size, and side lobes that carry signals from far away regions into the voxel. This contribution from other spatial regions to a given voxel is called voxel bleeding⁴⁰, and may be significant from outside the displayed grid boundaries or nominal voxel volumes⁴¹. Application of a suitable filter (Hamming filter) in k-space can smooth the SRF to minimize signal contamination, though at the cost of a larger effective voxel size.

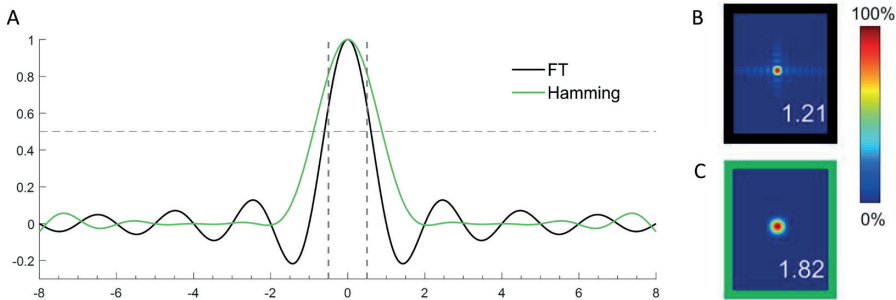


Figure 5: **A)** SRF in 1D after Fourier transform of k-space (black) and after Hamming filtering (green), dashed lines indicate nominal resolution width and height at half maximum **B)** 2D SRF of a central voxel after Fourier transform, and **C)** 2D SRF after Hamming filtering, numbers indicate width at half maximum relative to a nominal voxel width of 1 (adjusted from⁴²).

For the prostate, MRSI voxels of approximately 0.9 cm^3 are used to acquire sufficient metabolite signal. This low spatial resolution relative to the size of the prostate results in voxel bleeding with the SRF side-lobes extending over the full FOV of the MRSI grid, covering large parts of the prostate. Voxel bleed will be problematic as this spread of signal hinders precise localization of the signals of interest and causes the interference of other metabolites in the region of interest, specifically residual lipid signals outside of the prostate extending into the prostate tissue. Thereby, intravoxel variations of B_0 cannot be adequately addressed, and any line broadening resulting from it will remain. Hence, depending on the exact appearance of the SRF, spectral information bearing their specific local B_0 offsets from all over the FOV is “imported” into the voxel of interest.

Since the initial studies of MRSI in the prostate, new acquisition methods have shown substantially improved MRSI performance⁴³. Improvements in B_0 homogeneity and spatial localization, leading to robust acquisition and processing, may enhance again its clinical value in mpMRI. The big advantage of MRSI is that it can give a quantitative

measure for prostate cancer lesions, which could be especially beneficial in a repeat-MRI setting e.g. in active surveillance.

Imaging of lymph node metastases

After the detection and classification of the primary PCa tumor, the next step is to assess the presence of metastases in patients in the intermediate and high-risk groups. Determining if the disease has a local or systemic presentation defines patient prognosis and treatment strategy, e.g. with curative or palliative intent. One of the routes by which PCa spreads is via lymph nodes, with lymph node metastases as a result. To determine the lymph node status in a patient, an extended pelvic lymph node dissection is the reference standard⁴⁴ with histopathology of excised nodes establishing the clinical nodal-stage diagnosis. These surgical staging procedures have disadvantages as they are associated with (co-)morbidity, can miss small positive nodes within the resection field, and will miss any positive nodes outside the resection field⁴⁵⁻⁴⁷. Thereby, the clinical benefit of removing metastatic lymph nodes is a subject of debate as studies show similar clinical outcomes in patients in whom lymph node dissection was or was not performed at radical prostatectomy^{48,49}.

There is a great clinical need for precise, reliable, and non-invasive nodal staging in patients with prostate cancer and ⁶⁸Ga- or ¹⁸F-PSMA-PET/CT is fulfilling most of these requirements. Traditionally, only an increased size and deviating shape of lymph nodes on a CT or MRI scan has been a non-invasive indicator for the possible presence of metastases in the nodes. The often small size of lymph node metastases in PCa^{50,51} limits the value of lymph node assessment by CT or MRI, which explains the recent advances in functional imaging techniques. Over the last years, multiple small molecules with high binding affinity to prostate-specific membrane antigen (PSMA) have been labeled with positron emitters (⁶⁸Ga or ¹⁸F) to enable whole-body tumor detection using PET/CT, for possible clinical use in prostate cancer patients. PSMA is a transmembrane protein that is highly overexpressed in prostate cancer compared to healthy prostate cells, both in the primary tumor as well as metastatic sites. With a large extracellular part, it presents as an ideal target for an imaging agent to detect metastatic tumor cells. Thereby, the expression is positively correlated to tumor aggressiveness⁵². Initial results of PSMA-PET/CT showed promising results for detecting lymph node metastases. This imaging technique outperformed anatomical imaging by CT or MRI⁵³ with good specificity (67-100%, pooled 0.95) though high variation in reported sensitivity (23-100%, pooled 0.58)⁵³⁻⁵⁵. Sensitivity is hindered by the spatial resolution of PET/CT, around 4-5 mm⁵⁶, which still makes it difficult to detect lymph nodes smaller than 5 mm.

For detection of those smallest LN, we need to resort to the spatial resolution possible with MRI, though now in combination with a functional contrast agent. The excellent soft-tissue contrast of MRI enables visualization of lymph nodes within the surrounding lipid tissue. Using a functional MRI contrast like ferumoxtran-10, where a solution of ultra-small iron-oxide nanoparticles (USPIO) is intravenously administered in patients⁵⁰, one can discriminate between normal lymphatic tissue and metastatic lymph nodes. These particles are internalized by macrophages that accumulate inside normally functioning lymph nodes (Fig. 6). The presence of paramagnetic iron oxide particles locally disturbs the magnetic field homogeneity, causing MR signal loss in healthy lymph nodes on T2*-weighted imaging. Lymph nodes that are (partially) occupied with metastatic cancer cells do not accumulate the nanoparticles and retain MR signal intensity. This mechanism provides a positive contrast for lymph node metastases 24 to 36 hours after administration.

The lower limit of detectable lymph node size with this imaging modality is not based on the contrast agent or level of activity as in PET/CT, but on the attainable spatial resolution by MRI which is much higher than for PET/CT. Initial studies regarding the application of USPIO to prostate cancer imaging, since the early 2000s, were performed at a main magnetic field strength of 1.5 T with 2D multislice series and a spatial resolution of around $0.56 \times 0.56 \times 3$ mm⁵⁷. With these resolutions, USPIO-enhanced MRI reached sensitivities of up to 90% and specificities of up to 96% for nodal involvement in several types of cancer⁵⁸.

The added value of USPIO-enhanced MRI has already been shown at 1.5 T as studies found lymph nodes outside the standard PLND area and standard radiation field⁵⁹⁻⁶¹. This indicates that lymph node imaging can avoid underestimation of metastatic disease spread and lead to a more accurate match between treatment and disease extent. Thereby, metastases were detected in normal-sized lymph nodes that would not appear suspicious for metastases on regular MRI imaging^{50,51,60}. Detecting small lymph node metastases or detecting limited metastatic disease provides a more accurate prognosis and provides opportunities for more patient-tailored therapy.

Since 2014, with the reintroduction of 'nano-MRI', USPIO-enhanced MRI has been performed with 3D T2* weighted acquisitions at 3 T, allowing a resolution of 0.85 mm isotropic, improving the detection of lymph nodes suspicious for metastases, especially those smaller than 5 mm⁵⁷. While imaging at 7 T comes with challenges for body imaging that were successfully overcome⁶², this ultra-high field strength offers a more pronounced T2* decrease in non-metastatic lymph nodes due to increased susceptibility effects, which increases the signal difference

between USPIO accumulating healthy lymph nodes and metastatic lymph nodes⁶³. Thereby, 7 T offers an increase in SNR which can be used to further increase spatial resolution, allowing a resolution of $0.66 \times 0.66 \times 0.66$ mm for body imaging⁶².

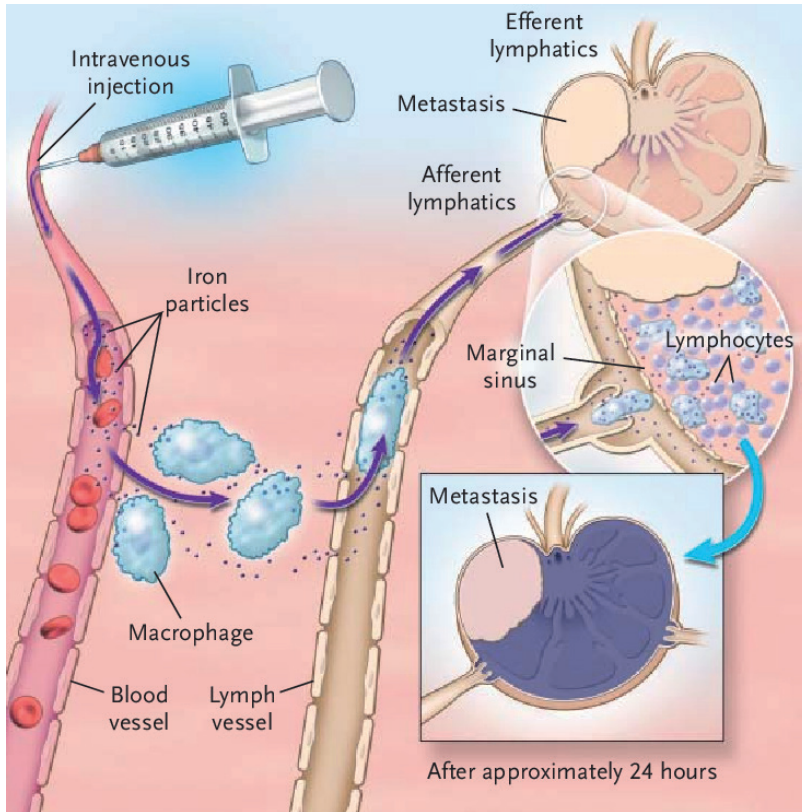


Figure 6: Mechanism of action of USPIO particles. The USPIO particles gain access to the interstitium and are drained through lymphatic vessels. The particles are internalized by macrophages that accumulate inside normally functioning lymph nodes. Disturbances in lymph flow or in nodal architecture caused by metastases lead to abnormal patterns of accumulation of USPIO particles, which are detectable by MRI. Figure adapted from Harisinghani et al.⁵⁰

As the described developments in imaging make it possible to detect the first small lymph node metastasis in PCa, this disease stage, called the oligometastatic stage, is currently seen as a distinct clinical disease state between locally confined and systemic disease. Oligometastatic disease is defined as early metastatic disease with few (typically ≤ 5) loco-regional metastatic lesions⁶⁴⁻⁶⁶, as determined on PSMA PET/CT.

With the parallel expansion of possible treatments, enabling image-guided surgery, focal ablations, or radiotherapy targeted at metastases, sensitive detection of these first small lymph node metastases is essential. If lymphatic spread has only just begun, an early and accurate, targeted, image-guided focal treatment of the first metastases could delay the course of the disease, and potentially provide a cure⁶⁷. At the same time, increased certainty of the absence of lymph node metastases is important as it could prevent precautionary overtreatment. Only a few prospective trials have been completed that assess metastasis directed therapy, and indicate a safe and possibly beneficial metastasis-directed therapy in oligometastatic disease⁶⁸. Still, disease recurrence is common in the treated cohort of patients with oligometastatic disease, due to the heterogeneous patient group. While the underlying biology of the various forms of oligometastatic disease state is not completely understood, genomic mutations appear to have prognostic value in this patient population⁶⁸. Stratification of patients and optimizing metastasis-directed therapy asks for accurate prediction of metastatic potential of primary tumors and accurate detection and monitoring of oligometastatic disease. The required predictive and prognostic imaging techniques indicate a further increasing impact of imaging in PCa management.

General goal of the thesis

Scientific work over the last decade has stimulated and supported the routine use of mpMRI as a reliable and sensitive noninvasive imaging modality for detecting and characterizing focal regions within the prostate. Clinical guidelines have incorporated mpMRI as a recommendation in men who are suspected of having clinically significant disease to be performed before biopsy. The mpMRI exam with the resulting PI-RADS score serves to determine the need for a biopsy and to direct the biopsy procedure. This role of mpMRI in diagnosing and local staging of PCa, which influences the prognosis and proposed therapy, demands high accuracy. After PCa is diagnosed, mpMRI could establish a role in the subsequent management of the disease. When further improvements are established, mpMRI could prove of additional value for determining the extent of the disease by assessing lymph node involvement and for monitoring the disease over time. This thesis covers several studies aimed to optimize the technical aspects of MRI of the prostate, both on software and hardware, aiming to facilitate the assessment of prostate cancer.

For assessing the local prostate lesion, while the accuracy of prostate biopsy is improved with the MRI-pathway, a biopsy is still not ideal to perform repeatedly in an active surveillance setting. PSA values are used as a quantitative signaling marker but lack the specificity to pass as a follow-up measure. Quantitative mpMRI parameters are desired to decrease the high inter-reader variability of PI-RADS and provide a reliable follow-up measure in a repeat setting. For MRSI to provide a reliable quantitative assessment of prostate cancer, we have to improve this technique on robustness so it can be more easily applied again in the clinic, as in the original PI-RADS.

For staging the lymph node status of PCa, image-based assessment of lymph node metastases has led to the recently defined oligometastatic stage. Pathological assessment and correlation of pelvic lymph nodes is not easy, while sensitive detection of these first small lymph node metastases is essential for metastases-directed therapy to be possible. USPIO-enhanced MRI can play a role in the staging of PCa and acquiring this technique at a magnetic field strength of 7 T holds the promise of detection of small lymph nodes.

By extending mpMRI with ^1H -MRSI and USPIO-enhanced techniques, we aim to assess the aggressiveness of PCa lesions and the spread of the disease to lymph nodes. This could enable the prediction of metastatic potential of primary tumors and accurate detection of oligometastatic disease, leading to accurate staging and personalized image-based treatment.

Outline of the thesis

The first section covers two studies that were performed in close collaboration with companies. A direct link to industry, with a large company as Siemens on MR software and with a small company MRShim on MR hardware, can help in ensuring the performed studies have more than a scientific impact and can be directly applied in the clinic. In **Chapter 2** we evaluate a scanning workflow protocol from Siemens, in which initial automatic segmentation of the prostate aids setting up subsequent sequences. This workflow is aimed at enabling easy performing MRSI next to the clinical mpMRI sequences, improving usability as setting up is made easier and can be done while scanning previous sequences. In **Chapter 3**, we collaborated with the company MRShim to develop and analyze an add-on local shim array to ensure a homogeneous main magnetic field over the prostate. With

this additional hardware, we aim to ensure a robust quality of DWI and MRSI, as artifacts caused by bowel peristalsis, rectal gas, or hip prostheses can be minimized.

Next to solutions for fast and robust acquisition of MRSI, software improvements can also be directed to the elaborate processing of acquired MRSI data. We have successfully implemented a post-processing method on MRSI data in **Chapter 4**, to increase the quality of spectra and the spatial resolution of metabolite maps and hence their match to underlying anatomical structures.

While all data in the chapters so far was acquired with the clinical 3 T MR systems at the Radboudumc, the second section covers ultra-high field, 7 T, MRI. At this higher magnetic field strength, research scanners with increased sensitivity and spectral resolution hold the promise of imaging and spectroscopy of the prostate with unprecedented detail. **Chapter 5** gives an overview of the challenges that come with this field strength and solutions that were found over the years for body imaging on 7 T. Furthermore, the first, different methods of acquiring mpMRI of prostate cancer at 7 T were reviewed in this chapter. One application of this ultra-high field, the detection of lymph nodes suspicious for metastases is described in **Chapter 6**, where we compared USPIO-enhanced MRI on 3 T and 7 T for detecting small lymph nodes in prostate cancer, concluding that we actually can visualize more small lymph nodes with 7 T.

Finally, **Chapter 7** provides a discussion of the findings and future perspectives, followed by a summary of the work presented in this thesis in **Chapter 8 and 9**.

References

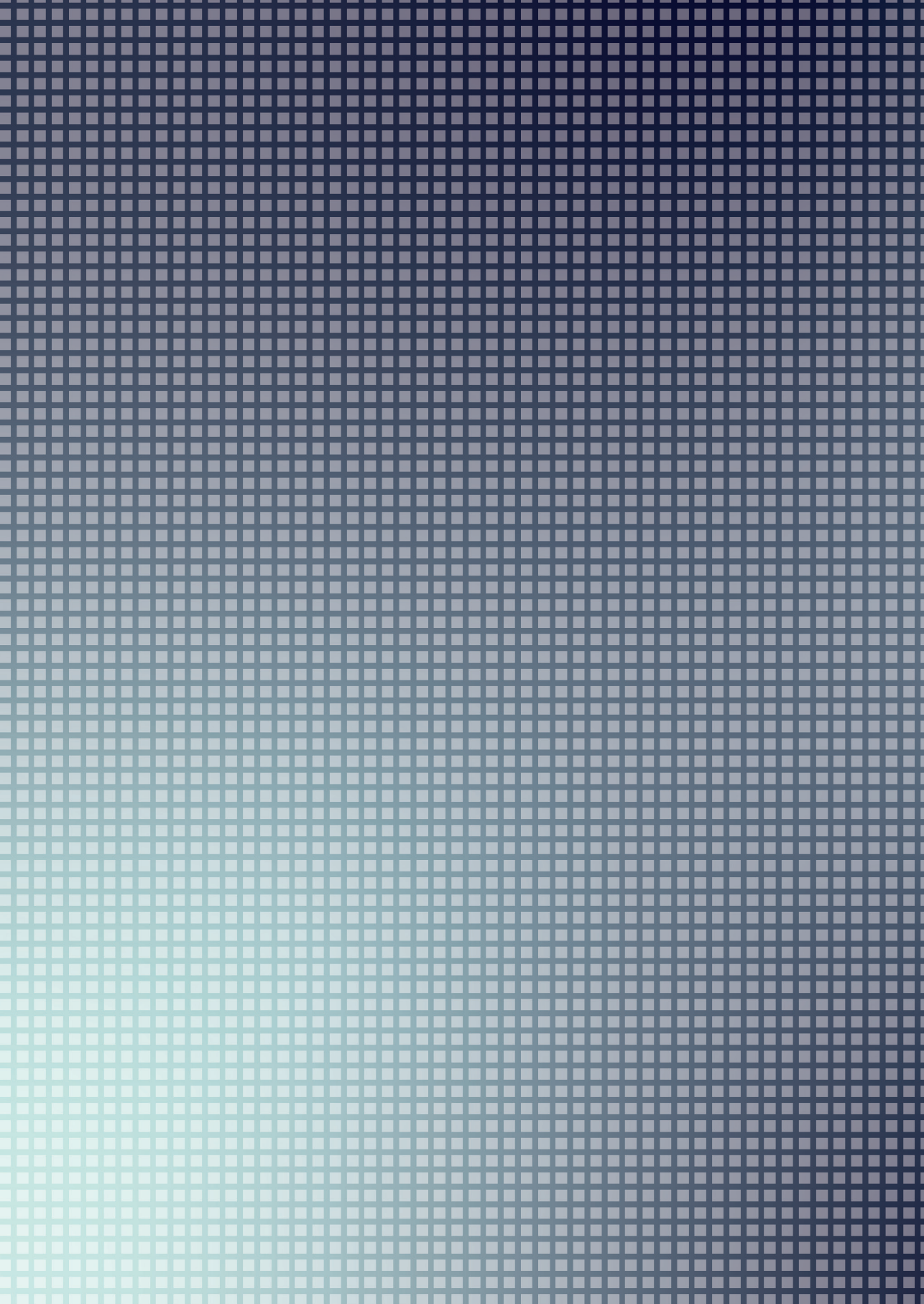
- 1 Mycielska ME, Patel A, Rizaner N, Mazurek MP, Keun H, Patel A, et al. Citrate transport and metabolism in mammalian cells. *BioEssays* 2009;31(1):10-20.
- 2 Verze P, Cai T, Lorenzetti S. The role of the prostate in male fertility, health and disease. *Nat Rev Urol* 2016;13(7):379-86.
- 3 Rebello RJ, Oing C, Knudsen KE, Loeb S, Johnson DC, Reiter RE, et al. Prostate cancer. *Nature Reviews Disease Primers* 2021;7(1):9.
- 4 Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024; 74(3): 229-263.
- 5 Nederlandse Kankerregistratie (NKR), IKNL. Obtained via nkr-cijfers.iknl.nl, on Oct 12th 2024.
- 6 IKNL. Kanker in Nederland; trends & prognoses tot en met 2032. 2022:66-8.
- 7 Stenman UH, Leinonen J, Zhang WM, Finne P. Prostate-specific antigen. *Semin Cancer Biol* 1999;9(2):83-93.
- 8 Brierley JD, et al.,. The TNM Classification of Malignant Tumours, 8th Edition - UICC International Union Against Cancer.; 2017.
- 9 Epstein JI, William C. Allsbrook J, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *American journal of Surgical Pathology* 2005;29(9):1228-42.
- 10 Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. *Eur Urol* 2016;69(3):428-35.
- 11 Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2021;79(2):243-62.
- 12 Kane CJ, Eggener SE, Shindel AW, Andriole GL. Variability in Outcomes for Patients with Intermediate-risk Prostate Cancer (Gleason Score 7, International Society of Urological Pathology Gleason Group 2–3) and Implications for Risk Stratification: A Systematic Review. *European Urology Focus* 2017;3(4):487-97.
- 13 Stabile A, Giganti F, Rosenkrantz AB, Taneja SS, Villeirs G, Gill IS, et al. Multiparametric MRI for prostate cancer diagnosis: current status and future directions. *Nature Reviews Urology* 2020;17(1):41-61.
- 14 Bottomley PA. The Basics. *eMagRes.* 2015, Vol 4: 505–524.
- 15 Levitt MH. *Spin Dynamics: Basics of Nuclear Magnetic Resonance.* Second ed.: John Wiley & Sons Ltd; 2008.
- 16 Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *European Urology* 2019;Sep(76):340-51.
- 17 Hambrock T, Somford DM, Huisman H, Oort IMv, Witjes JA, Hulsbergen-van de Kaa C, et al. Relationship between Apparent Diffusion Coefficients at 3.0-T MR Imaging and Gleason Grade in Peripheral Zone Prostate Cancer. *Radiology* 2011;259(2).
- 18 Boesen L, Chabanova E, Løgager V, Balslev I, Thomsen HS. Apparent diffusion coefficient ratio correlates significantly with prostate cancer gleason score at final pathology. *Journal of Magnetic Resonance Imaging* 2015;42(2):446-53.

- 19 Belue MJ, Yilmaz EC, Daryanani A, Turkbey B. Current Status of Biparametric MRI in Prostate Cancer Diagnosis: Literature Analysis. *Life (Basel)* 2022;12(6).
- 20 Israël B, Leest MV, Sedelaar M, Padhani AR, Zámecnik P, Barentsz JO. Multiparametric Magnetic Resonance Imaging for the Detection of Clinically Significant Prostate Cancer: What Urologists Need to Know. Part 2: Interpretation. *Eur Urol* 2020;77(4):469-80.
- 21 Bratan F, Niaf E, Melodelima C, Chesnais AL, Souchon R, Mege-Lechevallier F, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. *European radiology* 2013;23(7):2019-29.
- 22 Borofsky S, George AK, Gaur S, Bernardo M, Greer MD, Mertan FV, et al. What Are We Missing? False-Negative Cancers at Multiparametric MR Imaging of the Prostate. *Radiology* 2018;286(1):186-95.
- 23 Johnson DC, Raman SS, Mirak SA, Kwan L, Bajgirani AM, Hsu W, et al. Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging. *European Urology* 2019;75(5):712-20.
- 24 Oerther B, Engel H, Bamberg F, Sigle A, Gratzke C, Benndorf M. Cancer detection rates of the PI-RADSv2.1 assessment categories: systematic review and meta-analysis on lesion level and patient level. *Prostate Cancer and Prostatic Diseases* 2022;25(2):256-63.
- 25 Drost FH, Osses D, Nieboer D, Bangma CH, Steyerberg EW, Roobol MJ, et al. Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis. *European Urology* 2020; 77(1):78-94.
- 26 Elwenspoek MMC, Sheppard AL, McInnes MDF, Merriel SWD, Rowe EWJ, Bryant RJ, et al. Comparison of Multiparametric Magnetic Resonance Imaging and Targeted Biopsy With Systematic Biopsy Alone for the Diagnosis of Prostate Cancer: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2019;2(8):e198427.
- 27 Mazzone E, Gandaglia G, Ploussard G, Marra G, Valerio M, Campi R, et al. Risk Stratification of Patients Candidate to Radical Prostatectomy Based on Clinical and Multiparametric Magnetic Resonance Imaging Parameters: Development and External Validation of Novel Risk Groups. *European Urology* 2022;81(2):193-203.
- 28 Bommelaere T, Villers A, Puech P, Ploussard G, Labreuche J, Drumez E, et al. Risk Estimation of Metastatic Recurrence After Prostatectomy: A Model Using Preoperative Magnetic Resonance Imaging and Targeted Biopsy. *European Urology Open Science* 2022;41:24-34.
- 29 Ploussard G, Manceau C, Beauval JB, Lesourd M, Almeras C, Gautier JR, et al. Decreased accuracy of the prostate cancer EAU risk group classification in the era of imaging-guided diagnostic pathway: proposal for a new classification based on MRI-targeted biopsies and early oncologic outcomes after surgery. *World J Urol* 2020;38(10):2493-500.
- 30 Ashrafi AN, Tafuri A, Cacciamani GE, Park D, de Castro Abreu AL, IS G. Focal therapy for prostate cancer: concepts and future directions. *Curr Opin Urol* 2018;2018 Nov(28):536-43.
- 31 Lee CH VB, Tan CH.. Comparison of diagnostic performance and inter-reader agreement between PI-RADS v2.1 and PI-RADS v2: systematic review and meta-analysis. *Br J Radiol* 2022;95.
- 32 Kobus T, Hambrock T, Hulsbergen-van de Kaa CA, Wright AJ, Barentsz JO, Heerschap A, et al. In vivo assessment of prostate cancer aggressiveness using magnetic resonance spectroscopic imaging at 3 T with an endorectal coil. *Eur Urol* 2011;60(5):1074-80.
- 33 Tayari N, Steinseifer IK, Selnæs KM, Bathen TF, Maas MC, Heerschap A. High-Quality 3-Dimensional 1H Magnetic Resonance Spectroscopic Imaging of the Prostate Without Endorectal Receive Coil Using A Semi-LASER Sequence. *Investigative Radiology* 2017;52(10):640-6.

- 34 Scheenen TWJ, Fütterer J, Weiland E, Hecke Pv, Lemort M, Zechmann C, et al. Discriminating Cancer From Noncancer Tissue in the Prostate by 3-Dimensional Proton Magnetic Resonance Spectroscopic Imaging. *Invest Radiol* 2011;46(1):25-33.
- 35 Steinseifer IK, Asten JJA, Weiland E, Scheenen TWJ, Maas MC, Heerschap A. Improved Volume Selective 1H MR Spectroscopic Imaging of the Prostate with Gradient Offset Independent Adiabaticity Pulses at 3 Tesla. *Magnetic resonance in medicine* 2015;74:915-24.
- 36 Maas MC, Litjens GJS, Wright AJ, Attenberger UI, Haider MA, Helbich TH, et al. A Single-Arm, Multicenter Validation Study of Prostate Cancer Localization and Aggressiveness With a Quantitative Multiparametric Magnetic Resonance Imaging Approach. *Investigative Radiology* 2019;54(7):437-47.
- 37 Stamatelatos A, Scheenen TWJ, Heerschap A. Developments in proton MR spectroscopic imaging of prostate cancer. *Magnetic Resonance Materials in Physics, Biology and Medicine* 2022;35(4):645-65.
- 38 Shrestha Kakkar L, Usman M, Arridge S, Kirkham A, Atkinson D. Characterization of B(0)-field fluctuations in prostate MRI. *Physics in medicine and biology* 2020;65(21):21nt01.
- 39 Dydak U, Weiger M, Pruessmann KP, Meier D, Boesiger P. Sensitivity-encoded spectroscopic imaging. *Magnetic resonance in medicine* 2001;46(4):713-22.
- 40 Skoch A, Jiru F, Bunke J. Spectroscopic imaging: basic principles. *European journal of radiology* 2008;67(2):230-9.
- 41 Wilson M, Andronesi O, Barker PB, Barth A, Bizzi A, Bolan PJ, et al. Methodological consensus on clinical proton MRS of the brain: Review and recommendations. *Magnetic resonance in medicine* 2019;82(2):527-50.
- 42 Kirchner T, Fillmer A, Tsao J, Pruessmann KP, Henning A. Reduction of voxel bleeding in highly accelerated parallel (1) H MRSI by direct control of the spatial response function. *Magnetic resonance in medicine* 2015;73(2):469-80.
- 43 Tayari N, Heerschap A, Scheenen TWJ, Kobus T. In vivo MR spectroscopic imaging of the prostate, from application to interpretation. *Anal Biochem* 2017;529:158-70.
- 44 Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol* 2014;65(1):124-37.
- 45 Schilham MGM, Küsters-Vandeveld H, Somford DM, Rijkema M, Gotthardt M. How image-guided pathology can improve the detection lymph node metastases in prostate cancer. *Clinical Nuclear Medicine* 2022;47:559-61.
- 46 Prendeville S, van der Kwast TH. Lymph node staging in prostate cancer: perspective for the pathologist. *J Clin Pathol* 2016;69(12):1039-45.
- 47 Conti A, Santoni M, Burattini L, Scarpelli M, Mazzucchelli R, Galosi AB, et al. Update on histopathological evaluation of lymph node specimens from prostate cancer patients. *World J Urol* 2017;35:517-26.
- 48 Fossati N, Willemse PM, Van den Broeck T, van den Bergh RCN, Yuan CY, Briers E, et al. The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A Systematic Review. *Eur Urol* 2017;72(1):84-109.
- 49 Preisser F, van den Bergh RCN, Gandaglia G, Ost P, Surcel CI, Sooriakumaran P, et al. Effect of Extended Pelvic Lymph Node Dissection on Oncologic Outcomes in Patients with D'Amico Intermediate and High Risk Prostate Cancer Treated with Radical Prostatectomy: A Multi-Institutional Study. *J Urol* 2020;203(2):338-43.

- 50 Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tabatabaei S, van de Kaa CH, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med* 2003;348(25):2491-9.
- 51 Fortuin AS, Deserno WM, Meijer HJ, Jager GJ, Takahashi S, Debats OA, et al. Value of PET/CT and MR lymphography in treatment of prostate cancer patients with lymph node metastases. *Int J Radiat Oncol Biol Phys* 2012;84(3):712-8.
- 52 Wright GL, Jr., Haley C, Beckett ML, Schellhammer PF. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. *Urol Oncol* 1995;1(1):18-28.
- 53 Petersen LJ, Zacho HD. PSMA PET for primary lymph node staging of intermediate and high-risk prostate cancer: an expedited systematic review. *Cancer Imaging* 2020;20(10).
- 54 Abrams-Pompe RS, Fanti S, Schoots IG, Moore CM, Turkbey B, Vickers AJ, et al. The Role of Magnetic Resonance Imaging and Positron Emission Tomography/Computed Tomography in the Primary Staging of Newly Diagnosed Prostate Cancer: A Systematic Review of the Literature. *Eur Urol Oncol* 2021;4(3):370-95.
- 55 Stabile A, Antony Pellegrino, Elio Mazzone, Donato Cannoletta, Mario de Angelis, Francesco Barletta, et al. Can Negative Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Avoid the Need for Pelvic Lymph Node Dissection in Newly Diagnosed Prostate Cancer Patients? A Systematic Review and Meta-analysis with Backup Histology as Reference Standard. *European Urology oncology* 2022;5:1-17.
- 56 Wang K. Feasibility of High Spatial Resolution Working Modes for Clinical PET Scanner. *International Journal of Medical Physics, Clinical Engineering and Radiation Oncology* 2018;7:539-52.
- 57 Scheenen TWJ, Zamecnik P. The Role of Magnetic Resonance Imaging in (Future) Cancer Staging: Note the Nodes. *Invest Radiol* 2021;2021(56):42-9.
- 58 Wu L, Cao Y, Liao C, Huang J, Gao F. Diagnostic performance of USPIO-enhanced MRI for lymph-node metastases in different body regions: A meta-analysis. *European journal of radiology* 2011;80(2):582-9.
- 59 Heesakkers RAM, Jager GJ, Hovels AM, Hoop Bd, Bosch HCMvd, Raat F, et al. Prostate cancer: Detection of lymph node metastases outside the routine surgical area with Ferumoxtran-10-enhanced MR Imaging. *Radiology* 2009;251(2):408-14.
- 60 Meijer HJ, Debats OA, van Lin EN, Witjes JA, Kaanders JH, Barentsz JO. A retrospective analysis of the prognosis of prostate cancer patients with lymph node involvement on MR lymphography: who might be cured. *Radiat Oncol* 2013;8:190.
- 61 Meijer HJ, Fortuin AS, van Lin EN, Debats OA, Alfred Witjes J, Kaanders JH, et al. Geographical distribution of lymph node metastases on MR lymphography in prostate cancer patients. *Radiother Oncol* 2013;106(1):59-63.
- 62 Philips BWJ, Fortuin AS, Orzada S, Scheenen TWJ, Maas MC. High resolution MR imaging of pelvic lymph nodes at 7 Tesla. *Magnetic resonance in medicine* 2017;78(3):1020-8.
- 63 Philips BWJ, Stijns RCH, Rietsch SHG, Brunheim S, Barentsz JO, Fortuin AS, et al. USPIO-enhanced MRI of pelvic lymph nodes at 7-T: preliminary experience. *European radiology* 2019;29(12):6529-38.
- 64 Hellman S, Weichselbaum RR. Oligometastases. *Journal of Clinical Oncology* 1995;13(1):8-10.
- 65 Singh D, Yi WS, Brasacchio RA, Muhs AG, Smudzin T, Williams JP, et al. Is there a favorable subset of patients with prostate cancer who develop oligometastases? *Int J Radiat Oncol Biol Phys* 2004;58(1):3-10.

- 66 Juan GR, Laura FH, Javier PV, Natalia VC, Maria Isabel GR, Enrique RG, et al. Where Do We Stand in the Management of Oligometastatic Prostate Cancer? A Comprehensive Review. *Cancers (Basel)* 2022;14(8).
- 67 Battaglia A, De Meerleer G, Tosco L, Moris L, Van den Broeck T, Devos G, et al. Novel Insights into the Management of Oligometastatic Prostate Cancer: A Comprehensive Review. *Eur Urol Oncol* 2019;2(2):174-88.
- 68 Deek MP, Van der Eecken K, Sutera P, Deek RA, Fonteyne V, Mendes AA, et al. Long-Term Outcomes and Genetic Predictors of Response to Metastasis-Directed Therapy Versus Observation in Oligometastatic Prostate Cancer: Analysis of STOMP and ORIOLE Trials. *Journal of Clinical Oncology* 2022;40(29):3377-82.



Section I:

MRSI and DWI of the prostate at 3 T

Chapter 2

Evaluation of prostate DOT Engine and slaser sequence

Final Report of public-private research collaboration on an automated workflow for MRI of the prostate: the Siemens Dot engine Prostate

Carlijn J.A.Tenbergen and Tom W.J. Scheenen

Subjects

34 subjects were scanned in the Radboudumc with the prostate Dot engine workflow. Within the Dot environment diagnostic T2w, DWI and DCE sequences are performed with the addition of a spectroscopic imaging sequence. Therefore we can evaluate segmentation, tilting and auto-alignment for T2w, diffusion, MRSI and DCE sequences. All subjects, except for one, completed the scan session. Subject number D18086 has only undergone the clinical sequences, with segmentation data and tilting reported, but no MRSI was performed.

The first 30 subjects were scanned with version WIP 1029D. The Nijmegen adjusted version has an added fast T2w image after the localizer to get a better idea of the position of the prostate since in a localizer it can be hard to visualize all borders if the coil wasn't properly centered. From the 7th subject onwards, we have replaced the T2w transversal sequence by the fast version which was performed additionally in previous subjects when the T2w tra scan was blurry because of movement (which was the case in the 3rd to 6th subject). From the 7th subject the fast scan was the standard T2w tra scan performed.

Subjects E19024 to E19032 were scanned with the updated WIP 1029E version. Evaluation of these subjects will be covered separately under topic d.

Data from another six subjects were received from Trondheim, St. Olavs hospital. Only the resulting images were shared, no information obtained during scanning can be given in this report.

Details for each subject, regarding segmentation results, tilting or spectroscopic imaging settings can be found in the Excel file.

Altogether 40 patients have been scanned at two centers, for which all data will be anonymously provided to Siemens: the patient gave consent for sharing the data.

a) Evaluation of segmentation

In general the automatic segmentation of the prostate performs well; the prostate is nicely contoured at the mid-section. The borders of the prostate at the apex and base are sometimes wrongly indicated by the segmentation algorithm. Small errors in these regions have little impact for the planning of diagnostic scans, since these scans are made with margins in these sections. For the MRSI sequence, these errors can have influence on VOI size and OVS band placement.

In some subjects (8/40) the segmentation algorithm resulted in large errors. Figure 1 shows a subject with errors in segmenting the base of the prostate leading to the need for manual input for planning of the subsequent sequences.

For three subjects out of those 8, the cause for segmentation failure can be found in previous treatment: presence of brachytherapy seeds (subjects D18103 and D19014) and focal laser therapy (subject D19013).



Fig. 1: Subject D19011, large error in segmentation of the base of the prostate: the top part extending into the bladder is missed by the segmentation algorithm.

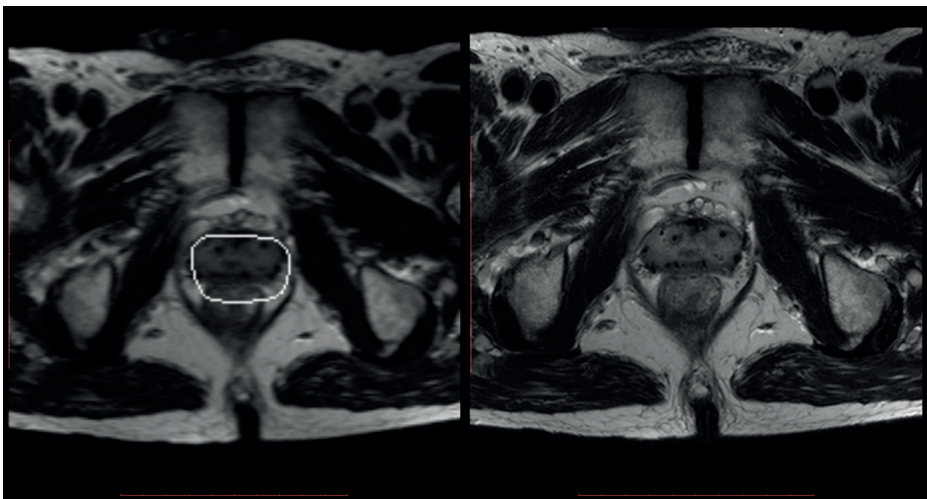


Fig. 2: Subject D18103, segmentation is off, possibly due to presence of brachytherapy seeds.

In two subjects with good segmentation results, the resulting segmentation line appeared grey instead of white. This is probably due to a high intensity region in the transversal images. This makes the line of segmentation hard to see and this cannot be improved by scaling of the image series. (Subjects D18086 and D19022)

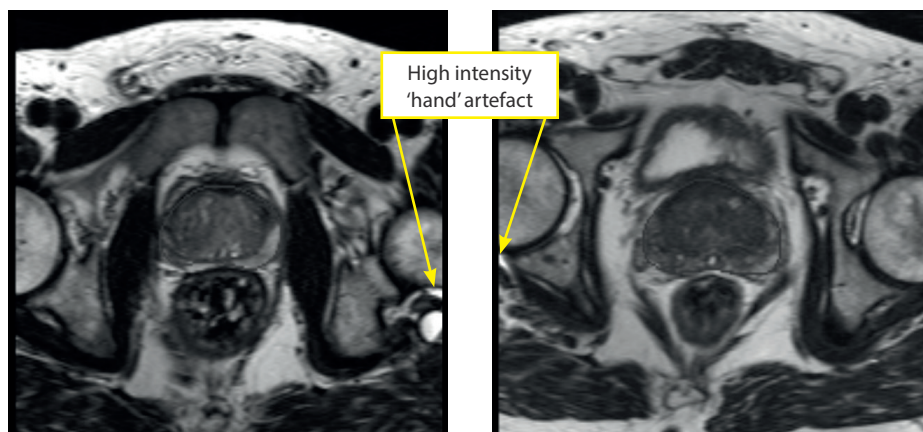


Fig. 3: Subject D18086 and D19022: due to high intensity in the artifact from the hand, the segmentation line is scaled to grey which prevents easy checking during the workflow.

Conclusion

Overall segmentation goes well, the prostate is nicely contoured. With a quick check of the segmentation result, one can easily see which areas could be causing trouble later on in the protocol and need more attention. When the segmentation is off, it would be nice to do a rerun of the segmentation after the diagnostic T2w images. The protocol is not ready for subjects with brachytherapy seeds present in the prostate.

Recommendation

For the best segmentation result, consider a rerun of segmentation after the clinical T2w tra sequence has run. This image series with higher SNR might be better as a start for the segmentation algorithm. This is important if the volume of the prostate needs to be reported accurately, but also for automated positioning of VOI and OVS slabs of spectroscopic imaging

b) Initial tilting: in accordance to the land marks (i.e. perpendicular to the axis bladder neck / prostatic exit of urethra)?

Initial tilting of the slice packages for transversal and coronal imaging is set by the Dot engine protocol. This tilting is based on the line between the landmarks bladder neck/prostatic exit of the urethra. These landmarks and forthcoming axis were located accurately. In two subjects, numbers D18102 and D19013, the found land marks are questionable.

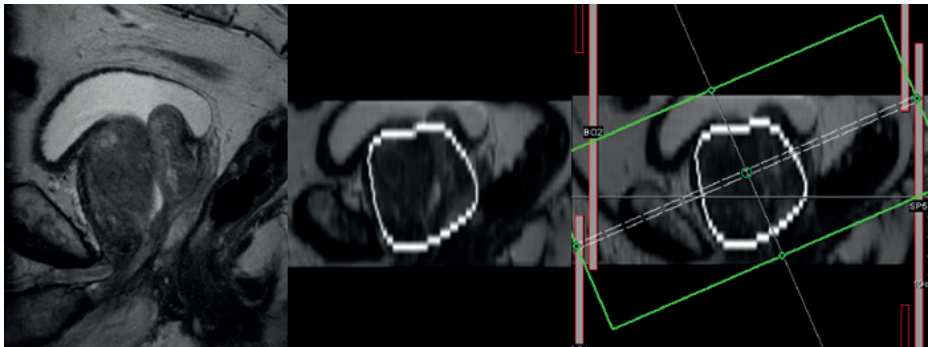


Fig. 4: Subject D19013, suggested axis between landmarks is questionable, as bladder neck is located at the top mid of the prostate.



Fig. 5: Subject D19012, with abnormal position of the bladder resulting in a suggested tilting towards the posterior part in accordance with the preferred tilting.

In subject D19012, the bladder had an unusual position relative to the prostate. Despite this abnormal positioning, the landmarks were found accurately in this prostate. The resulting tilting was in accordance with the preferred tilting and only in this subject, no manual adjustments were performed.

In all other subjects from the Radboudumc, we changed the given angulation to match the tilting of the anterior wall of the rectum and posterior border of the

prostate. This manual tilting from the suggested axis ranges from 11 to 44 degrees, with a mean of 25 degrees.

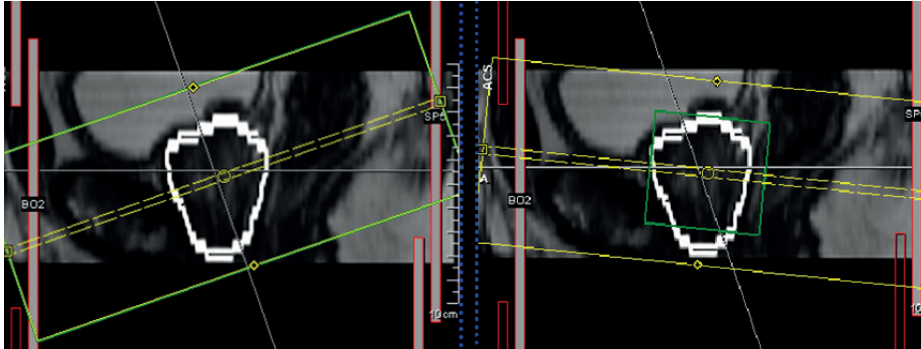


Fig. 6: axial view from subject D19022, the tilting for axial scanning is shown both suggested by the dot engine protocol and next manually adjusted to align parallel to the anterior wall of the rectum. This change in angle measures 25°.

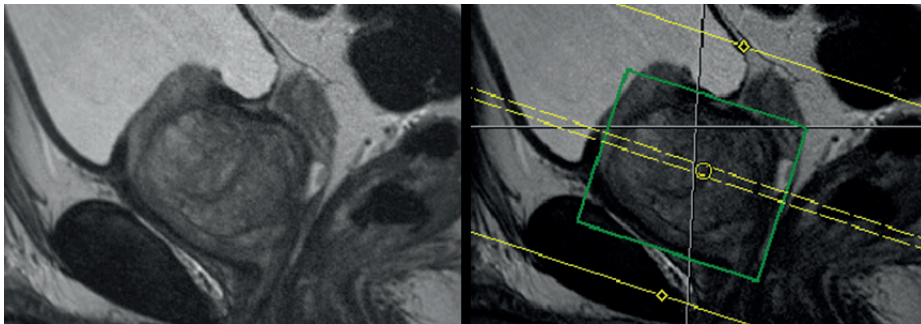


Fig. 7: Subject number E19025. In these sagittal planes, the prostate shows its orientation towards the anterior/ventral side. The grey vertical line suggests the tilting of the axial planes with already an offset of -35 degrees. The slice package in yellow shows the chosen tilting which was 15 degrees more towards the posterior side, making an angle of -50 degrees with the original line between the landmarks in the prostate.

As a consequence of the tilting, the coronal sequence is moved or tilted a bit more in a few subjects to cover more of the seminal vesicles.

In version E it is possible to give in an offset angle, and it was suggested that this could work with an angle of -35 degrees. This offset is tested in the 4 subjects scanned with WIP1029E. The first subject out of 4 did not need any change from this offset angle; the angle of -35 was kept for the transversal acquisition. In one subject, the tilting angle was enlarged from -35 to -50 degrees (see Fig. 7). This

subject (number E19025) has an unusual prostate shape, leading to a large angle for the transversal plane. With the last 2 subjects, the angle was decreased from -35 to -26 and -23 degrees respectively.

When looking at all Radboudumc subjects, it was found that averagely we tilted the slices packages for the transversal sequence with an angle of 25 degrees. With 13 out of 34 subjects showing a tilt angle between 20 and 30 degrees, using an offset of 25 degrees would mean no or very little manual tilting is needed in these subjects and time and labor is saved in more than a third of the subjects.

Conclusion

With a large variance in the anatomy and size and shape of the prostate, the tilting of slice package for transversal imaging will remain a step within the scan protocol that perhaps needs manual adjustment. The offset, possible in version E, leading to a tilt in the right direction can make this manual adjustment smaller or even unnecessary in a number of subjects and can therefore make this step faster.

c) Image quality/ spectral quality (i.e. ok for diagnostic purposes, no detailed assessment)

Image quality

After subjects D18073 to D18081 were scanned with the addition of the fast T2w tse tra to compensate for blurry initial T2w tra image, the fast sequence was set to standard for all subsequent subjects. After this change, the T2w tra sequence is only rerun in three subjects because of poor image quality of the first T2w tra image. The sagittal T2w tse is also rerun in three subjects.

In four subjects, the quality of the DWI sequence was low and a resolve diffusion sequence was run additionally. This sequence is less influenced by artefacts.

The coronal or DCE sequence was found of good quality in all subjects and therefore never performed twice in one subject.

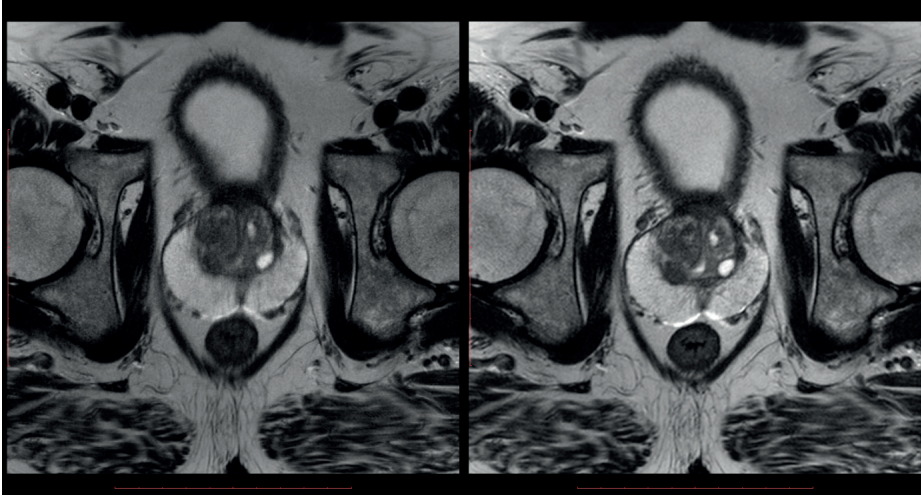


Fig. 8: Subject D18073, more detail can be distinguished in the transition zone in the right fast image compared to the left image.

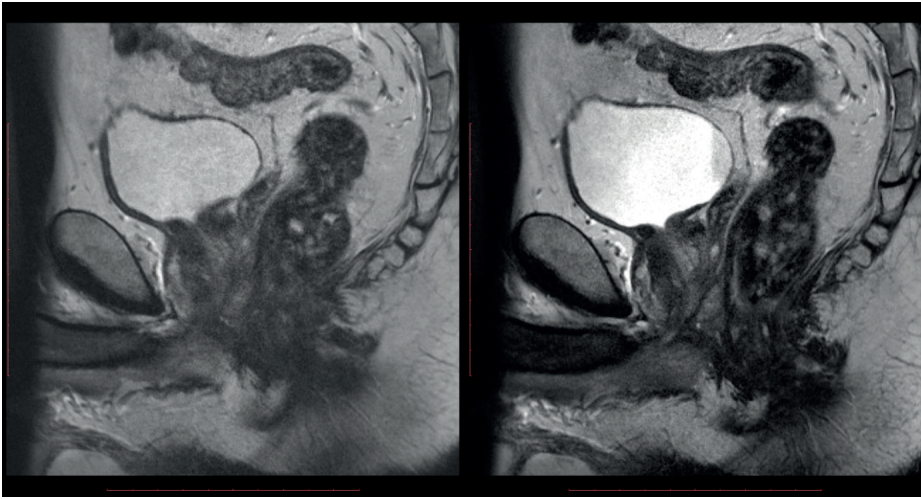


Fig. 9: Subject D18104, sagittal sequence is repeated with improved results.

Spectral quality

Spectral quality was assessed by a post-processing workflow in Syngo.Via. A high amount of good quality voxels is found in most subjects, with an average of 84% in the first 20 subjects. For this quality control, we applied conditions that were focused on metabolite peak fit to noise ratio, lipid residual and citrate peak phase.

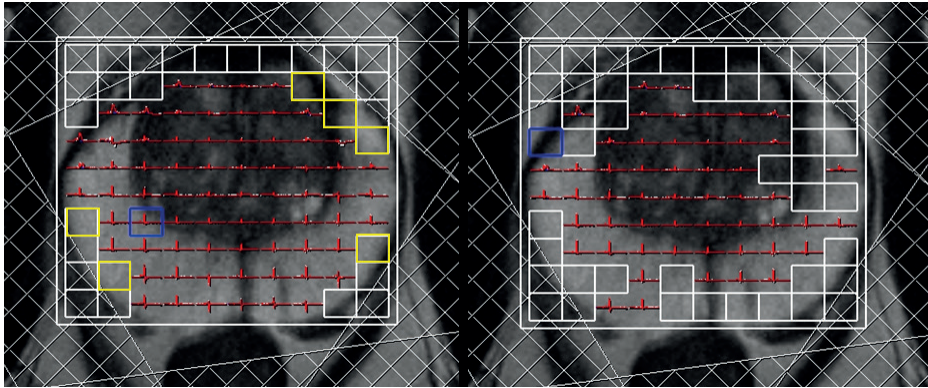


Fig. 10: Left: Voxels influenced by an OVS band are indicated with a white box. The bands cover more voxels than wanted (indicated by yellow boxes) and these spectra should be visible. Shown on the right is the image after quality control, with 17 of the 70 non-saturated voxels defined as low quality, resulting in 75% good quality voxels for this slice.

When evaluating the VOI or OVS bands in the post-processing view, there is more time to go over the placement in detail. Often it shows that there is either a band or VOI border that could have been better positioned. It tends that in most cases, some voxels at the base or apex are either too little or too much covered by OVS bands or included within the VOI. In the post-processing it is easy to see which voxels are suppressed and sometimes there are more voxels suppressed than intended. This results from a small overlap of a band over some voxels which is not noticed in the Exam tab and sometimes not even visible in Syngo.Via (example in Fig. 9).

Recommendation

The normal T2w scan can be replaced by the 'fast' version, as has been done in our clinical practice (outside DOT engine use) as well. This would simplify the Dot engine, as the option to acquire an additional fast T2w can be taken out (that sequence has become the standard).

Regarding MRSI, spectra from voxels that only partially have been touched by an OVS band (e.g. less than 75%) could be normally visualized. At this moment, Syngo.

Via takes away too many voxels, which leaves spectra of too many voxels at the edges of the prostate invisible. It does not harm to look at a voxel that was for a small part saturated: this does not add any signal contamination.

d) Workflow: pros and cons, and version E changes

The workflow is easy to get acquainted with. The guidance screen, providing a view of the desired positioning of slice packages, is practical and gives a quick look on if and what manual adjustments are needed. It is practical that acquired images are immediately shown and subsequent settings can be made with these images visible in the exam tab, e.g. the segmentation results are immediately visible in the exam view. Throughout the workflow the necessary images are presented at the exam tab and there is no need for manual selection or changing of shown images in the exam tab to go smoothly through the workflow.

MRSI settings need only small manual adjustments and result in good quality spectra. For this sequence we check the size and position of the VOI, then the matrix and voxel size is checked, we ensure that there is an odd matrix size so that we have the desired voxel size. Then the OVS bands are looked at. Adjusting the OVS bands can take up some time. The whole process of setting up the MRSI sequence never extended over the scantime of the previous sequences, so we were always ready with setting up the MRSI when the previous sequence was done and we could start the MRSI right away.

There is quite some manual copying of parameters necessary, which is prone to improvement (Version D). We set the adjustment volume before we run the T2w tra scan. The adjustment volume then needs to be copied from the T2w tra scan to the DWI and MRSI sequences. For the MRSI scan we copy the adjustment volume and slices (for orientation of the VOI box) from the T2w tra, and next reset the rotation angle from 44° to 0° (long existing bug). These are some extra steps before the check of MRSI settings can start. Copying these parameters (especially orientation of the VOI and FOV) automatically would be better (this seems to have improved in the E-version).

One point of consideration is the repetition of T2 sequences. When one of the anatomical sequences result in blurry images, possibly by subject movement or muscle contraction, the sagittal and coronal scans can easily be redone by dragging the sequence down in the protocol list. For the transversal sequence, this is not the desired way as dragging down the T2_tse_tra sequence also induces the segmentation algorithm to rerun, resulting in new segmented images, and

the accompanying suggested tilt angle. *Recommendation:* provide a warning when dragging down the T2_tse_tra sequence for a rerun, that this will involve recalculation of the segmented volume and tilt angle. If the T2_tse_tra needs a rerun, one should go to the dot engine start screen and select the fast T2w for movement. This can still be done after the protocol is started. We did not test what happens with rerunning the transversal sequence in the E version.

Shimming

Generally, advanced shimming is necessary for diffusion-weighted imaging (EPI-based) and for spectroscopic imaging. Currently, we choose the shim volume already before running the T2_tse_tra, and already (and only) at that point advanced shimming is performed. This is suboptimal, as it prolongs the time from shimming to the most critical (shim-dependent) pulse sequences. TSE sequences do not need advanced shimming, and could be run with standard shimming of the slice package. Advanced shimming is necessary for DWI, with an adjustment volume of the area with prostate and rectum; ¹H-MRSI needs advanced shimming and a visual check of the VOI. Both could be done automatically, but if the shim FWHM before the start of MRSI is not to our liking, we continue the sequence (to be able to shim manually with the automated adjustment as starting point), then stop it, copy the sequence and then manually adapt the shim. An improvement would be to have the automated shim values available when cancelling the suggested shim FWHM (rather than the current start, stop, copy and rerun the sequence just to have these values available as starting point for manual shim).

In version E we noticed that the adjustment volume is automatically copied to the DWI sequence. This makes that this DWI sequence no longer needs a visual check or any manual input. Not having to check this sequence is an improvement, however keep in mind the previous suggestions for shimming. The main changes in version E of the tilting offset and the order of T2w sequences are well appreciated.

One recommendation for the E version is to adjust the tilting of the slice packages for the coronal T2w sequence. In version D the tilting angle for the coronal sequence was automatically derived from the chosen tilting of the transversal package. In version E this is not the case, the coronal slice package starts with the initially calculated offset angle regardless of manual adjustments made to the tilting in the transversal T2w sequence.

A minor disadvantage of the E version is that the time bar for the segmentation is gone. The bar showing that the segmentation was in progress was a nice way to

show that the system is working and no action is needed for a few seconds. This would also be favorable for MR technicians who prefer not to wait during scanning. Maybe also a short description of the desired tilting could be added to the text in the guidance view.

e) Reproducibility, if repeated scan sessions are available for some subjects.

With subjects there is no opportunity of scanning people twice. When testing the version E protocol with a volunteer, there was the opportunity to run the segmentation twice. The segmentation scan was repeated within one session, after having run the TSE, DWI and MRSI sequences, so the localizer and positioning for the segmentation were the same.

Table 1: Results of repeated segmentation in one volunteer

	Segmentation 1	Segmentation 2	Error relative to 1 (%)
Anterior – posterior (mm)	37.39	42.51	13.7
Right – left (mm)	45.83	47.92	4.56
Foot – head (mm)	42.53	35.48	16.58
Segmentation volume (ml)	38.25	34.88	8.81

This difference can be seen when comparing the segmentation results within the images, but would not lead to differences in further scanning settings. It would affect PSA density calculations.

Chapter 3

Improving magnetic field homogeneity in prostate MR imaging and spectroscopy using an add-on local external shim array coil

Angeliki Stamatelatos, Carlijn J.A. Tenbergen, Sahar Nassirpour, Paul Chang,
Jack J. van Asten, Arend Heerschap, Tom W.J. Scheenen

Abstract

Purpose: Magnetic resonance (MR) techniques require optimal magnetic field (B0) homogeneity for high-quality acquisitions. Imaging the prostate presents challenges due to susceptibility differences induced by bowel gas and motion, resulting in complex B0 field distortions. This study introduces the first version of a customized external add-on local shim coil array to improve B0 field homogeneity in prostate MR imaging and spectroscopy.

Methods: The influence of the shim coil array on MR system performance was assessed with standard measures. To address B0 field distortions in the prostate, the proposed methodology combined optimized add-on shim coil array currents with 1st-order shim values of the MR scanner, which was compared to the reference standard of conventional 1st and 2nd-order shimming of the MR system. The effectiveness of the shim coil array was evaluated in seven healthy volunteers, using the standard deviation (SD) of off-resonance frequencies ($\Delta B0$) derived from B0-maps, the distortion of diffusion-weighted images (DWI), assessed by the Dice similarity coefficient (DSC) with reference to T2W images, and the citrate linewidths of ^1H -MR spectroscopic imaging (^1H -MRSI) of the prostate.

Results: The prototype shim coil array decreased overall SNR of the system with 20%. In DWI, an overall improvement in the DSC was observed, rising from 0.90 ± 0.02 with conventional shimming to 0.92 ± 0.02 with the add-on shim coil array ($p=0.01$), accompanied by a reduction in the SD of $\Delta B0$ from 18.5 ± 4.7 Hz to 16.5 ± 3.6 Hz, respectively. In ^1H -MRSI citrate linewidths improved, decreasing from 8.3 ± 5.7 Hz with conventional shimming to 7.9 ± 3.6 Hz with the add-on shim coil ($p=0.018$), accompanied by the SD of $\Delta B0$ from 19.3 ± 4.8 Hz to 19.1 ± 4.7 Hz with the add-on shim coil.

Conclusion: An external add-on shim coil array can improve B0 homogeneity in the prostate. When interactions between shim coil array and RF receive coils are resolved, this innovative technology can contribute to improved image quality, reduced artifacts, and enhanced precision in multi-parametric MRI.

Introduction

The reliability and quality of MR examinations heavily rely on the uniformity of the main magnetic field (B_0), as it directly impacts image quality, spatial registration, signal strength, and spectral resolution¹⁻⁴. Achieving optimal magnetic field homogeneity is particularly challenging in the prostate, an organ situated in the lower abdomen. The presence of susceptibility differences between air and tissue, attributed to bowel gas and amplified by motion, imposes complex B_0 field distortions, predominantly affecting the posterior region of the prostate^{3,5}.

Echo-planar imaging (EPI) based diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) techniques employed in prostate imaging are particularly susceptible to B_0 field inhomogeneities. In DWI, off-resonance effects can result in geometric distortions. Distortion correction methods based on spatially varying B_0 field maps have been developed to address these challenges, providing effective correction schemes for warped EPI images, especially in the prostate^{1,6}. However, potential temporal changes in the B_0 field resulting from physiological or patient motion⁷ can introduce inaccuracies in pixel shifts across a DW dataset, hindering the accurate computation of apparent diffusion coefficient (ADC) maps for prostate cancer assessments⁸. In MRSI, off-resonance effects can cause spectral line broadening and frequency shifts, thereby compromising water suppression and introducing lipid contamination within prostate spectra^{9,10}. Temporal B_0 field changes can also result in incorrect frequency shifts and spectral line broadening in MRS, both of which contribute to overlapping signals and decreased spectroscopic imaging accuracy¹¹. Consequently, understanding and accounting for B_0 field variations is crucial in prostate MRI^{3,4}.

Existing solutions in optimizing the uniformity of the B_0 field in the prostate have primarily focused on mitigating susceptibility artifacts caused by air within the rectum through patient preparation techniques. These techniques involve the administration of antispasmodic agents, such as hyoscine butylbromide (Buscopan, Boehringer, Ingelheim, Germany) or Glucagon (GlucaGen, Novo Nordisk A/S, Bagsvaerd, Denmark), and the insertion of rectal catheters¹². While these methods have shown some effectiveness in preventing artifacts¹³, they do not specifically address the challenges associated with improving B_0 field homogeneity in the prostate.

Various methods have been documented to improve B_0 field homogeneity during the acquisition process as well as to correct induced artifacts in post-processing,

mainly in the field of brain imaging. These post-processing techniques involve correcting spatial mis-registration^{2,14}, but require additional reference data or extra scans^{1,15,16}, using the point-spread function^{17,18} or data acquired with phase-encoding gradients of opposing polarity to correct image distortion^{19,20}. It is important to note that despite these post-processing efforts, some signal loss remains irrecoverable²¹.

During the acquisition phase, selecting suitable MR acquisition parameters can effectively reduce artifacts caused by magnetic field fluctuations. A higher spatial resolution - SNR permitting - effectively mitigates fluctuations within a voxel, thereby decreasing signal dephasing. High-bandwidth RF pulses with large slice selection gradients will minimize displacement artifacts²². Increased acquisition bandwidths reduce spatial misalignment and image distortion^{23,24}. Additionally, both passive and active shimming techniques can be deployed. Passive shimming approaches involve correcting magnetic field inhomogeneities by strategically positioning magnetically susceptible materials within the scanner bore. This approach has limitations in adapting to experiment-specific conditions and varying shim requirements originating from differences in subject anatomy or placement. Active shimming, on the other hand, is the most common approach and involves B_0 homogenization through correction fields generated by electrical coils. The conventional strategy for minimizing magnetic field variations using active shimming is to overlay magnetic fields characterized by spatial variations governed by spherical harmonic functions^{25,26}. Generally, the higher the maximum spherical harmonic order applied for B_0 shimming, the closer it aligns with the spatial characteristics of the specific B_0 distortions, facilitating their subsequent compensation. Numerous methodologies in this area have been developed over the years, primarily focusing on applications related to brain imaging^{21,27-33}.

Motivated by the success of local shimming methods in the brain, in this pilot work we introduce the design, implementation, and analysis of the first external add-on local shim coil array specifically tailored to the prostate. The purpose of this add-on shim coil is to improve B_0 field homogeneity within the prostate, leading to enhanced image quality, reduced artifacts, and improved accuracy in multi-parametric MRI. The effectiveness of this shim array is assessed by analysis of B_0 -maps, EPI-based DWI, and ^1H -MRSI.

Methods

Hardware

All measurements were conducted using a clinical 3T MR system (MAGNETOM Prisma-Fit, Siemens Healthineers, Erlangen, Germany) equipped with external multi-channel body and spine phased-array coils for signal reception.

The experimental setup featured a custom-designed 16-channel external add-on shim coil array, structured into four distinct "shim" modules (*Dia*, MR Shim GmbH, Reutlingen, Germany). The geometry, shape, and number of turns of the shim coils were selected to achieve maximum coverage while taking into consideration the available space and mechanical constraints of the MRI setup. The shim coils have a standard circular shape, and the number of turns and size (20 turns and 6 cm diameter) were chosen such that the shim coils can fit inside the shim holder while keeping the thickness of the shim holder below 1 cm, and to ensure that the required current for each channel remains below 1 A. The shim cables were made with 20 AWG wires as twisted pairs.

The shim coil setup included eight channels on the anterior side, divided into two modules (blue frames in Fig. 1a), and eight channels on the posterior side, distributed across two modules (red frame in Figure 1a), for full coverage. On the posterior side, the eight channels were uniformly distributed in the available space of the patient bed using a shim coil holder with a width of approximately 35 cm. To maximize coverage, the eight shim coils were arranged in two rows, resulting in a shim coil holder length of ~16 cm. For the anterior coils, the shim holder design was constrained by the shape of the body array receive coil, to which the coils were mechanically fixed. A configuration of two columns was chosen (four shim coils in each column in a shim holder covering a span of approximately 38 cm in the head-foot direction). To configure this setup, the anterior modules were positioned on the 18-channel RF body receive array coil, while the posterior modules were positioned underneath the patient's bed mattress on top of the RF spine-array coil, as indicated in Figure 1b. Each rigid shim module had fiducial markers embedded in the housing, enabling the detection of the position of the shim coils for each subject.

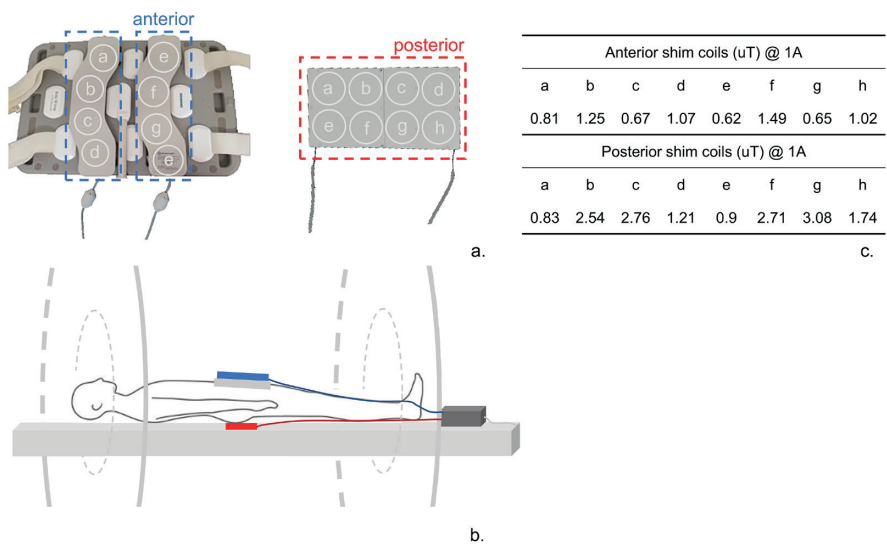


Figure 1. Experimental setup of an external shim coil array. **a.** the 16-channel local shim coil array, consisting of two posterior modules (red frame) and two anterior modules (blue frame). The anterior modules are positioned on top of the external RF 18-channel body phased-array coil. **b.** System configuration. The anterior shimming modules (blue) are positioned around the receive RF coil and the posterior modules (red) are placed under the mattress of the patient bed. The shim modules are connected to the filtered shim interface box. **c.** the maximum field strengths of the coil elements observed *in vivo* within the prostate of a representative volunteer at a current of 1 A.

A filtered shim interface box was positioned at the head of the scanner table. This interface box served as the central hub for the connection of the four shim modules. To drive the shim coils with electric currents, two amplifier units (Jupiter, MR Shim GmbH Reutlingen, Germany) were deployed. These amplifier units were positioned in the corner of the scanner room situated beyond the 100 Gauss line. Adjacent to the amplifier units, a non-magnetic Ethernet-to-fiber optic converter box was powered by a 5V power adapter, which was also connected to the mains supply. The box was linked to the master shim amplifier unit through a short Ethernet cable, and to its counterpart outside of the magnet room positioned next to the host computer using a duplex fiber optic cable. This cable was threaded through the waveguide opening of the MRI room penetration panel, ensuring an interference-free connection. In the MRI control room, the Fiber optic-to-Ethernet converter box was powered using a 5V power adapter and connected to the shim controller PC through an Ethernet cable.

Using the Biot-Savart Law for circular loops and the shim coil parameters used in this study, the calculated magnetic field strength for a shim coil at a distance of 20 cm was approximately 1.367 μT for 1 A. Typical amplitudes of scanner shim terms used for shimming were assumed to be $\sim 100 \mu\text{T/m}$ and $\sim 100 \mu\text{T/m}^2$, for first and second-order spherical harmonic terms, respectively. Therefore, for a prostate of approximately 40 x 40 x 40 mm, the amplitude of the first and second-order terms would be 4 $\mu\text{T/m}$ and 0.16 $\mu\text{T/m}^2$. The reported theoretical strengths of the local shim coils and scanner shims closely resemble the maximum field strengths observed *in vivo* within the prostate of a representative volunteer at currents below 1 A. These corresponding values are illustrated in Figure 1c, denoting the eight anterior and eight posterior shim modules as labeled in the figure. The lateral coils of the arrays contribute less than the closer ones, but their contribution is not insignificant (e.g. compared to what second-order scanner shim strengths could deliver). The scanner's shim terms utilized for shimming were measured at 2.81, 1.56, and 2.92 μT for first-order terms at 100 $\mu\text{T/m}$, and 0.086, 0.072, 0.05, 0.062, and 0.1 for second-order spherical harmonic terms at 100 $\mu\text{T/m}^2$.

Shim coils calibration

Reference B_0 field maps from each individual shim coil were acquired on a phantom and served as the reference calibration data set. The exact positions of the shim modules during each pursuing scan session were detectable on T2W localizer images by the fiducial markers embedded in the housing. As these shim modules vary in each subject and table position from the initial phantom shim coil calibration session, manual marking of fiducial markers on T2W localizer images for each subject is crucial. Using these newly identified fiducial marker locations, the magnetic field generated by each shim coil is calibrated to match the current position and orientation of the markers in each subject³⁴. This alignment ensures optimal imaging quality by adapting the magnetic field to the subject's specific anatomy and positioning. Furthermore, rigid transformations, encompassing translation and rotation, are calculated utilizing singular-value decomposition³⁵.

Influence of add-on shim coil array on MR system performance

Tests were conducted using the homogeneous Siemens spherical D240 body loader tissue phantom to ensure compliance with performance criteria outlined by the National Electrical Manufacturers Association (NEMA) and the Acceptance Testing and Quality Assurance Procedures for Magnetic Resonance Imaging Facilities (AAPM). These tests aimed to evaluate RF interactions resulting from the presence of the shim coils. Measurements were conducted using body and spine array coils

for signal reception and were performed twice: once with the shim coils present but without current running through them, and once without the shim coils.

Flip angle maps were obtained using the turbo flash B1+ mapping product sequence (tfl_b1map) with the following parameters: TR/TE 5280/1.8 ms, field of view (FOV) 300 x 300 mm², base resolution 64 x 64.

Additionally, a 2D multi-slice T2-weighted (T2W) spin echo pulse sequence was employed with the following parameters: TR/TE 6000/96 ms, field of view (FOV) 350 x 350 mm², 70 slices of 3.5 mm, and base resolution 256 x 256. From these images, the following parameters were assessed:

1. the signal to noise ratio (SNR), where a noise region and signal (S) region were selected on the slice on iso-center and SNR was calculated according to

$$SNR_{NEMA} = \frac{\sqrt{2S}}{\sigma} \quad \text{Equation 1}$$

where σ is the standard deviation of the noise in the noise region.

2. image uniformity, where a signal region (S) was selected on the slice on the iso-center and the peak deviation non-uniformity measure was calculated according to

$$N = 100 \frac{S_{max} - S_{min}}{S_{max} + S_{min}} \quad \text{Equation 2}$$

3. percentage of signal ghosting, where a signal region (S), and two sets of background regions (one in the frequency-encoding direction (S_{FE1} , S_{FE2}) and one in phase-encoding direction (S_{PE1} , S_{PE2})) were selected on the slice at iso-center and the percentage ghosting signal was calculated, through the ghosting ratio (GR), according to

$$GR = 100 \left| \frac{(S_{FE1} + S_{FE2}) - (S_{PE1} + S_{PE2})}{2S} \right| \quad \text{Equation 3}$$

Acquisition protocol

Subjects

We examined seven healthy volunteers (V1 to V7), with a mean age of 40.7 years (range 28 to 65 years). These volunteers underwent scanning without any prior bowel preparation. Ethical approval for the study was obtained from the local ethical committees at Radboudumc, Nijmegen, the Netherlands.

Shimming procedures

All of the supplementary hardware described above was operated via a controller PC utilizing the *Arche* shimming software (MR Shim GmbH Reutlingen, Germany).

The shimming procedures using the 16-channel add-on local shim coil in combination with the scanner's shimming system involved the steps outlined below and depicted in Figure 2, to achieve a high 3D volumetric magnetic field homogeneity around the prostate.

For experimental shimming with the shim coil array, we identified a rectangular *in vivo* volume, indicated for B_0 homogeneity optimization, known as the adjustment volume. This volume was precisely positioned on T2W localizer images, on the scanner's host PC and software, selecting the prostate while minimizing the inclusion of surrounding tissues. Next, a double echo gradient echo pulse sequence was acquired for offline mapping of the B_0 field within the adjustment volume. After obtaining the B_0 field map, the optimal combination of 1st-order shim values of the MR scanner along with the settings for the add-on shim coil array was calculated on the shim controller PC. The higher-order shim values of the MR scanner were left unchanged at the tune-up values. To minimize B_0 field disturbances within the adjustment volume, a least-squares minimization approach of the sum of the original B_0 field heterogeneity and the targeted combined B_0 shim field of the 1st-order scanner shims and the add-on shim coil array, was used. The shim values were computed using a non-iterative approach via the *Arche* shim software, which employed a constrained convex optimization algorithm. Once calculated, these shim values were applied to the scanner's 1st order shims in the interactive Adjustments window, and to the corresponding shim array amplifiers and coils on the separate shim controller PC.

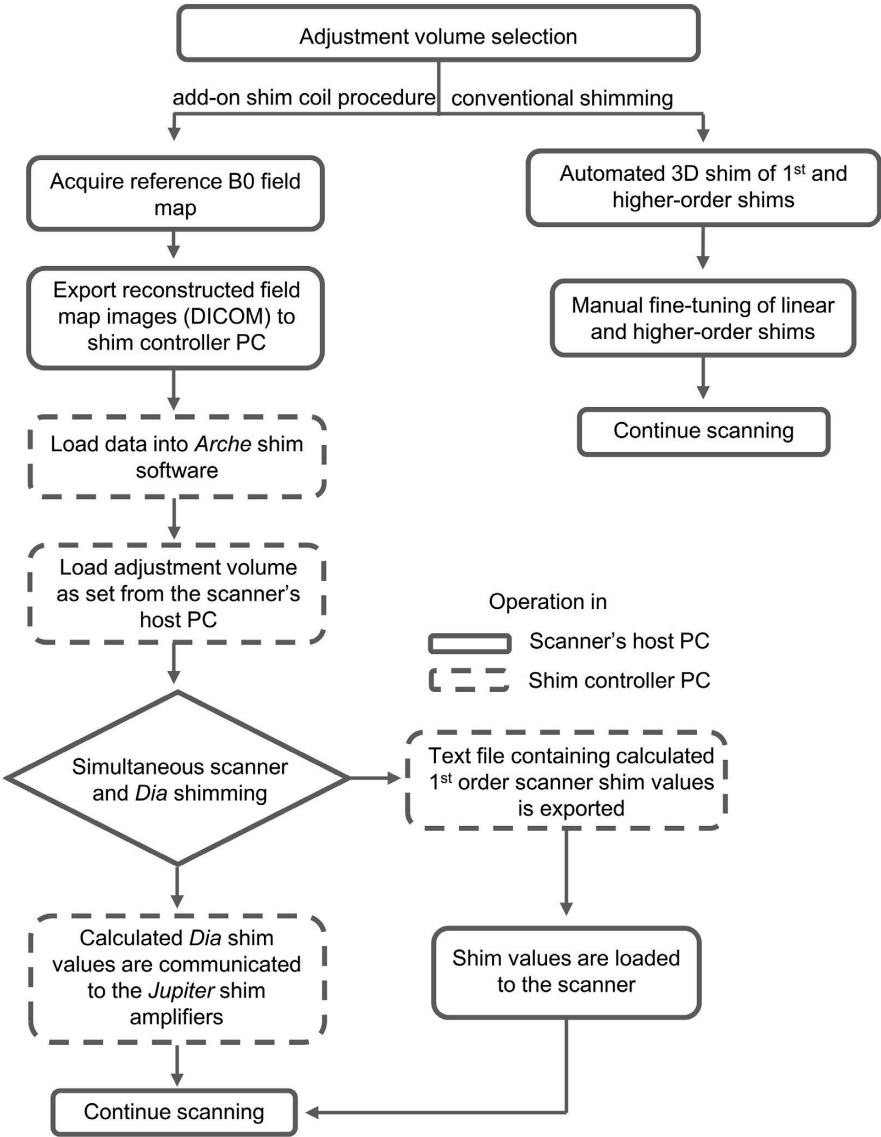


Figure 2. Flowchart providing an overview of the shimming process. **Left:** the add-on shim coil procedure **Right:** conventional shimming procedure

As a reference standard, we used the MR scanner's 3D map shimming routine to calculate all available shim values (1st and 2nd order), specifically optimized for the prostate, following the protocol used in clinical routine. This was complemented by manual fine-tuning, where an experienced spectroscopist made interactive

adjustments to the scanner settings. Our consistent goal during manual fine-tuning was to achieve a magnitude full width at half maximum (FWHM) of approximately 30 Hz within the adjustment volume around the prostate. In many instances, we achieved better results, well below the 30 Hz target.

Imaging protocol

The anterior modules of the add-on shim coil were fixed to the RF body receive array coil, while the posterior modules were fixed under the mattress of the patient bed. During subject positioning, care was taken to ensure the optimal placement of the prostate between the anterior and posterior shim coils.

The MR acquisition protocol and associated settings are detailed in Table 1. The acquisition procedure consisted of localizer scans, B_0 field maps, T_2 -weighted (T2W) imaging, DWI, and ^1H -MRSI. B_0 field maps were acquired with a dual-echo gradient echo sequence. The anatomical T2W scans were obtained in three orthogonal orientations using a clinical turbo spin-echo (TSE) pulse sequence. For DWI, we employed a spin-echo EPI sequence with a b-value of 50 s/mm² and repeated the sequence with b-values 50, 400, and 800 s/mm², from which a b-value of 1400 s/mm² was calculated. The 3D ^1H -MRSI data were acquired with a GOIA semi-LASER pulse sequence with MEGA lipid and water suppression³⁶. The acquisition matrix was an elliptically sampled k-space matrix of 8 x 8 x 11 phase encode steps zero filled to 16 x 16 x 16 after hamming filtering.

To minimize effects of motion between separate parts of the examination and to compare the two shimming approaches (add-on coil array vs reference standard), the shimming procedure was repeated twice during the protocol, involving separate B_0 field acquisitions and recalculating shim values before both the DWI acquisition and the ^1H -MRSI pulse sequence in both separate shimming approaches.

Table 1. The MR acquisition protocol and associated settings

	B₀	T2W tra	T2W sag
Sequence	dual-GRE	TSE	TSE
TR (ms)	8	5660	6000
TE (ms)	2.46/4.92	92	96
FOV (mm)	410x410	256x240	400x400
Resolution (mm)	3.2x3.2x3.0	0.3x0.3x3.0	1.3x1.3x3.5
Averages	1	2	2
Slice thickness (mm)	3	3	3
TA (min)	1:33	2:10	1:20

MR, magnetic resonance; DWI, diffusion-weighted imaging; MRSI, magnetic resonance spectroscopic imaging; T2W, T₂-weighted imaging; tra, transverse; sag, sagittal; cor, coronal; GRE, Gradient echo; TSE, turbo spin-echo; EPI, echo-planar imaging; GOIA, gradient offset independent adiabaticity; sLASER, semi-adiabatic localization by adiabatic selective refocusing; TR, repetition time; TE, echo time; TA, acquisition time;

Analysis

The analysis of the B₀ and DWI data was conducted using Matlab (version 9.11 R2021b; MathWorks, Natick, MA).

B₀-maps

To quantitatively assess B₀ homogeneity, the standard deviation (SD) of off-resonance frequencies (ΔB₀) was calculated per slice of the B₀ maps. The local field variation ΔB₀ is proportional to the acquired phase ϕ at voxel position *r* and the employed *TE*:

$$\Delta B_0(\vec{r}) = \frac{\varphi_0 - \varphi(\vec{r}, TE)}{\gamma \cdot TE}$$

Equation 4

with the gyromagnetic ratio γ = 42.57 MHz/T for protons. The double echo gradient echo acquisition allowed the calculation of voxel-specific ΔB₀. This method was used to generate volumetric B₀ field information in Hertz across the adjustment volume.

The SD of ΔB₀ results from the adjustment volume in the B₀ maps was calculated to assess potential differences between the two shimming approaches. This analysis was conducted on a slice-by-slice basis for each volunteer and for the entire volunteer cohort.

T2W cor	DWI		¹ H-MRSI
TSE	EPI - b50	EPI for ADC	GOIA sLASER
6000	3200	3600	750
96	63	63	88
350x350	256x240	256x200	77x56x56
1.1x1.1x3.5	2.0x2.0x3.0	2.0x2.0x3.0	Nominal, 7 × 7 × 7 mm; true spherical volume, 1.0 cm ³
2	3		6
3	3	3	
1:20	1:38	4:50	4:38

DWI analysis

The two-image series with b-value of 50 s/mm² (b50-maps) acquired with the add-on shim coil and with conventional shimming were by rigid registration matched to the transversal T2W scan as an undistorted anatomical reference, with interpolation of the EPI images to ensure resolution matching. A single reader manually segmented the entire prostate gland on each slice across the T2W series and the two b50-maps of both shimming methods. The contours of the b50-maps were aligned to the T2W images by matching the centroids of the corresponding contours.

Subsequently, the Dice similarity coefficient (DSC)^{37,38} was calculated to assess the agreement of the outlined prostate between both b50-images with the anatomical T2W images. In the DSC metric, the closer a value is to 1, the more precise the geometry of the prostate aligns in the b-50 DWI images as well as in the T2W images. This analysis was conducted on a slice-by-slice basis for each volunteer and for the entire cohort of volunteers. Statistical significance of the DSC's was determined by a paired analysis using the Wilcoxon signed-rank test.

¹H-MRSI analysis

Spectroscopic imaging data were analyzed by fitting citrate (Cit), which metabolite is abundantly present in the prostate and assessing its linewidth. Fitting was performed using AMARES within the jMRUI software³⁹. Although Cit consists of a strongly coupled spin system with a pulse sequence timing and B0 field-dependent complex line shape, we could model the center two lines of this shape by two

coupled Lorentzian line shape models. This way, possible presence of individual variation in the small satellite signals around the two central lines do not interfere with the linewidth assessment. In the fitting procedure, all spectra within the volume of interest (VOI) were included, followed by a quality control (QC) step. Spectral fits with a Cramer Rao Lower Bound (CRLB) of the linewidth smaller than 20% were accepted as good estimates of the linewidth. The percentage of the spectra passing the QC in both shimming techniques was calculated. Spectra that satisfied the QC criterion in both shimming protocols were retained for subsequent analysis steps. To assess the statistical differences in Cit linewidth between the two shimming techniques, a paired t-test for statistical evaluation was performed, both on an individual volunteer basis and for the entire volunteer cohort. Additionally, exemplary Cit linewidth metabolite maps for three slices from a single volunteer were generated, and histograms were created to visually depict the distribution of Cit linewidths among the volunteers.

Results

The phantom results are presented in Table 2. Although the SNR in the presence of the shim coils remained well within performance criteria of the MR scanner, the shim coils decreased the SNR by 20%.

Table 2. Phantom results

Metric	Presence of shim coils	Absence of shim coils	% difference with and without shim coils	Performance criteria
average flip angles [degrees]	78.38	80.21	-2.28	
SNR	863.87	1079.60	-19.98	>215
image non-uniformity [%]	16.17	6.79	+9.3	< 50%
ghosting [%]	0.33	0.34	+0.01	≤1%

All volunteers completed the full protocol successfully, except for one subject, V5, where an MRI system error prevented the DWI acquisition process.

Figure 3 depicts the impact of the add-on shim coil on B_0 maps and b50-maps derived from DWI, illustrated by an example case (V3). Specifically, for one slice the anatomical T2W reference is shown with the delineated prostate within the marked adjustment volume (white frame) (Fig. 3a). The B_0 maps from both conventional

shimming and the add-on shim coil highlighted a reduced frequency offset when using the add-on shim coil (Fig. 3b). The DWI b50-maps for both shimming techniques are depicted with their respective prostate contours (Fig. 3c). Overlaying the T2W image contour onto the b50-maps revealed improved alignment with the use of the add-on shim coil compared to conventional shimming (Fig. 3d), signifying less distortion in the b50-maps when employing the add-on shim coil.

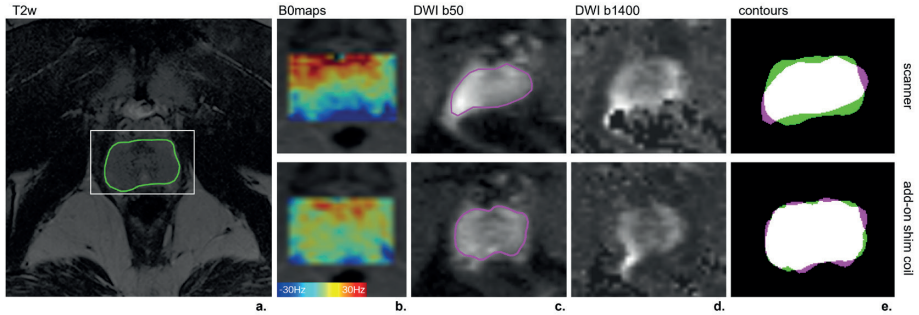


Figure 3. DWI analysis of an example slice in a subject (V3) using both conventional shimming (top) and the add-on shim coil (bottom) approaches **a.** Transversal T2W image as an anatomical reference with the prostate outlined in green and the selected shimming adjustment volume (white frame) **b.** B_0 maps **c.** b-50 EPI images with the prostate outlined in purple **d.** b-1400 EPI images **e.** resulting overlaid prostate segmentations of T2W contour (green) and b-50 DWI contour (purple) (scanner DSC = 0.87; add-on shim coil DSC = 0.94).

The SD of ΔB_0 , extracted from B_0 maps, and DSC, calculated per slice, were compared between both shimming techniques, on the entire cohort and on a per-volunteer basis. Using the add-on shim coil resulted in a statistically significant overall improvement in reducing distortion in b50-maps (Table 3). On a per-volunteer basis, in volunteers 1 and 3, the add-on shim coil outperformed conventional shimming, resulting in a higher mean DSC, translating to less distortion. In volunteers 2, 4, and 7, no statistical difference was found between the DSCs of the two shimming methods. In volunteer 6, conventional shimming achieved excellent field homogeneity and showed superior results compared to the add-on shim coil.

Table 3. Overview of results on B_0 map and DWI for all volunteers for conventional shimming and the add-on shim coil.

	B ₀ for DWI		DSC from DWI		
Volunteer #	SD of ΔB ₀ Hz		DSC _{mean} ± SD		p-value
	add-on shim coil	conventional	add-on shim coil	conventional	
1	21.7	23.9	0.91 ± 0.01	0.88 ± 0.02	0.05*
2	12.4	12.8	0.92 ± 0.03	0.91 ± 0.02	0.87
3	18.1	24.7	0.93 ± 0.01	0.84 ± 0.02	0.03*
4	19.2	18.5	0.92 ± 0.02	0.92 ± 0.02	0.58
5					
6	11.6	13.3	0.94 ± 0.02	0.95 ± 0.01	0.02*
7	15.7	15.6	0.88 ± 0.02	0.88 ± 0.01	0.19
ALL	16.5 ± 3.6	18.5 ± 4.7	0.92 ± 0.02	0.90 ± 0.02	0.01*

*significant differences with $p < 0.05$, ΔB_0 , off-resonance frequencies; SD, standard deviation; DSC, Dice similarity coefficient; DWI, Diffusion-weighted imaging;

Examining the potential relationship between the B_0 inhomogeneity reflected by the SD of ΔB_0 from the B_0 maps, and the distortion of EPI images in b50-maps, the SD of ΔB_0 of each volunteer was plotted in relation to the mean DSC (Fig. 4a). In volunteers with an SD of ΔB_0 exceeding 20 Hz in conventional shimming (two out of the six cases), the add-on shim coil achieved a lower SD of ΔB_0 and higher DSC values, indicating an improvement in magnetic field homogeneity. Additionally, we plotted the values of all slices within the prostates of all the volunteers (Fig. 4b). In the per-slice analysis, the slices with lower DSC values in conventional shimming displayed higher DSC values when using the add-on shim coil.

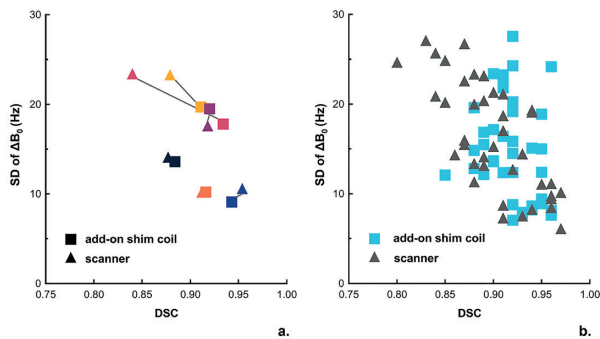


Figure 4. DWI analysis of the full cohort of examined subjects. **a.** SD of ΔB_0 as calculated from B_0 maps in relation to DSC of the b-50 DWI when compared with T2W images, displayed on a per-volunteer basis **b.** SD of ΔB_0 calculated from B_0 maps in relation to the DSC of the b-50 DWI when compared with T2W images, presented on a per-slice basis

Figure 5 displays the impact of both shim methods on ^1H -MRSI, showing the comparison using B_0 maps and Cit linewidth maps. Results from conventional shimming and the add-on shim coil are presented across three slices of an exemplary volunteer (V7). B_0 maps offered insights into both the full adjustment volume and a zoomed-in region (Fig. 5a and b), revealing reduced frequency offsets with the add-on shim coil, particularly evident in the zoomed-in panels. The voxels that successfully passed the QC in both shimming approaches are visualized in Figures 5c and 5e through Cit linewidth maps. Additionally, the spectral profiles of selected voxels, marked within Figs 5c and 5e, are presented in Figures 5d and 5f. Using the add-on shim coil resulted in narrower Cit linewidths in the spectra.

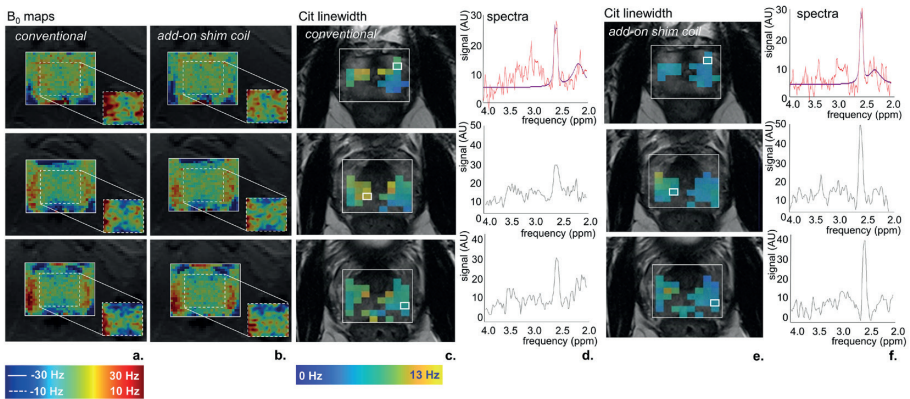


Figure 5. Shimming comparison in MRSI of conventional shimming and the add-on shim coil in three slices of an exemplary volunteer (V7). **a.** B_0 maps with conventional shimming **b.** B_0 maps with the add-on shim coil. The solid line frame represents the full adjustment volume with a frequency range of [-30, 30] Hz, while the dashed line frame is zoomed in with a frequency range of [-10, 10] Hz. **c.** Cit linewidth maps from conventional shimming. The voxels that successfully passed the QC in both shimming approaches are visualized in the figure. **d.** Spectra from indicated voxels in column c. In the top spectrum, the signal is in red and the fitting profile is in purple. **e.** Cit linewidth maps from the add-on shim coil. The voxels that successfully passed the QC in both shimming approaches are visualized in the figure. **f.** Spectra from indicated voxels in column e. In the top spectrum, the signal is in red and the fitting profile is in purple.

In terms of quantitative and statistical analysis, the QC evaluation revealed a comparable percentage of voxels within the complete VOI meeting the quality test criteria for both shimming techniques, achieving the same success rate of 43 % for both the add-on shim coil and conventional shimming. The statistical analysis was performed on all spectra that successfully passed the quality assessment in both techniques, revealing a significant difference in Cit linewidths ($p < 0.05$) between the two approaches along the full cohort. Specifically, the mean Cit linewidth

value for the add-on shim coil method was 7.9 ± 3.6 Hz, whereas conventional shimming resulted in a significantly higher value of 8.3 ± 5.7 Hz ($p = 0.018$). Further investigation into individual subjects showed varying outcomes among the seven cases under examination. Volunteers 2, 3, 5, and 7 demonstrated a significant improvement when the add-on shim coil was employed. Conversely, for volunteers 1 and 5, linewidths from the two techniques did not significantly differ. In the case of volunteer 6, significantly better results were found with the conventional shimming method. Similar to the DWI part of the examination, volunteer 6 had an excellent shim with conventional shimming. The subject-specific results are presented in Table 4.

Table 4. Overview of results on B_0 maps and MRSI all volunteers for conventional shimming and the add-on shim coil.

	B ₀ for MRSI		¹ H-MRSI Cit		
Volunteer #	SD of ΔB ₀ Hz		linewidth ± SD Hz		p-value
	add-on shim coil	conventional	add-on shim coil	conventional	
1	25.2	25.8	11.4 ± 3.0	11.6 ± 6.1	0.59
2	13.5	14.2	5.4 ± 1.3	6.9 ± 2.4	< 0.0001 *
3	21.7	21.9	8.5 ± 1.2	12.2 ± 1.1	0.0066 *
4	21.1	23.2	7.0 ± 3.9	19.0 ± 9.0	< 0.0001 *
5	23.9	22.2	10.6 ± 2.9	9.8 ± 6.5	0.0743
6	12.6	12.4	6.4 ± 1.2	5.2 ± 1.3	< 0.0001 *
7	15.6	15.1	6.6 ± 2.6	7.8 ± 2.8	<0.0001 *
ALL	19.1 ± 4.7	19.3 ± 4.8	7.9 ± 3.6	8.3 ± 5.7	0.018 *

*significant differences with $p < 0.05$, ΔB_0 , off-resonance frequencies; SD, standard deviation; $^1\text{H-MRSI}$, ^1H Magnetic Resonance Spectroscopic Imaging;

For a more detailed perspective on Cit linewidth results within each subject, Figure 6 presents histograms depicting the distribution of Cit linewidths. The panels in this figure include all voxels that successfully passed the QC assessment in both shimming approaches. A global shift of the histogram towards smaller linewidths demonstrates an overall improvement in linewidths, across the majority of volunteers. This improvement was especially evident in cases like V5, where conventional shimming showed particularly poor results.

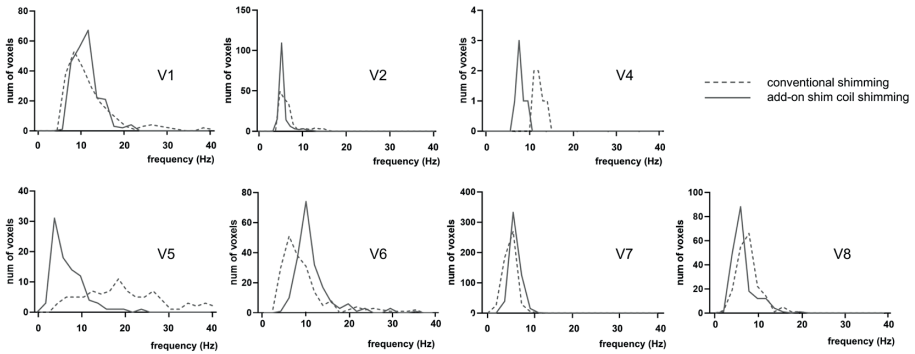


Figure 6. Cit linewidth distribution histograms on a per-subject basis. Cit linewidths from ^1H -MRSI acquisitions with the add-on shim coil (solid line) and conventional shimming (dashed line) from all voxels that passed QC per volunteer.

Discussion

Achieving a homogeneous B_0 field in the organ of interest is a fundamental requirement for successful MR acquisitions. High-quality B_0 shimming hinges on various crucial factors, such as carefully calibrating the B_0 shim coil hardware of the MRI system, employing robust methodologies to evaluate the B_0 homogeneity in the volume of interest, as well as precise computation of shim coil currents to modify the subject-specific field homogeneity with additional B_0 shim coils⁴. In this study, our objective was to enhance B_0 homogeneity in prostate imaging using an add-on shim coil array.

The presence of the shim coils affected the RF performance of the scanner. Nevertheless, the performance criteria set by NEMA and AAPM were satisfied. Transmit efficiency decreased by 2.3%, and the shim coil array presence imposed an SNR penalty of 20%, as measured on the T2W images. For future work, the interaction of the shim coils with the receive coil arrays needs to be minimized following recently published methods⁴⁰ to achieve “RF transparent” multi-turn shim coils. This work aimed at studying the effect of the prototype shim coil array on local magnetic field homogeneity, and in all the MRSI and DWI comparisons the shim coils were present for both shim settings to keep the comparisons consistent.

Using the add-on coil array for shimming consisted of acquiring a reference B_0 map, followed by subsequent calculations to determine the optimal currents for the add-on shim coil in combination with the 1st-order shim currents of the MR scanner. The

higher-order shim coils of the MR scanner were not included in this combination and were set to the tune-up values. We aimed to demonstrate that specific strong localized field inhomogeneities, such as those caused by the rectal air cavity, can be more effectively addressed using targeted fields generated by the add-on shim coil array.

Although it could provide additional shim fields, we did not incorporate the 2nd order spherical harmonics shim coils of the scanner in the calculations with the add-on shim coil array. Combining higher order shims with the external shim coil array demands for a very precise localization of the shim coil array within the higher order shim coils of the scanner, and knowledge of their mutual interaction⁴², to work in harmony. In this first study in the body, we decided therefore not to combine with the scanner's higher order shims. We opted to use the 1st order spherical harmonics from the scanner in conjunction with the local array as a compromise between the total amount of tunable shim coils and robustness, leaving the higher-order shim coils of the scanner out of the equation. This choice enhances the methodology's generalizability, as adapting spherical harmonic shims of the scanner shims requires accounting for any deviation between the actual shim fields produced by these coils compared to the analytical spherical harmonic mathematical functions that they were built after (in contrast to the linear shim terms which are also used in image encoding and are hence generally more pure)⁴¹.

We assessed the performance of the add-on shim coil array against the conventional shimming methodology of the MR scanner for prostate imaging (including higher-order shim coils), as typically performed in clinical practice, supplemented by manual fine-tuning. Manual fine-tuning is a common practice in prostate spectroscopy, aiming to achieve optimal shimming performance within the constraints of the conventional scanner's approach. The effectiveness of the two shimming procedures was evaluated on B_0 field maps, DWI, and ^1H -MRSI acquisitions.

B_0 field maps

Two sets of B_0 field maps were obtained after shimming: one before DWI and another before ^1H -MRSI, ensuring the repetition of the shimming process for both approaches. The comparative analysis, detailed in Tables 3 and 4, shows a decrease in the SD of ΔB_0 values in four out of six cases around the DWI acquisition, and in four out of the seven cases around ^1H -MRSI, respectively. A reduction is observed across the entire cohort of volunteers on a per-slice basis. Such reductions indicate improvements in field homogeneity throughout the entire adjustment volume for each volunteer involved in the study.

In assessing the repeatability of the shimming procedure, we performed the shimming procedure twice, immediately before the ^1H -MRSI and immediately before the DWI acquisitions. This approach aimed to mitigate potential influences stemming from physiological variations occurring within a scan session. Our observations, based on the homogeneity of B_0 maps, revealed consistent values when comparing each volunteer, attained by each shimming method across both sets of acquisitions conducted before DWI and ^1H -MRSI. This consistency underscores the association between the achievable shimming performance and various physiological characteristics of each subject, a common observation in prostate studies³, encompassing factors such as subject size, prostate size, subject anatomy, and bowel motion.

DWI

DWI, facilitated by EPI sequences, offers rapid acquisition of the entire k-space, crucial for accurate localization of prostate malignancies, especially in the peripheral zone of the prostate gland^{43,44}. Poor shimming can compromise the diagnostic value of mpMRI^{45,46}, particularly in patients with metallic hip arthroplasties, where susceptibility artifacts are commonly seen⁴⁷. Additional shimming can improve data quality, aiding in precise diagnoses of conditions like BPH, prostatitis, or cancer.

To evaluate the add-on shim coil's effectiveness with DWI, we assessed image distortion using DSC on b50-maps with an EPI sequence due to its short acquisition time (TA= 1:38 min). As a reference, we used T2W images acquired through a TSE sequence, known for its resilience to B_0 inhomogeneities⁴⁸ due to multiple refocusing pulses preventing the accumulation of phase errors⁴⁹. The add-on shim coil showed a better performance in three out of the six cases, similar performance in both shimming methods in two cases, and in one case the conventional shimming performed better. However, when analyzing the entire cohort across all slices of all the volunteers, statistically significant improvement was observed with the add-on shim coil. In cases where no significant difference was detected in the per-volunteer analysis (Volunteers 2 and 4), the DSC values were also at a high level with conventional shimming. When we analyzed the results from both DWI and B_0 maps on a per-slice basis, it became evident that when the add-on shim coil was used, in certain slices a high SD of ΔB_0 was found, as well as high DSC values. This contradictory finding can be attributed to the calculation of the SD of ΔB_0 on the complete 3D adjustment volume around the prostate, while the DSC value specifically pertains to the prostate contour within this volume. Furthermore, shimming was optimized on the entire 3D adjustment volume, which can still leave variation between slices. So, while efforts were made to ensure uniformity across

the entire volume of interest, slight differences in tissue composition or small movements during scanning may result in localized variations between individual slices of the imaging data.

¹H-MRSI

¹H-MRSI is a valuable tool for assessing tissue metabolites⁵⁰ and is substantially affected by B_0 field inhomogeneity. The spectral quality of MRSI data is highly influenced by B_0 field variations. Intra-voxel variations cause line broadening, and inter-voxel variations across the organ, introduce line shifts from one voxel to another^{51,52}. Addressing these is crucial for accurate metabolic assessments, as spectral overlap can adversely affect the quantification of key metabolites.

In our assessment of ¹H-MRSI, involving evaluation of the linewidth of Cit, we observed an overall improvement when utilizing the add-on shim coil. In the only case, volunteer 6, where conventional shimming yielded significantly better results, exceptional shimming quality had already been achieved through the conventional method. It is evident that even small variations, better visible in the zoomed-in panels of the B_0 field maps shown in Figure 5, have impact on Cit linewidths highlighting the necessity of homogeneous B_0 fields for ¹H-MRSI acquisitions.

Challenges and Future Aims

This study presents some challenges and limitations. The selection of the adjustment volume is important to ensure robust and repeatable results, especially in abdominal positions where proximity to the rectum can introduce air into the adjustment volume, potentially impacting shimming accuracy. Additionally, it is essential to confirm a stable water resonance frequency between scans and repeat the shimming process if a difference is detected to account for potential motion, organ displacement, and alignment issues between the organ of interest and the adjustment volume.

As a prospective goal, our next aim involves extending this approach to patient populations where the use of medication to suppress bowel motion is standard practice. This group often includes individuals with metallic hip implants that strongly deteriorate local field homogeneity. Enhanced shimming flexibility could offer substantial benefits to this group. Furthermore, concerning equipment development, investigating the incorporation of the shim coils into the RF receive array and automated detection of their position but without mutual interaction between RF and shim array, as well as implementing a feedback control system to continuously monitor shimming quality between consecutive acquisitions is of

interest. Such a system would enable prompt re-shimming if a decline in quality is detected. Additionally, the exploration of dynamic shimming techniques holds promise in further enhancing shimming performance within the targeted organ. Finally, despite the challenges posed by the precise understanding of their spatial dependencies and the need to accommodate any discrepancies between the actual shim fields and the theoretical spherical harmonic functions they are based on, pursuing further exploration into the combination of the shim coil array with higher order shims of the scanner would be of interest.

Conclusion

In this work, we presented the first version of a local external add-on shim coil array, tailored for prostate applications. Extensive assessments involving B_0 -maps, EPI-based DWI, and ^1H -MRSI have provided evidence of the effectiveness of this shim coil array. Our primary objective was to show the feasibility of this approach and to enhance B_0 field homogeneity within the prostate, leading to improved image quality and reduced image artifacts in DWI and MRSI, potentially enhancing precision in MR examinations of the prostate.

References

1. Jezzard P, Balaban RS. Correction for geometric distortion in echo planar images from B0 field variations. *Magn Reson Med*. 1995;34(1). doi:10.1002/mrm.1910340111
2. Jezzard P. Correction of geometric distortion in fMRI data. *Neuroimage*. 2012;62(2). doi:10.1016/j.neuroimage.2011.09.010
3. Shrestha Kakkar L, Usman M, Arridge S, Kirkham A, Atkinson D. Characterization of B0-field fluctuations in prostate MRI. *Phys Med Biol*. 2020;65(21). doi:10.1088/1361-6560/abbc7f
4. Juchem C, Cudalbu C, de Graaf RA, et al. B0 shimming for in vivo magnetic resonance spectroscopy: Experts' consensus recommendations. *NMR Biomed*. 2021;34(5). doi:10.1002/nbm.4350
5. de Graaf RA. In Vivo NMR Spectroscopy: Principles and Techniques: 2nd Edition.; 2007. doi:10.1002/9780470512968
6. Usman M, Kakkar L, Kirkham A, Arridge S, Atkinson D. Model-based reconstruction framework for correction of signal pile-up and geometric distortions in prostate diffusion MRI. *Magn Reson Med*. 2019;81(3). doi:10.1002/mrm.27547
7. Alhamud A, Taylor PA, van der Kouwe AJW, Meintjes EM. Real-time measurement and correction of both B0 changes and subject motion in diffusion tensor imaging using a double volumetric navigated (DvNav) sequence. *Neuroimage*. 2016;126. doi:10.1016/j.neuroimage.2015.11.022
8. Nketiah G, Selnaes KM, Sandsmark E, et al. Geometric distortion correction in prostate diffusion-weighted MRI and its effect on quantitative apparent diffusion coefficient analysis. *Magn Reson Med*. 2018;79(5). doi:10.1002/mrm.26899
9. Jezzard P, Clare S. Sources of distortion in functional MRI data. In: *Human Brain Mapping*. Vol 8.; 1999. doi:10.1002/(SICI)1097-0193(1999)8:2/3<80::AID-HBM2>3.0.CO;2-C
10. Graaf RA de. In Vivo NMR Spectroscopy: Principles and Techniques 3rd.; 2019.
11. Scheenen TWJ, Heijmink SWTPJ, Roell SA, et al. Three-dimensional proton MR spectroscopy of human prostate at 3 T without endorectal coil: Feasibility. *Radiology*. 2007;245(2). doi:10.1148/radiol.2451061444
12. Engels RRM, Israël B, Padhani AR, Barentsz JO. Multiparametric Magnetic Resonance Imaging for the Detection of Clinically Significant Prostate Cancer: What Urologists Need to Know. Part 1: Acquisition. *Eur Urol*. 2020;77(4). doi:10.1016/j.eururo.2019.09.021
13. Slough RA, Caglic I, Hansen NL, Patterson AJ, Barrett T. Effect of hyoscine butylbromide on prostate multiparametric MRI anatomical and functional image quality. *Clin Radiol*. 2018;73(2). doi:10.1016/j.crad.2017.07.013
14. Fernandez-Seara MA, Wehrli FW. Postprocessing technique to correct for background gradients in image-based R2/(*) measurements. *Magn Reson Med*. 2000;44(3). doi:10.1002/1522-2594(200009)44:3<358::AID-MRM3>3.0.CO;2-I
15. Cusack R, Brett M, Osswald K. An evaluation of the use of magnetic field maps to undistort echo-planar images. *Neuroimage*. 2003;18(1). doi:10.1006/nimg.2002.1281
16. Weiskopf N, Klose U, Birbaumer N, Mathiak K. Single-shot compensation of image distortions and BOLD contrast optimization using multi-echo EPI for real-time fMRI. *Neuroimage*. 2005;24(4). doi:10.1016/j.neuroimage.2004.10.012
17. Robson MD, Gore JC, Constable RT. Measurement of the point spread function in MRI using constant time imaging. *Magn Reson Med*. 1997;38(5). doi:10.1002/mrm.1910380509

18. Zaitsev M, Hennig J, Speck O. Point spread function mapping with parallel imaging techniques and high acceleration factors: Fast, robust, and flexible method for echo-planar imaging distortion correction. *Magn Reson Med*. 2004;52(5). doi:10.1002/mrm.20261
19. Andersson JLR, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: Application to diffusion tensor imaging. *Neuroimage*. 2003;20(2). doi:10.1016/S1053-8119(03)00336-7
20. Morgan PS, Bowtell RW, McIntyre DJO, Worthington BS. Correction of Spatial Distortion in EPI Due to Inhomogeneous Static Magnetic Fields Using the Reversed Gradient Method. *J Magn Reson Imaging*. 2004;19(4). doi:10.1002/jmri.20032
21. Juchem C, Umesh Rudrapatna S, Nixon TW, de Graaf RA. Dynamic multi-coil technique (DYNAMITE) shimming for echo-planar imaging of the human brain at 7 Tesla. *Neuroimage*. 2015;105. doi:10.1016/j.neuroimage.2014.11.011
22. Hargreaves BA, Worters PW, Pauly KB, Pauly JM, Koch KM, Gold GE. Metal-induced artifacts in MRI. *Am J Roentgenol*. 2011;197(3). doi:10.2214/AJR.11.7364
23. Speck O, Stadler J, Zaitsev M. High resolution single-shot EPI at 7T. *Magn Reson Mater Physics, Biol Med*. 2008;21(1-2). doi:10.1007/s10334-007-0087-x
24. Deichmann R, Gottfried JA, Hutton C, Turner R. Optimized EPI for fMRI studies of the orbitofrontal cortex. *Neuroimage*. 2003;19(2). doi:10.1016/S1053-8119(03)00073-9
25. Golay MJE. Field homogenizing coils for nuclear spin resonance instrumentation. *Rev Sci Instrum*. 1958;29(4). doi:10.1063/1.1716184
26. Roméo F, Hoult DI. Magnet field profiling: Analysis and correcting coil design. *Magn Reson Med*. 1984;1(1). doi:10.1002/mrm.1910010107
27. Koch KM, Sacolick LI, Nixon TW, McIntyre S, Rothman DL, De Graaf RA. Dynamically shimmed multivoxel ¹H magnetic resonance spectroscopy and multislice magnetic resonance spectroscopic imaging of the human brain. *Magn Reson Med*. 2007;57(3). doi:10.1002/mrm.21141
28. Meneses BP, Amadon A. Physical limits to human brain B0 shimming with spherical harmonics, engineering implications thereof. *Magn Reson Mater Physics, Biol Med*. 2022;35(6). doi:10.1007/s10334-022-01025-3
29. Stockmann JP, Arango NS, Witzel T, et al. A 31-channel integrated “AC/DC” B0 shim and radiofrequency receive array coil for improved 7T MRI. *Magn Reson Med*. 2022;87(2). doi:10.1002/mrm.29022
30. Juchem C, Theilenberg S, Kumaragamage C, et al. Dynamic multicoil technique (DYNAMITE) MRI on human brain. *Magn Reson Med*. 2020;84(6). doi:10.1002/mrm.28323
31. Zhou J, Stockmann JP, Arango N, et al. An orthogonal shim coil for 3T brain imaging. *Magn Reson Med*. 2020;83(4). doi:10.1002/mrm.28010
32. Stockmann JP, Wald LL. In vivo B0 field shimming methods for MRI at 7 T. *Neuroimage*. 2018;168. doi:10.1016/j.neuroimage.2017.06.013
33. Juchem C, de Graaf RA. B0 magnetic field homogeneity and shimming for in vivo magnetic resonance spectroscopy. *Anal Biochem*. 2017;529. doi:10.1016/j.ab.2016.06.003
34. Nassirpour S, Chang Y. Method to shim a magnetic field and magnetic resonance arrangement. Published online 2020.
35. Arun KS, Huang TS, Blostein SD. Least-Squares Fitting of Two 3-D Point Sets. *IEEE Trans Pattern Anal Mach Intell*. 1987;PAMI-9(5). doi:10.1109/TPAMI.1987.4767965

36. Steinseifer IK, Van Asten JJA, Weiland E, Scheenen TWJ, Maas MC, Heerschap A. Improved volume selective ¹H MR spectroscopic imaging of the prostate with gradient offset independent adiabaticity pulses at 3 tesla. In: *Magnetic Resonance in Medicine*. Vol 74.; 2015. doi:10.1002/mrm.25476
37. Chen X, Zhang Y, Cao Y, et al. A feasible study on using multiplexed sensitivity-encoding to reduce geometric distortion in diffusion-weighted echo planar imaging. *Magn Reson Imaging*. 2018;54. doi:10.1016/j.mri.2018.08.022
38. Dice LR. Measures of the Amount of Ecologic Association Between Species. *Ecology*. 1945;26(3). doi:10.2307/1932409
39. Stefan D, Cesare F Di, Andrasescu A, et al. Quantitation of magnetic resonance spectroscopy signals: The jMRUI software package. *Meas Sci Technol*. 2009;20(10). doi:10.1088/0957-0233/20/10/104035
40. Yan X. "RF transparent" local B0 shim coil. In: *Proc. Intl. Soc. Mag. Reson. Med*. 29.; 2021:3106.
41. Chang P, Nassirpour S, Henning A. Modeling real shim fields for very high degree (and order) B0 shimming of the human brain at 9.4 T. *Magn Reson Med*. 2018;79(1). doi:10.1002/mrm.26658
42. Sengupta S, Welch EB, Zhao Y, et al. Dynamic B0 shimming at 7 T. *Magn Reson Imaging*. 2011;29(4). doi:10.1016/j.mri.2011.01.002
43. Padhani AR, Barentsz J, Villeirs G, et al. PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway. *Radiology*. 2019;292(2). doi:10.1148/radiol.2019182946
44. Maurer MH, Heverhagen JT. Diffusion weighted imaging of the prostate-principles, application, and advances. *Transl Androl Urol*. 2017;6(3). doi:10.21037/tau.2017.05.06
45. Bammer R, Stollberger R, Augustin M, et al. Diffusion-weighted imaging with navigated interleaved echo-planar imaging and a conventional gradient system. *Radiology*. 1999;211(3). doi:10.1148/radiology.211.3.r99jn15799
46. Thierfelder KM, Scherr MK, Notohamiprodjo M, et al. Diffusion-weighted MRI of the Prostate: Advantages of Zoomed EPI with Parallel-transmit-accelerated 2D-selective Excitation Imaging. *Eur Radiol*. 2014;24(12). doi:10.1007/s00330-014-3347-y
47. Boschheidgen M, Ullrich T, Blondin D, et al. Comparison and prediction of artefact severity due to total hip replacement in 1.5 T versus 3 T MRI of the prostate. *Eur J Radiol*. 2021;144. doi:10.1016/j.ejrad.2021.109949
48. Mugler JP. Optimized three-dimensional fast-spin-echo MRI. *J Magn Reson Imaging*. 2014;39(4). doi:10.1002/jmri.24542
49. Yoshizako T, Yoshida R, Asou H, Nakamura M, Kitagaki H. Comparison between turbo spin-echo and echo planar diffusion-weighted imaging of the female pelvis with 3T MRI. *Acta Radiol Open*. 2021;10(2). doi:10.1177/2058460121994737
50. Stamatelatos A, Bertinetto CG, Jansen JJ, et al. A multivariate curve resolution analysis of multicenter proton spectroscopic imaging of the prostate for cancer localization and assessment of aggressiveness. *NMR Biomed*. Published online 2023. doi:10.1002/nbm.5062
51. Shams Z, Klomp DWJ, Boer VO, Wijnen JP, Wiegers EC. Identifying the source of spurious signals caused by B0 inhomogeneities in single-voxel ¹H MRS. *Magn Reson Med*. 2022;88(1). doi:10.1002/mrm.29222
52. Motyka S, Moser P, Hingerl L, et al. The influence of spatial resolution on the spectral quality and quantification accuracy of whole-brain MRSI at 1.5T, 3T, 7T, and 9.4T. *Magn Reson Med*. 2019;82(2). doi:10.1002/mrm.27746

Acknowledgments

This project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement 813120. We acknowledge Siemens Healthineers for providing the MRSI GOIA-sLASER WIP pulse sequence.

Chapter 4

Improving the Effective Spatial Resolution in ^1H -MRSI of the Prostate with Three-Dimensional Overdiscretized Reconstructions

Carlijn J.A. Tenbergen, Loreen Ruhm, Sjoerd Ypma, Arend Heerschap, Anke Henning and Tom W.J. Scheenen

Abstract

In in vivo ^1H -MRSI of the prostate, small matrix sizes can cause voxel bleeding extending to regions far from a voxel, dispersing a signal of interest outside that voxel and mixing extra-prostatic residual lipid signals into the prostate. To resolve this problem, we developed a three-dimensional overdiscretized reconstruction method. Without increasing the acquisition time from current 3D MRSI acquisition methods, this method is aimed to improve the localization of metabolite signals in the prostate without compromising on SNR. The proposed method consists of a 3D spatial overdiscretization of the MRSI grid, followed by noise decorrelation with small random spectral shifts and weighted spatial averaging to reach a final target spatial resolution. We successfully applied the three-dimensional overdiscretized reconstruction method to 3D prostate ^1H -MRSI data at 3T. Both in phantom and in vivo, the method proved to be superior to conventional weighted sampling with Hamming filtering of k-space. Compared with the latter, the overdiscretized reconstructed data with smaller voxel size showed up to 10% less voxel bleed while maintaining higher SNR by a factor of 1.87 and 1.45 in phantom measurements. For in vivo measurements, within the same acquisition time and without loss of SNR compared with weighted k-space sampling and Hamming filtering, we achieved increased spatial resolution and improved localization in metabolite maps.

1. Introduction

Multiparametric MRI (mpMRI) of the prostate has emerged as a reliable non-invasive imaging modality for identifying clinically significant cancer, enabling selective sampling of high-risk regions with MRI-targeted biopsies, aiding in therapeutic planning and active surveillance [1,2]. A clinical mpMRI examination consists of the acquisition of T2-weighted (T2w) images, DWI, and a gadolinium-based DCE series, deriving both anatomical and functional information from the prostate. It has been suggested that combining mpMRI with blood-sampled PSA-derived biomarkers could relieve uncertainty in the initial diagnosis [3]. Radiomics in prostate cancer, focused on quantitative data from, e.g., MRI, could improve assessments of prostate cancer risk categories at initial diagnosis, allowing a personalized treatment approach [4,5].

Another quantitative MRI modality, proton magnetic resonance spectroscopic imaging (¹H-MRSI), has also been shown as useful because healthy and cancerous prostate tissue regions present different choline and citrate signal intensities [6–8]. Ratios including these metabolites in combination with anatomical T2w MR imaging can identify and localize prostate cancer [9]. Previous work in a multi-center setting has also shown a correlation between the metabolite ratios and prostate cancer aggressiveness classes [10], indicating a role for ¹H-MRSI in characterizing prostate cancer.

Clinical use of prostate spin-echo ¹H-MRSI methods, however, is hindered by its limited robustness. Challenges in acquisition and post-processing techniques require special expertise [11] and the relatively long acquisition time of 5 to 10 min might outweigh the additional value to routine multiparametric MRI [12]. Next to these long acquisition times, the large voxel sizes of approximately 0.9 cm³ to gain a sufficient metabolite signal in MRSI is regarded as a drawback. This low spatial resolution causes voxel bleeding to extend over larger parts of the prostate. Voxel bleeding is apparent from the side lobes of the spatial response function (SRF), describing the origin of the signal for a specific voxel of the MRSI matrix, which extends all over the field of view (FOV) of the MRSI grid [13]. This spread of signal hinders precise localization of the signals of interest and causes the interference of other metabolites in the region of interest, such as peri-prostatic residual lipid signals extending into prostate tissue.

The side lobes of the SRF can be suppressed by applying a Hamming filter to the k-space data before spatial Fourier transformation (FT), decreasing far-reaching

voxel bleeding [14]. In combination with the weighted sampling of k-space, this is currently of-ten used as an ^1H -MRSI acquisition strategy [15]. Applying this filter comes at the cost of an increase in the effective voxel size, seen as a widening of the SRF main lobe, leading to an even lower spatial resolution of the resulting metabolite maps [14].

As an alternative to weighted sampling, an overdiscretized SRF target-based reconstruction method was presented by Kirchner et al. [16]. Developed as an improved SENSE reconstruction method [17] for single-slice two-dimensional (2D) ^1H -MRSI brain data, the method was shown to be effective in suppressing near and far-reaching voxel bleed and correcting for intra-voxel coil sensitivity variations. In later work, a noise decorrelation was added to the method to correct for intra-voxel frequency shifts, improving spectral line shapes and increasing the signal-to-noise ratio (SNR) in the presence of the main magnetic (B_0) field inhomogeneities on top of the voxel bleeding effects [18]. These methods were applied to a single brain slice and limited to a spatial 2D field of view. The potential to extend the application to other regions within the human body studied with 3D-MRSI has not yet been explored.

In the prostate, a small organ in the center of the lower abdomen, the B_0 field is mostly quite homogeneous, with occasional B_0 field distortions at the posterior edge of the prostate resulting from the presence of rectal gas [19]. Without large intra-voxel B_0 inhomogeneities, the method of noise decorrelation with intra-voxel frequency shifts using B_0 field maps is not expected to improve the spectra too much. We propose the use of random frequency shifts for the noise decorrelation of the spectra before the last step of applying a target function to reconstruct the final voxel sizes.

In this work we present the development of a three-dimensional overdiscretized and target-based MRSI reconstruction method (3D ODR method) to improve the spatial resolution of the 3D volume-selective MRSI of the prostate. After the initial overdiscretization of the MRSI grid, we used random frequency shifts for noise decorrelation before the last step of applying a target function. We compared this method with the conventional 3D MRSI with weighted k-space sampling and Hamming filtering of k-space at 3 Tesla. Without increasing the acquisition time from current 3D MRSI acquisition methods, the aim is to improve the localization of metabolite signals in the prostate without compromising on SNR.

2. Materials and Methods

2.1. Theory

The overdiscretized reconstruction method consists of three steps: overdiscretization of the MRSI grid, noise decorrelation between the subvoxels, and application of a target function to return to the final spatial resolution [16,18,20]. For the current 3D volumetric application, multiple single-slice operations in the existing 2D approach were replaced by volumetric reconstructions, while parallel imaging was omitted, coil elements were combined by the scanning system, a spin-echo sequence is used, and the method of noise decorrelation is revised.

The reconstruction method starts with overdiscretizing the MRSI grid in k-space by zero-padding the original grid (of N voxels). This creates an intermediate grid with, after 3D FT, an increased interpolated spatial resolution. The size of the intermediate grid is determined by the choice of the overdiscretization factor (ζ). The same factor was applied to all three dimensions, resulting in a ζ^3 -fold overdiscretized spatial grid. In target-driven overdiscretized reconstruction [20], a minimization is performed of the cost function (Δ) for each voxel:

$$\Delta = \|(FE_{OD} - T)\|_2^2 \quad (1)$$

where F , and T are the reconstruction operator, the overdiscretized encoding matrix, and the target matrix, respectively. The analytical solution of the optimization problem is given by:

$$F = TF_{OD} \quad (2)$$

with

$$F_{OD} = (E_{OD}^H E_{OD})^\dagger E_{OD}^H \quad (3)$$

in which reconstructs to the intermediate spatial grid of $\zeta^3 N$ subvoxels. After applying on the zero-padded k-space data s_{OD} ,

$$\rho_{OD} = F_{OD} s_{OD} \quad (4)$$

the noise of the spectra's neighboring subvoxels in the intermediate grid ρ_{OD} are strongly correlated. This correlation can be decreased, as the second step in the

reconstruction, by a per-voxel frequency shift of the spectra ($\Delta f(\mathbf{r})$) of the subvoxels at locations $\mathbf{r}$, resulting in a corrected intermediate grid:

$$\rho_{OD}^{corr} = \rho_{OD}(\mathbf{r}, t) e^{-i2\pi\Delta f(\mathbf{r})t} \quad (5)$$

The frequency shifts per voxel for the noise decorrelation were constructed with a map with random spatially distributed shift factors applied on the intermediate grid of the subvoxels. With the random spatial distribution of spectral shift factors, it is ensured that the noise between subvoxels is decorrelated, decreasing noise after weighted summation with a target function in the next step. With the number of spectral points to shift chosen within a small range (ranging from minus 2 to plus 2 spectral points), the widening of metabolite peaks is constrained.

As the third and final step, a 3D target function (T) is applied to the spatial intermediate grid after noise decorrelation to act similar to a spatial averaging operator:

$$\rho = T\rho_{OD}^{corr} \quad (6)$$

This target function sums up spectra from the individual subvoxels in a weighted manner to return to the original grid resolution. This weighted spatial average of subvoxels, achieved by an SRF target with a 3D Gaussian shape that suppresses long-range signal bleeds, leads to the final effective voxel size of the reconstructed MRSI data, which is close to the original nominal voxel size.

A schematic representation of the 3D ODR method is shown in Figure 1. The reconstruction method acts on two aspects: the overdiscretization and target function improve the SRF shape and corresponding signal localization while the noise decorrelation results in improved SNR. From previous work, the combination of an overdiscretization factor of 3 and target function width (σ) of 1.5 subvoxels was adopted, as this was shown to be optimal for SRF shape improvement [16]. The SRF shape after ODR with these parameters has very low residual side lobes (Figure 1).

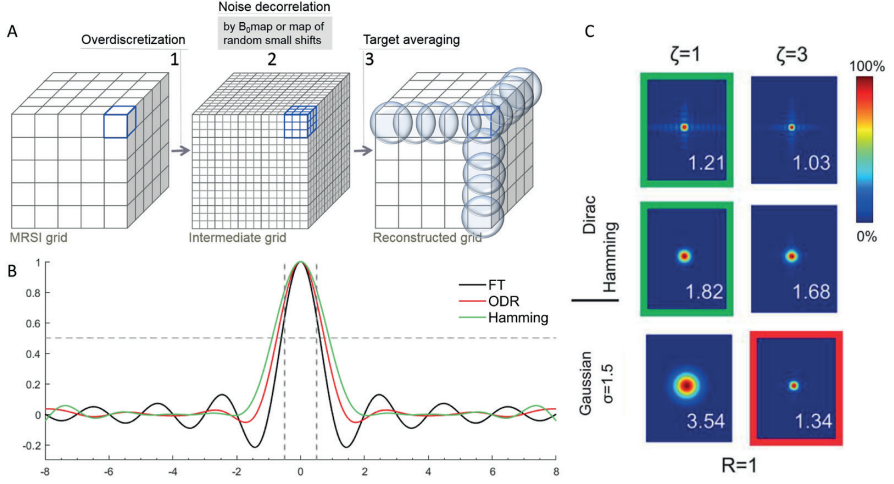


Figure 1. (A) Schematic overview of the 3D overdiscretized reconstruction method. The original MRSI grid is first transformed into a higher-resolution intermediate grid by zero-padding of k-space with factor 3. Each subvoxel spectrum is then frequency-shifted according to the corresponding B_0 map or random shifts. In the third step, the target resolution and shape of overlapping spheres is achieved by a weighted average of the subvoxels. (B) SRF in 1D after FT of fully sampled k-space and the SRF shapes after ODR reconstruction (red) and Hamming filtering (green), visualizing the main peak and side lobes for each reconstruction. Dashed lines indicate nominal resolution width and height at half maximum. (C) The FWHM of the main peak of 2D SRF of a central voxel is indicated by the numbers (adjusted and reproduced with permission [16]). The factors for overdiscretization ($\zeta = 3$) and gauss target width ($\sigma = 1.5$) of the SRF in the red box were extrapolated to 3D in this work and compared with Hamming filtering in the bottom green box.

With the chosen overdiscretization factor 3 and subsequent averaging with the target function of width 1.5, the resulting SRF has a width at a half height of 1.34 vs. 1.82 for the Hamming-filtered data (width relative to the nominal voxel width of the measurement) [16]. These numbers can be extended from a 2D voxel diameter representation to a 3D voxel volume representation, using half this width in the formula for calculating the volume of a sphere ($V = 4/3 \times \pi r^3$). An ODR dataset would represent a voxel volume of 1.26 times a nominal cubic voxel volume, as opposed to a voxel volume of 3.16 times the nominal volume for a conventional weighted dataset with Hamming filtering.

To illustrate the benefits of the improved SRF shape by our 3D ODR method we performed phantom measurements to analyze the effect of the reconstruction method on signal localization and measurements on a healthy volunteer to assess the feasibility in vivo for the application to ^1H -MRSI of the prostate.

2.2. Acquisition

All measurements were performed on a Siemens 3T MR system (MAGNETOM Prisma-fit, Siemens Healthineers AG, Erlangen, Germany) using an 18-channel body phased-array coil and a 32-channel spine phased-array coil for signal reception (Siemens Healthineers AG, Erlangen, Germany). T2w images, used as reference and anatomical background, were acquired in three directions by a TSE sequence (TE = 101 ms, 2 averages; Tra: TR = 5660 ms, $0.3 \times 0.3 \times 3.0$ mm; Sag: TR = 5590 ms, $0.6 \times 0.6 \times 3.0$ mm; Cor: TR = 5000 ms, $0.6 \times 0.6 \times 3.0$ mm). We acquired 3D ^1H -MRSI with a GOIA semi-LASER ^1H -MRSI sequence [21] with scan parameters: TR = 750 ms, TE = 88 ms, spectral bandwidth = 2.4 kHz, and 1024 time samples. As the signal from citrate, the most abundant metabolite in healthy prostate, originates from a strongly coupled spin system, its spectral shape depends on sequence timing. For the semi-LASER sequence, the echo time of 88 ms and corresponding pulse timing results in an optimal signal shape of citrate in the prostate [21].

The phantom used in this study is a cylindrical container filled with a sodium acetate solution with a cubic inner compartment with a creatine solution (Figure 2). This box-shaped inner compartment has distinct straight edges and can therefore be used for localization analyses. The singlet of creatine at 3.04 ppm in the inner cube is the signal of interest and the ^1H -MRSI is acquired with a matrix size of $11 \times 11 \times 11$ voxels and FOV of $77 \times 77 \times 77$ mm³. We used two acquisition approaches: one intended for ODR, in which k-space is fully sampled in an acquisition time of 16:40 min with 1 average; the other, in which k-space is sampled in a Hamming-weighted manner [14] with 8 k-space center averages to approximate a similar acquisition time (15:21 min). With these settings, both acquisitions yielded a similar acquisition time and matrix.

The acquisition strategy above does not result in equal voxel sizes for both datasets, as the width of the main lobe in the SRF is different for the weighted sampling and Hamming filtering versus the full k-space sampling with ODR. A second set of phantom measurements was aimed at acquiring similar final voxel sizes for both acquisition strategies within the same acquisition time. The mentioned SRF sizes, 1.34 vs. 1.82 times the radius of the spherical voxel for full k-space sampling with ODR and for weighted k-space sampling and Hamming filtering, respectively, were used to set up matrices resulting in equal voxel sizes. The first ^1H -MRSI acquisition with a full sampling of k-space was performed with a matrix of $11 \times 11 \times 11$ voxels, FOV of $88 \times 88 \times 88$ mm³, and 2 averages in 28:52 min (voxel radius = $0.5 \times 8 \times 1.34 = 5.36$ mm). The subsequent acquisition with weighted sampling of k-space was performed with 6 k-space center averages on a matrix of $15 \times 15 \times 15$ voxels, with

an FOV of $90 \times 90 \times 90 \text{ mm}^3$ and acquisition time of 30:23 min (voxel radius = $0.5 \times 6 \times 1.82 = 5.46 \text{ mm}$).

Next to the two sets of phantom measurements, datasets from a healthy 45-year-old male volunteer, obtained in accordance with local ethics regulations, were included. No preparation to suppress peristaltic motion was performed. First acquisition with full k-space sampling (1 average) was acquired in 11:10 min with a matrix size of $11 \times 9 \times 9$ voxels, FOV $88 \times 72 \times 72 \text{ mm}^3$, MEGA water, and fat suppression. A second acquisition with weighted k-space sampling was acquired with 9 averages and an acquired FOV size of $77 \times 63 \times 63 \text{ mm}^3$ (matrix size $11 \times 9 \times 9$) in an acquisition time of 11:04 min. With these measurements, a similar acquisition time and matrix were achieved for both acquisitions.

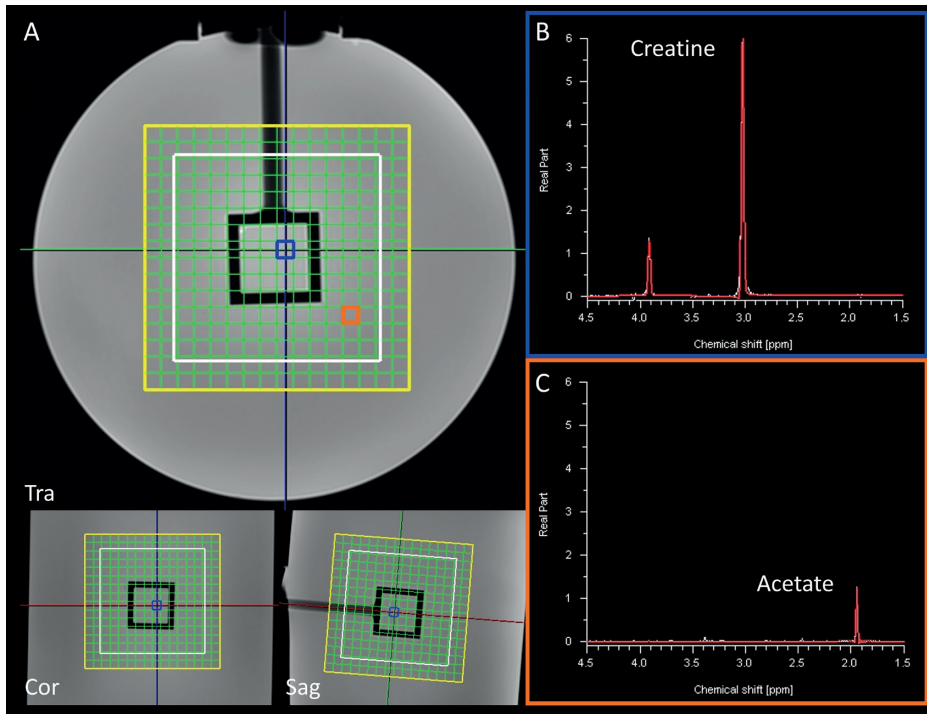


Figure 2. The phantom used in this study contains a creatine solution in the inner cube (spectrum from blue voxel, panel (B)) and acetate in the surrounding cylinder (spectrum from orange voxel, panel (C)). The matrix grid is indicated in yellow; the VOI is outlined in white (A). The colored lines in panel (A) show each plane in the other dimensions. The main peak of creatine (at 3.03 ppm) was set to represent the signal inside of the central cube and the integral of its fit was used to make creatine maps.

2.3. Reconstruction

The weighted datasets were reconstructed by Hamming filtering of k-space, followed by zero-filling to a matrix of $16 \times 16 \times 16$ voxels and spatial FT. This dataset functioned as a standard for comparison with the ODR pathway. The fully sampled datasets were zero-filled to $16 \times 16 \times 16$ matrices and were processed by the 3D overdiscretized reconstruction method in Matlab (The Mathworks, Natick, MA). For the first step, an overdiscretization factor of 3 increased the MRSI grid of $16 \times 16 \times 16$ voxels into an intermediate MRSI grid of $48 \times 48 \times 48$ subvoxels. Noise decorrelation was subsequently performed per voxel on the high-resolution intermediate grid. Random spatial distributions of shift factors were simulated with the same resolution, e.g., $48 \times 48 \times 48$, and frequency shifts were imposed on corresponding subvoxels. Shift factors were chosen in the range from -2 to 2 spectral points to ensure noise decorrelation while restraining spectral peak broadening. The noise-decorrelated intermediate spectroscopic image was transformed to the target resolution of $16 \times 16 \times 16$ voxels by the SRF target function with $\sigma = 1.5$ subvoxels, as shown successfully in combination with the overdiscretization factor 3 in previous 2D work [16].

2.4. Signal Analysis

The data processed with 3D ODR in Matlab and the originally acquired and postprocessed data (3D Hamming filter of zero-filled k-space) were imported in syngo.via (Siemens Healthineers AG, Erlangen, Germany) and all fitted with the same prior knowledge. For the phantom datasets, the signals of creatine (3.03 ± 0.05 ppm and 3.91 ± 0.05 ppm), lactate (1.34 ± 0.05 ppm), and acetate (1.9 ± 0.1 ppm) were fitted with a Gaussian function. The main peak of creatine (at 3.03 ppm) was chosen to represent the signal inside of the central inner cube and the integral of its fit was used to make metabolite maps. Creatine maps were normalized to the average integral value of the 8 voxels in the center of the cube. The creatine maps for the ODR data and Hamming-filtered data were compared both side to side as well as after subtracting one from the other in a difference map for a quantitative analysis of differences in voxel bleed. SNR was defined as the peak integral of creatine per voxel divided by the noise, stated as the standard deviation of the signal in an area of the spectrum not containing metabolites. To compare SNR values between the datasets with different voxel sizes, only voxels completely within the inner cube were chosen. These center 8 voxels overlapped with each other; the SNR values were therefore not independent. As the SNR is determined by both the SRF shape and the frequency shift, the separate contributions will be further analyzed by rendering an additional dataset for each experiment of full k-space sampling by applying ODR without the per-voxel frequency shift.

For the in vivo datasets, signals from citrate and residual lipids were fitted with appropriate line shapes at 2.6 ± 0.1 ppm and 2.3 ± 0.2 ppm, respectively. For the combination of total choline (3.21 ppm), polyamines (spermine at 3.12 ppm), and creatine (3.03 ppm) signals, the individual metabolite peaks were fitted as separate peaks. Metabolite maps of citrate and lipids were created and used for a qualitative analysis of signal localization. SNR values were extracted from the integral of the citrate peak over the noise value, where noise was again defined as the standard deviation of the signal in an area of the spectrum not containing metabolites. To compare spectral quality between ODR with and without frequency shift and Hamming-filtered data, SNR values from all datasets were compared in a voxel-wise manner, with a correction to account for the difference in relative voxel sizes. A selection of voxels from the same spatial location in all datasets, which were completely within the prostate with minimal overlap with each other, were chosen for SNR comparison. Localization of metabolite signals in both datasets was qualitatively analyzed by comparing citrate and lipids maps.

3. Results

To analyze the effects of the developed 3D ODR method on 3D ^1H -MRSI data, we assessed signal localization and the SNR of the methodology by a comparison with the traditional reconstruction with Hamming filtering.

3.1. Signal Localization

Signal localization for the two reconstruction methods was assessed by metabolite maps. The distribution of the creatine signal over the phantom was displayed in creatine maps with one partition of the 3D dataset in one orientation, representative of partitions through the center of the phantom in the other two directions (Figure 3). The creatine maps showed high signal intensity in the center of the inner cube of the phantom and decreasing intensity in voxels towards and over the edge of the cube for the weighted Hamming-filtered dataset. For the ODR dataset, this decrease in signal along the edges of the inner cube was more distinct, visualizing less voxel bleeding. This was due to the smaller main peak in the SRF, which resulted in a smaller effective voxel size for the ODR dataset compared with the weighted Hamming-filtered dataset. The difference map showed that this difference in voxel bleeding accounted for up to 10% of the normalized signal intensity.

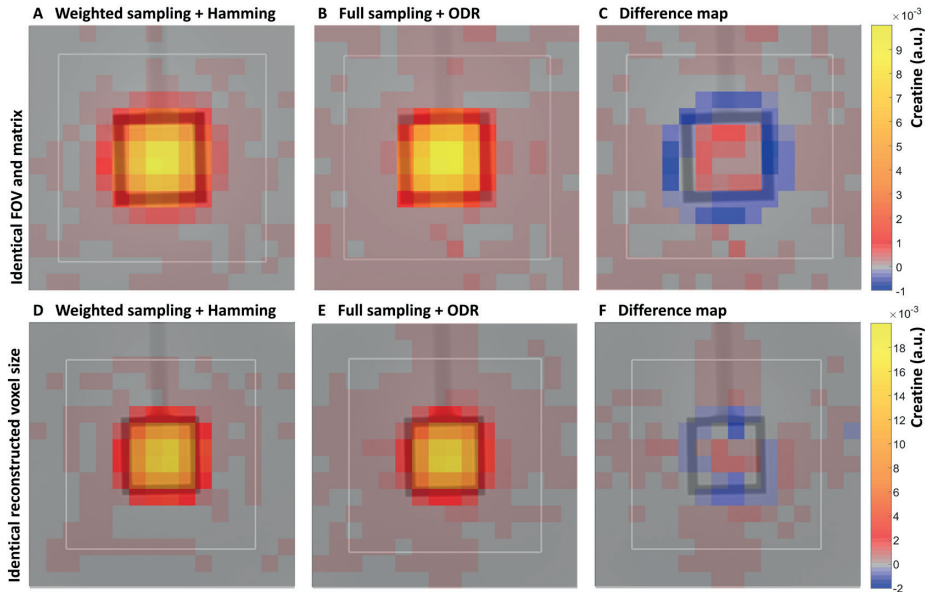


Figure 3. A phantom comparison of traditional sampling and ODR reconstruction. **(A)** Representative creatine intensity maps (in a.u.) of a center partition of the 3D datasets for weighted k-space sampling and Hamming filtering (matrix size: $11 \times 11 \times 11$, FOV: $77 \times 77 \times 77 \text{ mm}^3$). **(B)** Full k-space sampling and ODR reconstruction (matrix size: $11 \times 11 \times 11$, FOV: $77 \times 77 \times 77 \text{ mm}^3$). **(C)** Difference map **(A,B)** with same scaling shows localization of signal differences between datasets. The bottom row displays creatine maps from the second phantom acquisition aimed at equal voxel sizes: **(D)** weighted k-space sampling and Hamming filtering, **(E)** full k-space sampling and ODR reconstruction. **(F)** Difference **(D,E)** between the datasets is displayed with same scaling. Note that the creatine maps were separately normalized to the intensity of the center 8 voxels within the cube.

In the subsequent phantom dataset, where scan parameters were set up to acquire equal voxel sizes, the weighted k-space sampled and Hamming-filtered dataset was subtracted from the fully sampled k-space with the ODR dataset. In this difference map, the intensity in the center voxels was in the same range as background noise, so there was in-deed no distinct difference in localization when the two acquisitions were matched in effective voxel size.

A direct comparison between the two reconstruction approaches was made in all three orientations of the first phantom measurement (difference maps in Supplementary, Figure S1). The ODR dataset contained higher creatine signal intensities in the center cube of the phantom in comparison with the Hamming dataset. Negative values outside of the cube showed lower creatine levels in these voxels in the ODR dataset, which was indicative of improved signal localization ranging from 5 to 10% in all three directions in the ODR dataset, improving 3D SRF shape and signal localization.

Improved signal localization for the 3D ODR was also seen in the results from the volunteer measurement with representative partitions of the 3D citrate map in two orientations for the Hamming-filtered weighted dataset and fully sampled ODR dataset (Figure 4). The citrate signal in the ODR dataset was more confined to the healthy peripheral zone, with steeper edges and less bleed of signal along the edges outside of the prostate. When visualizing the spatial distribution of lipids around the prostate (Figure 5), a representative coronal slice of the lipid map shows less lipid contamination in the ODR dataset as the amount of signal originating from lipids in the surrounding tissues is decreased in the prostate tissue, as seen in the anatomical reference T2w image.

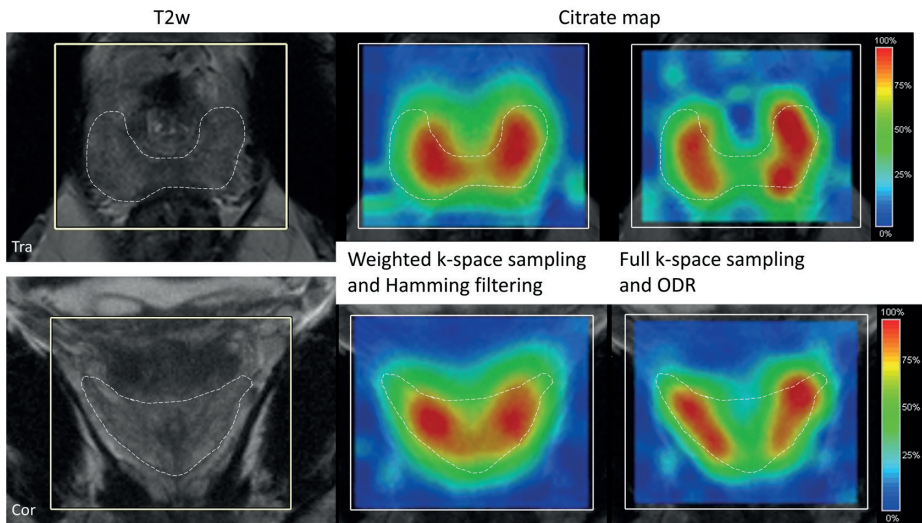


Figure 4. Citrate maps in transversal view (top) and coronal view (bottom) of a volunteer for the weighted k-space sampling and Hamming filtering (matrix size: $11 \times 9 \times 9$, FOV: $77 \times 63 \times 63 \text{ mm}^3$, 9 averages in 11:04 min acquisition time) (middle) and full k-space sampling and ODR (right) acquisition (matrix size: $11 \times 9 \times 9$, FOV: $88 \times 72 \times 72 \text{ mm}^3$, 11:10 min acquisition). Outlined is the peripheral zone of the prostate, where most of the citrate signal can be expected.

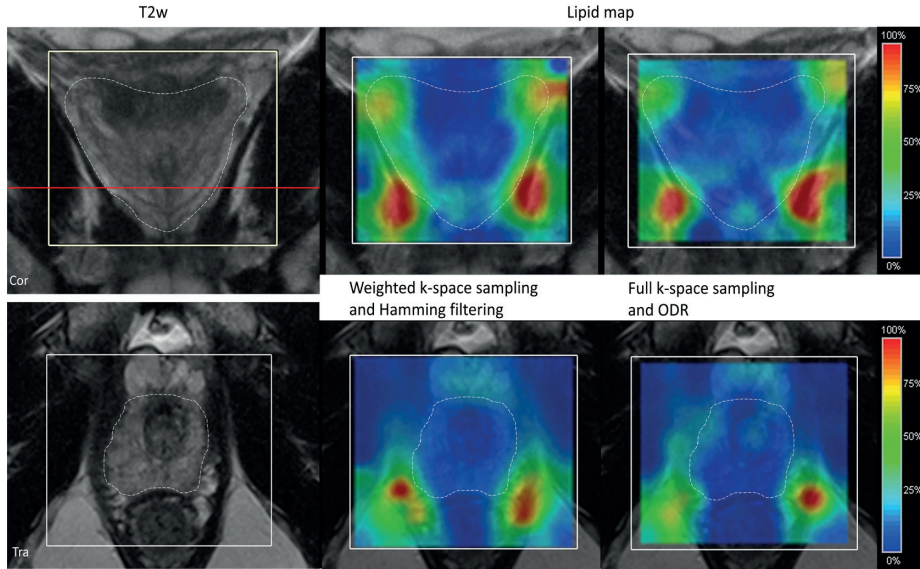


Figure 5. Lipid maps in coronal (top) and transversal (bottom) view of the volunteer for the weighted k-space sampling and Hamming filtering (matrix size: $11 \times 9 \times 9$, FOV: $77 \times 63 \times 63 \text{ mm}^3$, 9 averages in 11:04 min acquisition time) (middle) and full k-space sampling and ODR (right) (matrix size: $11 \times 9 \times 9$, FOV: $88 \times 72 \times 72 \text{ mm}^3$, 11:10 min acquisition). The dashed line indicates the edges of the prostate. The red line in the coronal view indicates the position of the transversal plane.

3.2. SNR

To assess whether the 3D ODR method compromises on SNR, corresponding voxels from both reconstruction methods were compared. The first phantom measurements resulted in an average SNR value in the central eight voxels of 8.30 (a.u.) for the ODR dataset, and 11.1 for the Hamming-filtered dataset (Table 1). The ODR dataset in the central eight voxels thus contains 0.75 times the SNR of the Hamming-filtered data, without corrections for corresponding voxel sizes. Correcting for the SRF-derived normalized calculated spherical voxel volumes (ODR: 1.26 vs. Hamming: 3.16 vs. hypothetical $1 \times 1 \times 1$ cube), the SNR for the ODR dataset in comparison to the Hamming-filtered dataset was increased on average with a factor of 1.87.

For the second phantom measurements, the SNR for the ODR dataset in comparison with the Hamming-filtered dataset is increased with a factor of 1.45 on average. While the voxel sizes were matched between the datasets, the center eight voxels indicated an SNR gain for the ODR.

Table 1. SNR results for the three different experiments. The last column shows the ratio of SNR value for the ODR dataset over the weighted sampling and Hamming-filtered dataset, corrected for relative voxel sizes.

		Effective Resolution	Voxel Radius	Mean SNR	Mean SNR Size Corrected	Ratio to Weighted Sampling + Hamming
phantom 1	Full k-space sampling	$8 \times 0.5 \times 1.34$	5.36	24.81	3.85	N/A
	Weighted sampling + Hamming filter	$8 \times 0.5 \times 1.82$	7.28	111.1	6.88	N/A
	ODR	$8 \times 0.5 \times 1.34$	5.36	83.02	12.87	1.87
	ODR w/o frequency shift	$8 \times 0.5 \times 1.34$	5.36	36.90	5.72	0.83
phantom 2	Full k-space sampling	$8 \times 0.5 \times 1.34$	5.36	35.57	N/A	N/A
	Weighted sampling + Hamming filter	$6 \times 0.5 \times 1.82$	5.46	84.56	N/A	N/A
	ODR	$8 \times 0.5 \times 1.34$	5.36	122.5	N/A	1.45
	ODR w/o frequency shift	$8 \times 0.5 \times 1.34$	5.36	51.44	N/A	0.61
volunteer	Full k-space sampling	$8 \times 0.5 \times 1.34$	5.36	5.26	0.81	N/A
	Weighted sampling + Hamming filter	$7 \times 0.5 \times 1.82$	6.37	20.6	1.90	N/A
	ODR	$8 \times 0.5 \times 1.34$	5.36	14.1	2.19	1.15
	ODR w/o frequency shift	$8 \times 0.5 \times 1.34$	5.36	6.79	1.05	0.55

The representative spectra of the volunteer measurement are shown in Figure 6. The dataset with weighted sampling and Hamming filtering showed clear and smooth peaks and low noise. The original fully sampled dataset had a high noise level, and by applying the ODR without the frequency shift, it decreases this noise due to the slight broadening of the main lobe of the SRF. In the case of ODR, including the frequency shift, the spectrum showed less high-frequency noise. The line broadening that is visible as a loss of some spectral resolution in the resonance groups of choline, spermine (polyamines), and creatine is comparable to the dataset of the weighted sampling and Hamming filtering. These three resonances often overlap in prostate MRSI, and assessment of individual linewidths in these groups is very challenging. In citrate, a strongly coupled spin system, line broadening only

caused a loss of separation of the two center peaks of the spectral shape, hardly affecting the total appearance of the total citrate signal.

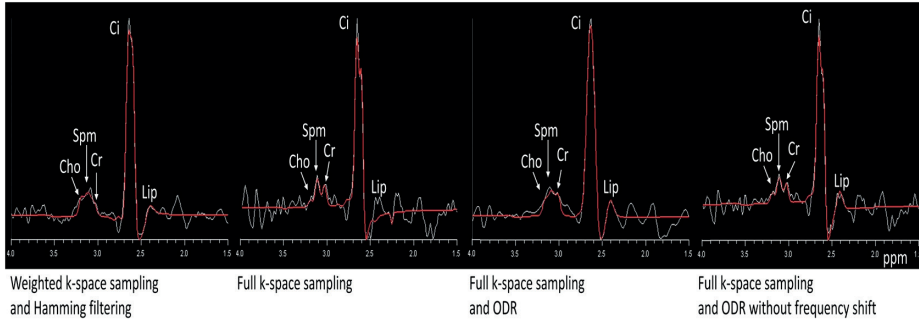


Figure 6. Spectra of a voxel within the peripheral zone of the prostate for the weighted k-space and Hamming filter dataset (left), next to a subsequently fully sampled dataset, full k-space sampling with ODR, and full k-space sampling with ODR without the frequency shift (right).

Comparing the ODR dataset with the Hamming-filtered dataset in eight independent voxels from the peripheral zone, the mean SNR values were 14.1 and 20.6 (a.u.), respectively. Thus, the ODR reached 0.68 times the SNR of the Hamming-filtered data. Correcting for the difference in voxel size, this translated to an increase in SNR with a factor of 1.15 for the ODR dataset compared with the Hamming-filtered dataset.

From Table 1 it can be appreciated that for all datasets, applying ODR without a frequency shift does improve SNR compared with the original full-sampling dataset because of SRF main-lobe broadening and side-lobe suppression. The ODR, including the frequency shift, however, combines SRF improvement and noise decorrelation, showing the mentioned gain in SNR compared with the Hamming-filtered datasets.

4. Discussion

In this work, we developed a 3D overdiscretized reconstruction method for semi-LASER 3D ^1H -MRSI and applied it to phantom and in vivo prostate measurements. With the 3D ODR method, it is possible to suppress far-reaching voxel bleed, with less increase in the effective voxel size as with weighted k-space sampling and Hamming filtering. In addition to the superior signal localization, a moderate gain in SNR was achieved.

Spatial resolution is an important aspect in MRSI, as a relatively large voxel size is needed to acquire signals from metabolites instead of water. This gives rise to partial volume effects, with one voxel representing a signal from different tissues, as is visible in the SRF, which hinders detecting or characterizing small lesions. With Hamming filtering, spatial resolution is traded for the suppression of far-reaching voxel bleed, with a widened main lobe of the SRF and decreased side lobes. The 3D ODR method increases the true spatial resolution of metabolite maps in comparison with Hamming filtering, matching underlying anatomical structures as found on clinical prostate MR imaging, and may therefore improve the metabolic characterization of small prostate cancer lesions.

For the second step of the ODR method, noise decorrelation of the overdiscretized 3D MRSI grid, two strategies can be used. The initial overdiscretization into an intermediate grid is created in real space by the zero-filling of the acquired k-space. Overlap of the respective SRFs is the major source of noise correlation in neighboring subvoxels of the intermediate grid. Imposing a small random frequency shift on the subvoxels before the third step of applying a target function to return to the final spatial resolution leads to noise decorrelation. If noise decorrelation is based on measured B0 maps, the frequency alignment of subvoxels can improve linewidths. However, with noise decorrelation based on random spectral shifts, instead of using a B0 map, spectral line widths can increase [18]. In phantom measurements with well-resolved and very narrow spectral lines, this spectral line broadening is visible. Choosing only few random spectral points to shift relative to the linewidth of the metabolites of interest prevents strong line broadening. Linewidths were larger in measurements of the prostate than in the phantom, not only because of tissue susceptibility differences but possibly also due to small body movements [22]. Noise decorrelation in the intermediate grid was based on random spectral point shifts between -2 and $+2$ points. The resulting spectra from the volunteer measurements showed some peak broadening. However, its impact on metabolite analysis is limited with the usual processing of quantifying the total spectral integral from 3.21 to 3.04 ppm with the sum of three spectral shapes of choline, spermine, and creatine, and with only a loss of the splitting of the two center peaks of the strongly coupled spectral shape of citrate.

Application of the ODR method, both to the phantom and volunteer measurements, showed an improved localization of signals of interest and decreased lipid contamination within the prostate of the volunteer. Metabolite localization and SNR could be directly compared in the phantom between weighted k-space sampling with Hamming filtering and full k-space sampling with ODR, as the

metabolite concentration and localization within the inner cube of the phantom was homogeneous and demarcated. The resulting difference maps in all three dimensions visualized the improved signal localization as a result of the improved 3D SRF shape when measuring with the same acquisition matrix in the same acquisition time. For the volunteer measurements, overlaying both datasets on anatomical T2w images provided the location of the peripheral zone or whole prostate gland as boundaries for estimated signal localization. However, comparing the signal intensities of voxels with different sizes remains challenging, as tissue metabolite signal intensity is not necessarily homogeneous, with varying metabolite concentrations across the whole prostate. Some studies have shown the use of anatomical boundaries to constrain metabolite signals within these boundaries, with the risk of biases in quantifying differences in metabolite signals within this anatomical region [23]. Apart from voxel definition by the two ways of MRSI data processing, accurate localization of metabolite signal within the whole volume of interest is also due to the use of a semi-LASER pulse sequence in the ^1H -MRSI acquisition of the phantom and volunteer. This volume selection already provides more accurate localization over a PRESS sequence for the whole VOI [21].

The effect of ODR on the observed SNR in the two separate phantom measurements needs clarification. An increase in SNR of 1.87 was achieved for the fully sampled and ODR dataset compared with the weighted k-space sampling and Hamming filtering data in the first measurement. This measurement involved different voxel sizes and a factor to correct for this choice. In the second phantom measurement we aimed at achieving a similar voxel volume for both the ODR dataset and the weighted Hamming-filtered dataset. Matching final voxel sizes was successful, as could be seen from the localization difference image between the two acquisitions (Figure 3F). The ODR method resulted in a SNR increase of 45%. In earlier work, Nassirpour et al. [20] found an average 23% SNR gain in ODR data with SENSE compared with reconstructing with SENSE alone (with $\zeta = 4$ at a field strength of 9.4T). Kirchner et al. [18] found an increase in SNR between the ODR data and the Hamming-filtered data with a factor of 3.7 (with $\zeta = 5$ at a field strength of 7T). There are several differences between those previous studies and the current one, and next to field strength and B0 homogeneity in the FOV, the spatial resolution of the MRSI datasets, the exact definition of SNR (peak or integral), and the upgrading to 3D can influence the SNR gain.

For the SNR comparison in the first phantom measurements, we calculated 3D voxel sizes extrapolated from simulated 2D SRF values, assuming spherical voxel sizes with a diameter of FWHM of the SRF. Moving from a 1D sinc-like, to a 2D circular shape, to a 3D spherical SRF facilitates calculations for effective voxel volume in 3D from the simulated numbers for 1D and 2D. The effective final voxel volumes were subsequently

used as the correction factor for SNR comparison. SRF line shape differences can cause differences in assumed voxel volumes between the two phantom measurements, resulting in different values for the correction factor for both signal and noise in the SNR of different voxel volumes.

In the datasets from the volunteer examination, it is more difficult to assess SNR gain. As the two datasets are of different spatial resolutions, one cannot choose the same position and voxel size in the two acquisitions; therefore, local tissue concentration differences can obscure a fair SNR comparison (even with correction for voxel size). SNR averaged over voxels completely within the peripheral zone was the best option here to compare both datasets, with full k-space sampling with ODR exceeding the SNR of the metabolites of interest over weighted k-space sampling with Hamming filtering.

Subsequent testing of the ODR method in patients with prostate cancer can establish the effect of improved signal localization and SNR for tumor characterization. With applying ODR on a fully sampled k-space dataset, the spatial resolution acquired in our in vivo examination required an acquisition time of 11 min. With expected differences in prostate sizes and larger prostate VOIs in older subjects, the acquisition time for MRSI might become too long. A solution would be to combine complete k-space sampling and ODR with accelerated read-outs, e.g., EPI or spiral read-out methods [24].

With an accelerated acquisition and automated post-processing workflow, resulting high-quality spectra could be of additional value in the clinical management of prostate cancer. Especially in repeated examinations per patient, as in active surveillance, we believe acquiring quantitative MRSI data enables direct comparison between scans and maximizes non-invasively acquired information of the prostate.

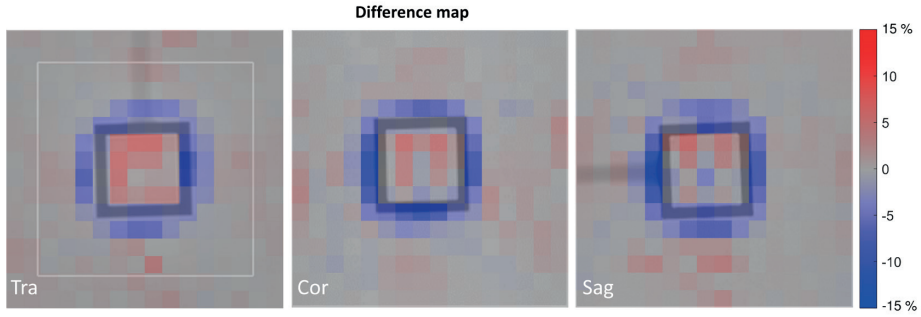
5. Conclusions

In this study, we successfully developed and implemented a three-dimensional over-discretized reconstruction method for semi-LASER 3D MRSI data of the prostate. Both in phantom and in vivo, the method proved to be superior in spatial resolution to conventional weighted sampling with Hamming filtering of k-space. Compared with the latter, data after overdiscretized reconstruction have a smaller voxel size while maintaining higher SNR. With an improved localization of metabolites in a phantom measurement and in vivo, the 3D ODR method is a promising tool to increase the quality of spectra and the spatial resolution of metabolite maps and hence their match to underlying anatomical structures.

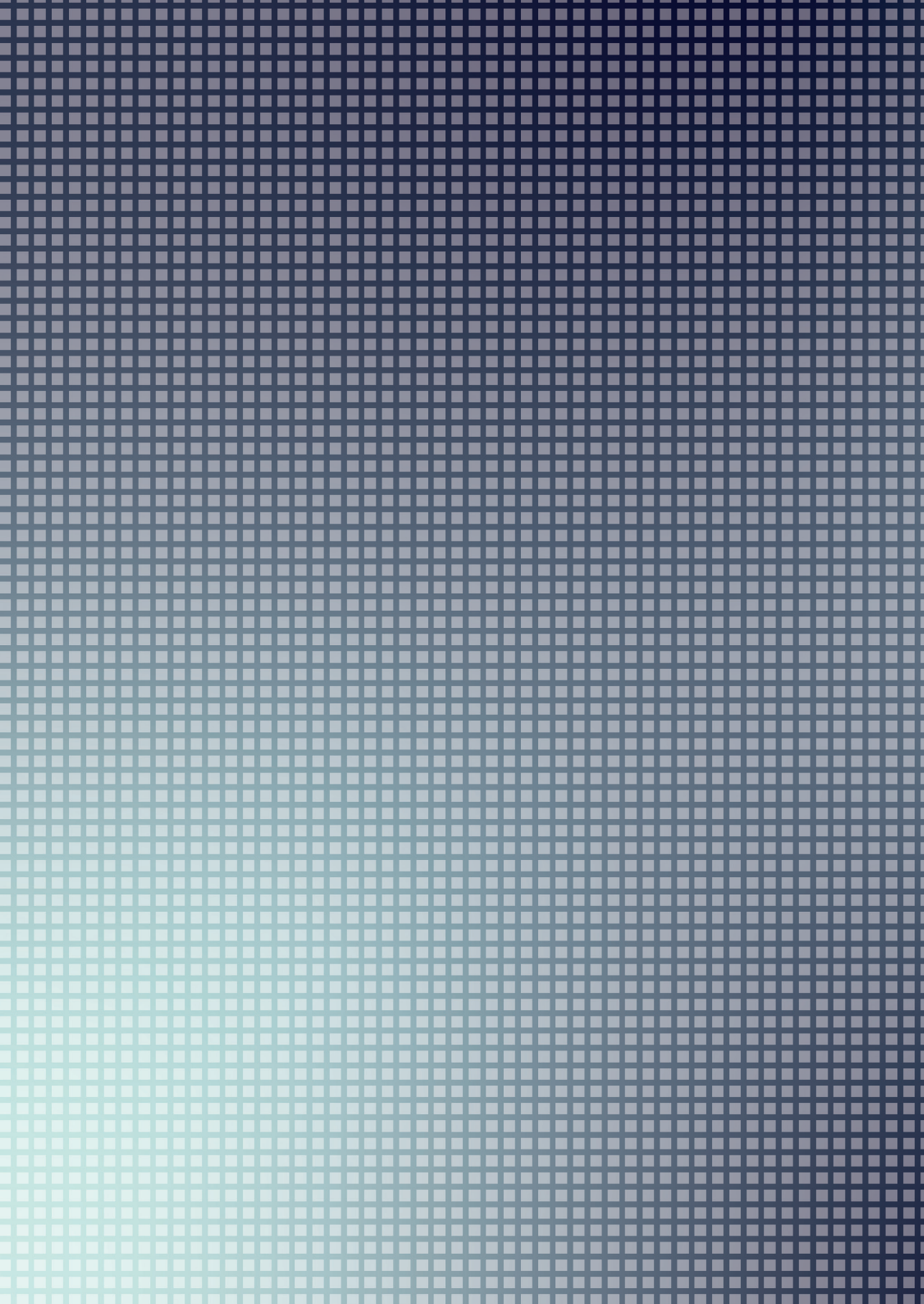
References

1. Cornford, P.; van den Bergh, R.C.N.; Briers, E.; Van den Broeck, T.; Cumberbatch, M.G.; De Santis, M.; Fanti, S.; Fossati, N.; Gandaglia, G.; Gillessen, S.; et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. *Eur. Urol.* 2021, 79, 263–282.
2. Massanova, M.; Robertson, S.; Barone, B.; Dutto, L.; Caputo, V.F.; Bhatt, J.R.; Ahmad, I.; Bada, M.; Obeidallah, A.; Crocetto, F. The Comparison of Imaging and Clinical Methods to Estimate Prostate Volume: A Single-Centre Retrospective Study. *Urol. Int.* 2021, 105, 804–810.
3. Ferro, M.; Crocetto, F.; Bruzzese, D.; Imbriaco, M.; Fusco, F.; Longo, N.; Napolitano, L.; La Civita, E.; Cennamo, M.; Liotti, A.; et al. Prostate Health Index and Multiparametric MRI: Partners in Crime Fighting Overdiagnosis and Overtreatment in Prostate Cancer. *Cancers* 2021, 13, 4723.
4. Ghezzi, S.; Bezzi, C.; Presotto, L.; Mapelli, P.; Bettinardi, V.; Savi, A.; Neri, I.; Preza, E.; Gajate, A.M.S.; De Cobelli, F.; et al. State of the art of radiomic analysis in the clinical management of prostate cancer: A systematic review. *Crit. Rev. Oncol. Hematol.* 2022, 169, 103544.
5. Ferro, M.; de Cobelli, O.; Musi, G.; Del Giudice, F.; Carrieri, G.; Busetto, G.M.; Falagario, U.G.; Sciarra, A.; Maggi, M.; Crocetto, F.; et al. Radiomics in prostate cancer: An up-to-date review. *Ther. Adv. Urol.* 2022, 14, 1–37.
6. Kurhanewicz, J.; Vigneron, D.B.; Nelson, S.J.; Hricak, H.; MacDonald, J.M.; Konety, B.; Narayan, P. Citrate as an in vivo marker to discriminate prostate cancer from benign prostatic hyperplasia and normal prostate peripheral zone: Detection via localized proton spectroscopy. *Urology* 1995, 45, 459–466.
7. Scheenen, T.W.; Futterer, J.; Weiland, E.; van Hecke, P.; Lemort, M.; Zechmann, C.; Schlemmer, H.; Broome, D.; Villeirs, G.; Lu, J.; et al. Discriminating cancer from noncancer tissue in the prostate by 3-dimensional proton magnetic resonance spectroscopic imaging: A prospective multicenter validation study. *Investig. Radiol.* 2011, 46, 25–33.
8. Heerschap, A.; Jager, G.J.; van der Graaf, M.; Barentsz, J.O.; de la Rosette, J.J.; Oosterhof, G.O.; Ruijter, E.T.; Ruijs, S.H. In vivo proton MR spectroscopy reveals altered metabolite content in malignant prostate tissue. *Anticancer Res.* 1997, 17, 1455–1460.
9. Futterer, J.J.; Scheenen, T.W.; Heijmink, S.W.; Huisman, H.J.; Hulsbergen-Van de Kaa, C.A.; Witjes, J.A.; Heerschap, A.; Barentsz, O.J. Standardized threshold approach using three-dimensional proton magnetic resonance spectroscopic imaging in prostate cancer localization of the entire prostate. *Investig. Radiol.* 2007, 42, 116–122.
10. Maas, M.C.; Litjens, G.J.S.; Wright, A.J.; Attenberger, U.I.; Haider, M.A.; Helbich, T.H.; Kiefer, B.; Macura, K.J.; Margolis, D.J.A.; Padhani, A.R.; et al. A Single-Arm, Multicenter Validation Study of Prostate Cancer Localization and Aggressiveness with a Quantitative Multiparametric Magnetic Resonance Imaging Approach. *Investig. Radiol.* 2019, 54, 437–447.
11. Scheenen, T.W.; Rosenkrantz, A.B.; Haider, M.A.; Futterer, J.J. Multiparametric Magnetic Resonance Imaging in Prostate Cancer Management: Current Status and Future Perspectives. *Investig. Radiol.* 2015, 50, 594–600.
12. Purysko, A.S.; Rosenkrantz, A.B.; Barentsz, J.O.; Weinreb, J.C.; Macura, K.J. PI-RADS Version 2: A Pictorial Update. *Radiographics* 2016, 36, 1354–1372.
13. Giskeødegård, G.F.; Bertilsson, H.; Selnaes, K.M.; Wright, A.J.; Bathen, T.F.; Viset, T.; Halgunset, J.; Angelsen, A.; Gribbestad, I.S.; Tessem, M.-B. Spermine and citrate as metabolic biomarkers for assessing prostate cancer aggressiveness. *PLoS ONE* 2013, 8, e62375.

14. Scheenen, T.W.; Klomp, D.W.; Roll, S.A.; Futterer, J.J.; Barentsz, J.O.; Heerschap, A. Fast acquisition-weighted three-dimensional proton MR spectroscopic imaging of the human prostate. *Magn. Reson. Med.* 2004, 52, 80–88.
15. Stamatelatos, A.; Scheenen, T.W.J.; Heerschap, A. Developments in proton MR spectroscopic imaging of prostate cancer. *MAGMA* 2022, 35, 645–665.
16. Kirchner, T.; Fillmer, A.; Tsao, J.; Pruessmann, K.P.; Henning, A. Reduction of voxel bleeding in highly accelerated parallel (1) H MRSI by direct control of the spatial response function. *Magn. Reson. Med.* 2015, 73, 469–480.
17. Sánchez-González, J.; Tsao, J.; Dydak, U.; Desco, M.; Boesiger, P.; Pruessmann, K.P. Minimum-Norm Reconstruction for Sensitivity-Encoded Magnetic Resonance Spectroscopic Imaging. *Magn. Reson. Med.* 2006, 55, 287–295.
18. Kirchner, T.; Fillmer, A.; Henning, A. Mechanisms of SNR and line shape improvement by B0 correction in overdiscrete MRSI reconstruction. *Magn. Reson. Med.* 2017, 77, 44–56.
19. Shrestha Kakkar, L.; Usman, M.; Arridge, S.; Kirkham, A.; Atkinson, D. Characterization of B(0)-field fluctuations in prostate MRI. *Phys. Med. Biol.* 2020, 65, 21NT01.
20. Nassirpour, S.; Chang, P.; Kirchner, T.; Henning, A. Over-discretized SENSE reconstruction and B0 correction for accelerated non-lipid-suppressed (1) H FID MRSI of the human brain at 9.4 T. *NMR Biomed.* 2018, 31, e4014.
21. Steinseifer, I.K.; van Asten, J.J.; Weiland, E.; Scheenen, T.W.; Maas, M.C.; Heerschap, A. Improved volume selective (1) H MR spectroscopic imaging of the prostate with gradient offset independent adiabaticity pulses at 3 tesla. *Magn. Reson. Med.* 2015, 74, 915–924.
22. Andronesi, O.C.; Bhattacharyya, P.K.; Bogner, W.; Choi, I.-Y.; Hess, A.T.; Lee, P.; Meintjes, E.M.; Tisdall, M.D.; Zaitsev, M.; van der Kouwe, A. Motion correction methods for MRS: experts' consensus recommendations. *NMR Biomed.* 2021, 34, e4364.
23. Kasten, J.; Klauser, A.; Lazeyras, F.; Van De Ville, D. Magnetic resonance spectroscopic imaging at superresolution: Overview and perspectives. *J. Magn. Reson.* 2016, 263, 193–208.
24. Steinseifer, I.K.; Philips, B.W.; Gagoski, B.; Weiland, E.; Scheenen, T.W.; Heerschap, A. Flexible Proton 3D MR Spectroscopic Imaging of the Prostate with Low-Power Adiabatic Pulses for Volume Selection and Spiral Readout. *Magn. Reson. Med.* 2017, 77, 928–935.



Supplementary Figure S1. Creatine difference maps from phantom acquisitions displayed in three dimensions. After subtracting the weighted and Hamming-filtered k-space dataset from the fully k-space sampled and ODR dataset, the difference between these creatine maps is expressed as a percentage. Voxels in red indicate higher signal in the ODR dataset, mainly inside of phantom inner cube (dashed line), while blue indicates higher signal intensity in the weighted k-space and Hamming filter dataset, along the edges outside of phantom. Signal intensities are normalized per dataset to total signal over the FOV.



Section II:

MR imaging of the prostate
and lymph nodes at 7 T

Chapter 5

Ultra-high-field MR in Prostate cancer: Feasibility and Potential

Carlijn J. A. Tenbergen, Gregory J. Metzger, Tom W. J. Scheenen

Abstract

Multiparametric MRI of the prostate at clinical magnetic field strengths (1.5/3 Tesla) has emerged as a reliable noninvasive imaging modality for identifying clinically significant cancer, enabling selective sampling of high-risk regions with MRI-targeted biopsies, and enabling minimally invasive focal treatment options. With increased sensitivity and spectral resolution, ultra-high-field (UHF) MRI (≥ 7 Tesla) holds the promise of imaging and spectroscopy of the prostate with unprecedented detail. However, exploiting the advantages of ultra-high magnetic field is challenging due to inhomogeneity of the radiofrequency field and high local specific absorption rates, raising local heating in the body as a safety concern. In this work, we review various coil designs and acquisition strategies to overcome these challenges and demonstrate the potential of UHF MRI in anatomical, functional and metabolic imaging of the prostate and pelvic lymph nodes. When difficulties with power deposition of many refocusing pulses are overcome and the full potential of metabolic spectroscopic imaging is used, UHF MR(S)I may aid in a better understanding of the development and progression of local prostate cancer. Together with large field-of-view and low-flip-angle anatomical 3D imaging, 7 T MRI can be used in its full strength to characterize different tumor stages and help explain the onset and spatial distribution of metastatic spread.

Introduction

MRI of the prostate has emerged as a reliable noninvasive imaging modality for identifying and characterizing focal regions within the prostate. A multiparametric MRI (mpMRI) examination consists of the acquisition of T2-weighted (T2w), diffusion-weighted (DWI) and gadolinium-based dynamic contrast-enhanced images (DCE), deriving both anatomical and functional information from the prostate. Qualitative and quantitative parameters from such an mpMRI exam correlate with pathological Gleason score and help identify clinically significant cancer [1, 2]. Identification of extra-prostatic extension of the lesion and seminal vesicle invasion is also possible on mpMRI, improving localized disease staging, which is essential for personalized treatment planning [3].

The ability of mpMRI to accurately localize areas suspicious for cancer in the prostate allow for selectively sampling of high-risk regions with MRI-targeted prostate biopsies. In comparison with standard systematic biopsy, guided by ultrasound, prebiopsy MRI followed by MRI-targeted biopsy has the potential to not only improve detection of clinically significant cancer, but also to reduce unnecessary biopsies and over-diagnosis of low-grade, clinically insignificant disease [4]. Active surveillance of low-grade cancer instead of direct therapy is considered a viable management option, as a recognition of the often slow progression of the disease and the importance of maintaining good quality of life [5].

Focal minimally invasive treatment options also take advantage of accurate localization and characterization by MRI for MRI-guidance during the procedures, as well as for the evaluation of treatment success after focal therapy [6]. Currently experimental focal therapies such as high-intensity focused ultrasound, cryoablation and focal laser ablation may become an alternative to radical prostatectomy and high-dose conformal radiotherapy. These focal methods of treatment for patients with organ-confined prostate cancer could reduce adverse events associated with radical treatment whereas retaining at least equivalent cancer control [7]. mpMRI may also play a crucial role in the evaluation of recurrent prostate cancer after focal or any whole gland treatment.

With the development of more personalized treatment options, determining the best treatment strategy for each patient becomes crucial. Whereas localization of a tumor within the prostate is now very well possible with mpMRI [4], assessing its aggressiveness and local and nodal stage still seems difficult, with current clinical mpMRI methodology showing large variation in performance between

sites and readers [8]. The use of mpMRI for management of prostate cancer coincided with the introduction of MRI scanners with a magnetic field strength of 3 Tesla in the clinical arena [9]. Using even higher magnetic fields (e.g., 7 T) may bring further benefits in answering clinical questions by allowing imaging of the prostate with unprecedented detail. To date only used in a research setting, the increased magnetic field strength comes with a higher signal-to-noise ratio (SNR) and increased spectral resolution, both of which benefit magnetic resonance spectroscopy studies of the prostate [10]. With increased SNR, existing imaging methods can be improved, but also methods such as phosphorus (^{31}P) spectroscopic imaging could become feasible as an imaging biomarker of prostate cancer aggressiveness despite its naturally lower sensitivity [11].

Moving beyond 3 T and making use of the advantages of an ultra-high magnetic field strength poses some challenges [12]. The most significant one being the heterogeneity in the electromagnetic fields in the radiofrequency (RF) range used to excite, refocus and receive the MR signals. The complexity of the transmit magnetic field (B_1+) distortions scale with field strength and the size of the imaging region of interest and can lead to a heterogeneous distribution of flip angles resulting in varying contrast and signal loss throughout the images. In parallel, the heterogeneity in the accompanying complex electric fields can result in high local specific absorption rates (SARs). Furthermore, as susceptibility effects also scale with static field strength (B_0), inhomogeneities in B_0 present additional challenges for prostate mpMRI and spectroscopy at 7 T. Finally, the use of ultra-high-field (UHF) body MRI requires custom hardware and software methods, as no vendor currently provides adequate solutions and no existing solutions are approved for clinical translation.

This review will describe the work performed by several research groups to overcome UHF challenges for prostate MR as well as the potential role for MRI/MRS at 7 T in prostate cancer management. We will present an overview of different RF coil designs to facilitate pelvic and prostate imaging at UHF, and we discuss the results of—and outlook for—in vivo measurements to illustrate the potential for a better understanding of prostate cancer and involved lymph nodes in the pelvis with anatomical, functional, and metabolic MRI.

Radiofrequency coil designs for pelvic MR at 7 T

At 7 T, the inhomogeneity of the RF transmit field combined with increased power requirements and power depositions hinders the use of whole-body RF transmit coils, as is the norm at 3 T. While there is some development on whole-body transmitters [13], local transmit coils which also function as receivers are most

practical and are most commonly used for 7 T body imaging. Still the complex B_1^+ fields and the greater power depositions at 7 T present challenges in the development and safe use of high-performance local transmit-receiver (transceiver) coil arrays for imaging of the prostate.

Coil designs with multiple independent transmit elements allow for parallel transmission to manipulate the transmit field distribution. These coils are most effectively used when coupled with a system equipped with parallel transmit hardware which has been previously described in the context of UHF body imaging [14]. The possibility to modulate the phase and/or magnitude of each transmit element in an array enables so-called B_1^+ shimming. Metzger et al. demonstrated for the first time successful prostate imaging at 7 T with an eight-channel stripline array combined with subject-dependent B_1^+ shimming [15]. Using a transceiver surface array coil and altering the input phase of each RF channel based on a relative B_1 phase map rapidly obtained in vivo for each channel, it was possible to maximize B_1^+ phase coherence and thus improve B_1^+ homogeneity and transmit efficiency in a region of interest around the prostate. The improved transmit efficiency reduced the required RF power for a given flip angle and reduced local SAR. By doubling the element density by going from an 8-channel to 16-channel stripline array [16], an increase in the expected transmit and parallel imaging performance was achieved at the expense of increased decoupling complexity. SNR increased by 22% for the 16-channel array while lower local and global SAR was exhibited.

As an alternative to the stripline array element, Raaijmakers et al. introduced variations on the dipole for constructing body imaging arrays [17]. Eight single-sided adapted dipole antennas were combined in a surface array aimed at imaging deeply located structures in the body at 7 T, e.g., the prostate. Comparisons to a loop-coil and stripline arrays show that the B_1^+ level at the deeper regions is higher for the dipole array with a more symmetrical and uniform B_1^+ field distribution. The addition of a tuned inductance in each leg of the dipole in the form of a modified conductor trace (i.e., meanders) leads to what was referred to as the fractionated dipole antenna. RF arrays of the fractionated dipoles lead to improved SAR performance and more homogeneous transmit and receive profiles in the body [18]. At relatively low SAR levels, dipole antennas provide improved B_1^+ efficiency and homogeneity at greater depths compared to loop or stripline elements, without the need for subject-specific tuning and matching [18, 19]. Another 8-channel array composed of center-fed microstripline resonators with meanders presented by Orzada et al. [20] also performs well for body imaging at 7 T with a similar quality where patient specific tuning and matching is not required.

As loop coils provide high transmit and receive performance at shallower depths, these coil designs are mostly seen in endorectal coils (ERC). Different configurations were developed, e.g., single-loop [21], two-loop, and microstrip-loop [22–24], either as transceiver or as receive only in combination with a transmit external surface array. In a direct comparison, a two-loop ERC performed best in SAR efficiency, and SNR at 3 cm from the coil, thereby enabling high-quality prostate imaging at 7 T in combination with an external surface array [23]. External transceiver loop-coil arrays have been used to image the heart at 7 T [25]. Loop coils have also been combined with dipole elements in an external transceiver array in work by Erturk et al. [26]. This 16-channel combined loop-dipole transceiver array exploited both the higher transmit and receive performance of the loop elements at shallower depths and improved the performance of the dipole elements at greater depths. The complimentary field patterns of the dipole and loop resonant structures lead to improved performance compared to arrays comprised of loops or dipoles alone.

Somewhat in line with more clinical coil setups, local receive loop-coil elements have also been added at 7 T to increase SNR closer to the body surface and allow larger acceleration factors in parallel imaging. An 8-channel stripline with meander elements array was combined with 24 additional receive-only loop coils for an 8Tx/32Rx setup [27], and also an 8-channel transceiver dipole array was extended with 16 receive-only loop elements, albeit first applied in the upper abdomen [28]. To fully resemble a clinical system with an integrated RF coil, a complete 32-channel parallel transmit system was designed of which the coil elements were placed in the gap between the gradient coil and liner of the patient tunnel [13]. This transmit array had a wide B_1 transmit field of 50 cm, and could be combined with receive-only loops [29]. Although this setup provides more freedom and comfort to the patient, as only a thin layer of loop coils is needed on top of and below the body, it remains challenging to transmit at high power with well-decoupled distant coil elements.

Power limits for the body: the specific absorption rate

With increasing magnetic field strength and correspondingly higher RF frequencies, SAR becomes a major issue in the human body. At 7 T and higher, RF field distributions in the torso become largely inhomogeneous, causing local SAR hot-spots inside the body. Using parallel transmit systems, the RF field can be tailored to manage RF inhomogeneity. Still the average RF power needs to be constrained to limit SAR below IEC guidelines [30], with regulatory limits reached much sooner than at 3 T. At UHF, the application of RF over time is generally not limited by whole-body average (global) SAR but rather by local SAR, which cannot be measured directly. Usually, local SAR is numerically estimated using detailed computer-aided models of the human body

and of the RF coil with a variety of B_1 shim settings [11, 16, 18, 26]. Worst-case SAR levels from these simulations lead to channel-specific RF power limits for subsequent in vivo imaging, where these conservative power limits translate into limitations in pulse sequences that traditionally are in need of this RF power (e.g., less slices, longer repetition times or longer RF pulse durations in turbo spin-echo sequences). Subject-specific RF shimming could personalize estimation of locally deposited RF power, and could, therefore, allow more power to be transmitted for individual subjects within SAR safety limits than the general worst-case scenario prescribes. A fast and robust assessment of B_1^+ fields in the body of the subject is a first step in this direction [31].

Specific for prostate applications, the extent of local SAR variability between subjects is investigated by Ipek et al. [32]. Four body models were created by segmenting water and fat separated MR images of four volunteers scanned at 1.5 T with the 7 T single-sided dipole antenna coil [17] in place. Simulations found maximum potential local SAR_{10g} levels for 1 W time-averaged accepted power per transmit channel ranging from 4.1 to 7.1 W/kg. These variations show that one model is not sufficient to determine safe power limits. To accommodate the fact that patient specific electromagnetic models are not practical to construct currently, the intersubject variability can be accounted for by assigning a safety factor of 1.7 which is used to scale the estimated SAR determined by the MRI system. After developments in coil design, a newer fractionated dipole antenna [18], was investigated by SAR simulations with the same method but now in 23 body models built from segmented 1.5 T images [33]. For this setup, the maximum local SAR_{10g} for 8×1 W input power ranged from 2.6 to 4.6 W/kg. This range still requires a safety margin for inter-subject variability of factor 1.78 when using only 1 model in testing of a specific coil design.

Fast subject-specific B_1^+ mapping in the pelvis in combination with an alternative way of calculating individualized SAR estimates has been explored for a multi-channel coil array setup [31]. This method used an intermediate offline step to calculate the shims and corresponding power limits taking about 2 min. Ideally, SAR calculations should be individualized to the subject on the table and calculated within a few seconds on the basis of a short preparation scan, altogether automated in one adjustment of the MR system. Meliado et al. aimed for subject-specific local SAR estimates by training a convolutional neural network to estimate a SAR distribution based on a B_1^+ map [34]. Training samples were created from the 23 subject-specific body models consisting of synthetic complex B_1^+ maps and local SAR distributions. After training, the network took a few milliseconds to predict the accurate local SAR distribution from the presented in vivo B_1^+ map. The peak local SAR estimation showed an overestimation error of 15%, reducing the uncertainty

in previous SAR assessment methods. This deep learning method allows online image-based subject-specific local SAR assessment, which could dramatically reduce the time for individual system adjustments in a 7 T MR examination.

A different approach to reduce time for system adjustments is the use of a single amplitude and phase shim setting of the transmit channels of a particular transmit coil for all subjects. A fixed RF shim based on the relative phase settings of 12 patients using an 8-channel transmit coil [35] demonstrated that this strategy works but at the expense of B_1^+ homogeneity and maximum achievable peak B_1^+ in the prostate. Incorporating gradient modulation during the RF pulse in the concept of universal pulses has been embraced for the brain [36] and holds promise for organs in the body as well.

Anatomical imaging of the prostate: T2-weighted imaging

Clinical anatomical imaging of the human prostate predominantly relies on T_2 contrast, as proton density and T_1 contrasts are minimal between prostate zones and tumor tissue [37, 38]. T_2w imaging is the dominant MR series in the overall assessment for abnormalities in the transition zone in the prostate imaging reporting and data system (PI-RADS) [37]. Prostate anatomical images are, therefore, most commonly acquired using a multislice 2D T_2w turbo spin-echo (TSE) sequence. Due to the high RF power deposition induced by the large number of refocusing pulses used by this sequence, it is restricted in its use at 7 T, currently often translated in the acquisition of fewer slices, prolonged refocusing pulse durations, or longer repetition times at 7 T.

For stripline arrays, initial studies of the feasibility of T_2w TSE imaging at 7 T in multiple slices or with multiple prostate cancer patients were performed using both an ERC and transceiver external surface stripline array [24, 39]. In work by Metzger et al., the combination of coils was compared to both of them separately [24]. The transceiver external coil (16-channel micro-stripline array) was able to provide a homogeneous B_1^+ with uniform contrast across the prostate, while the receive ERC increased the sensitivity near the rectum. The combined coil setup provided the highest SNR and an initial T_2w image with in plane resolution of $0.5 \times 0.5 \text{ mm}^2$ was acquired. Van den Bergen et al. showed that T2-weighted images can be obtained with the eight-element microstrip array within safety guidelines for RF power deposition [39]. Within the SAR limits, five slices of 3 mm could be imaged with a voxel size of $0.8 \times 0.8 \text{ mm}^2$ in a scan duration of 5 min. In the T_2w images obtained from a single patient, the prostate cancer lesion was visible next to the peripheral and central zone. Although a separate transceiver ERC can deliver a higher peak B_1^+

to the prostate, its inhomogeneous field is not suitable for many refocusing pulses in T_2w TSE, so the first use of this ERC was shown for spectroscopic imaging [21]. A combination of transceiving with both an external coil array and an ERC has not been tested.

As these studies demonstrated the feasibility of T_2w TSE imaging at 7 T using only a limited number of slices due to SAR restrictions, following work by Maas et al. was aimed to demonstrate full prostate coverage in T_2w imaging at 7 T [35]. Here, only an external transceiver body array coil was used [20]. After measuring T2 relaxation times, the T_2w -TSE protocol was defined with prolonged excitation and refocusing pulses to reduce the SAR levels. Results from 9 healthy volunteers and 12 prostate cancer patient showed high-quality T_2w images, acquired in less than 2 min in all subjects with a resolution of $0.75 \times 0.75 \times 3 \text{ mm}^3$. Within the set SAR limit (locally 10 W/kg), 28 consecutive slices could be obtained, sufficient for full prostate coverage with 3 mm slices. In the three patients with histopathological proven tumor localization, the tumors were clearly visible on 7 T T_2w imaging. The quality of the T_2w images obtained by this method at 7 T was clinically assessed in subsequent work [40]. Three radiologists scored T_2w images from 17 prostate cancer patients for image quality and the visibility of anatomical structures. Clinically significant cancer lesions were visible both in the peripheral and transition zone, confirming achievable adequate anatomical imaging at 7 T.

In a pilot study to extend the T_2w imaging to a mpMRI examination with DWI and ^1H -MRSI, an endorectal receive coil was used in combination with the external array coil for transmission [41]. In 13 patients, with this coil combination, T_2w imaging was achieved at a spatial resolution of $0.3 \times 0.3 \times 2 \text{ mm}^3$. Overall T_2w image quality was scored as fair (38%) to good or very good (55%), showing sufficient quality for diagnostic purposes at ultra-high resolution at 7 T. Areas of low SNR were encountered in the T_2w images, resulting possibly from an asymmetrical receive field of the ERC or inhomogeneous B_1^+ field resulting in varying flip angles throughout the prostate. Peri-prostatic lipid tissue is not visible on these images, because of opposite gradient polarity of excitation and refocusing pulses with different chemical shift artifacts (different pulse lengths). Muscles, lipids and bones outside the B_1^+ shimmed area are subject to low excitation and refocusing flip angles and are outside the receive profile of the ERC, strongly decreasing visibility.

A simplified coil design, getting around the need for parallel transmission and RF shimming, was proposed using loop elements by Rosenkrantz et al. [42]. Within the small ROI of the prostate, uniform flip angles were achieved and an SNR gain of

2.1 was seen versus 3 T imaging, while no comparison was made with other coil configurations. In two patients, 7 T T_2w imaging demonstrated higher estimated SNR in benign peripheral zone and tumor compared with 3 T, but lower SNR in fat and slight decreases in tumor-to-peripheral zone contrast and homogeneity of the peripheral zone of the prostate.

Dipole coil designs were also put to the test of acquiring T_2w images of the prostate. For the study of Steensma et al. [43], an 8-element fractionated dipole surface array was combined with a 16-channel receive-only loop-coil array. Compared to 3 T, SNR increased in a range from 1.7 to 2.8 times in the prostate, in a single slice for four volunteers. T_2w imaging showed improved tumor-to-tissue contrast at 7 T of a single patient, at an improved spatial resolution $0.5 \times 0.5 \times 2 \text{ mm}^3$. The same research group also tested the combination of the fractionated dipole surface array and a forward view antenna [44], an external cross-dipole transceiver element placed between the legs of a subject against the perineum. This addition led to an increase in SNR of 18% compared to fractionated dipole only. Further variations of a dipole surface array were aimed at reducing local SAR and increasing SAR efficiency [45–47], and although shown successful in simulations or a single volunteer, future measurements in patients are needed to assess the use in vivo at 7 T.

The studies described here show the feasibility of T_2w imaging of the prostate at 7 T with a significant increase in SNR. This advantage is heavily counteracted by SAR limitations and available transmit power, resulting in limitations for in plane resolutions, total number of slices, or repetition times. In a comparison to clinical T_2w MRI at 3 T (Fig. 1), the increased sensitivity at 7 T for T_2w TSE has not yet been fully exploited, which can be addressed through the continued development of optimal receiver arrays, RF management strategies and acquisition techniques. For example, new acquisition strategies providing more flexibility at 7 T may include 3D gradient echo imaging at high spatial resolution using magnetization preparation pulses. When prepared with T_2w modules [48], low-flip-angle excitations with gradient echo readouts could provide 3D high isotropic resolution with low SAR demands.

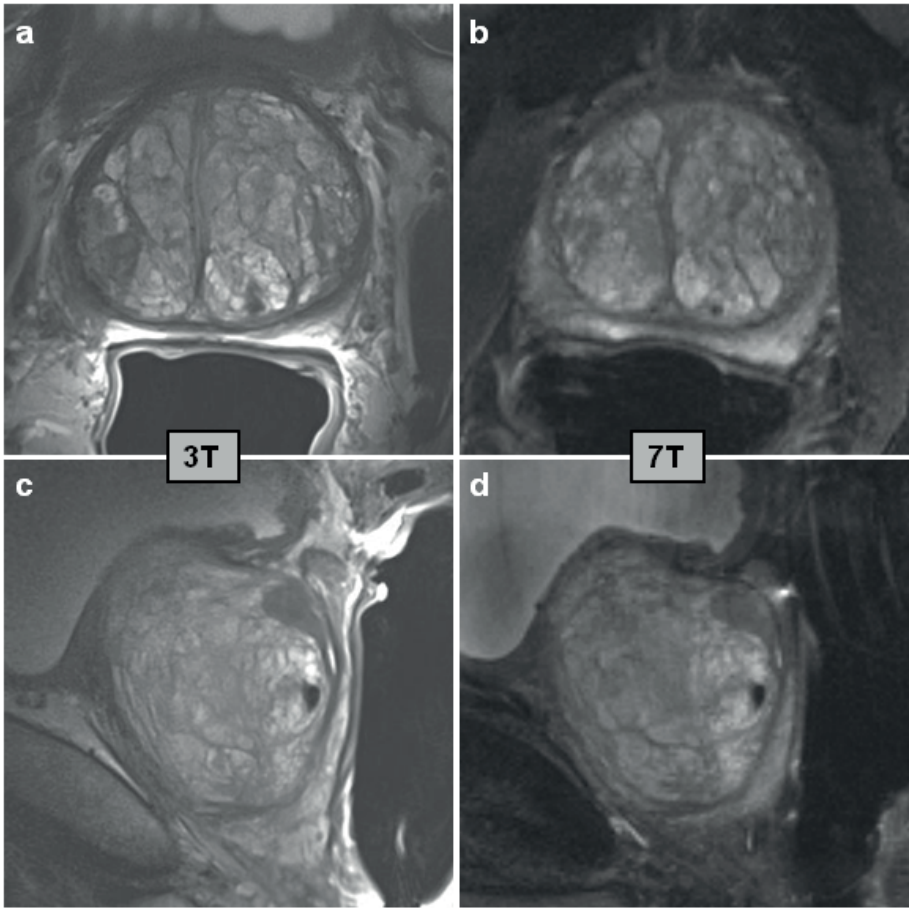


Fig. 1 T2w imaging of the prostate in two orientations. Axial (**a**, **b**) and sagittal (**c**, **d**) slices of the prostate of a patient with prostate cancer at 3 T (**a**, **c**) and at 7 T (**b**, **d**). The patient had a Gleason 3 + 4 lesion in the right midgland peripheral zone. The 3 T data was acquired with an endorectal coil (Medrad®, Pittsburgh, PA, US) at a spatial resolution of $0.4 \times 0.4 \times 3.0$ mm (TE 101 ms, acquisition time 4:21 min for each orientation). 7 T data was acquired as in [35] with an external 8-channel transceiver coil after phase shimming at a spatial resolution of $0.75 \times 0.75 \times 3.0$ mm (TE 71 ms, acquisition time 1:30 min for each orientation)

MRI of restrictions in water motion: diffusion-weighted imaging

In PI-RADS, DWI is the dominant mpMRI series for assessing peripheral zone lesions. Scores are assigned based on the lesions appearance on apparent diffusion coefficient (ADC) maps and DWI images at (calculated) high b values (≥ 1400 s/mm²) [37]. Increasing the magnetic field strength from clinical 3 T to experimental 7 T comes with an increase in magnetic susceptibility differences within tissue or at tissue-air interfaces. This makes DWI of the prostate at 7 T challenging.

In the mpMRI acquisition by Lagemaat et al. [41], DWI was acquired at 7 T with an external transmit array and endorectal receive coil using an echo-planar imaging (EPI) sequence with b-values of 0, 100, 400 and 800 s/mm². Apparent diffusion coefficient maps and b1400 images were calculated using a mono-exponential decay model. Results showed that DWI at a resolution of $1.75 \times 1.75 \times 2$ mm (or $1.4 \times 1.4 \times 2$ mm in two patients) was possible at 7 T at a rating of good to very good in 11 out of 12 patients. Anatomical structures, as well as the cancer lesions, were visible on the ADC maps since geometric distortion of the prostate with respect to T₂w imaging was very small (Fig. 2). DWI images were affected by a ghosting artifact of the rectal wall in the readout direction limiting the robustness of this technique.

Improved DWI performance at 7 T can be obtained by adopting methods currently used clinically at 3 T but have yet to be implemented on UHF systems. Along with parallel imaging, reducing the imaging FOV in the phase encode direction through the use of 2D selective excitation pulses reduces susceptibility artifacts and minimizes SNR with a shortened gradient echo train length and echo times. A similar strategy was implemented where a reduced FOV in the anterior–posterior (AP) direction was facilitated using AP regional saturation bands when using a body array for transmit and a combined endorectal-body array for receive [49]. Alternatively, similar to T2w preparation modules, diffusion-preparation modules could be combined with low-flip-angle excitations and gradient echo readouts, although no examples at 7 T currently exist.

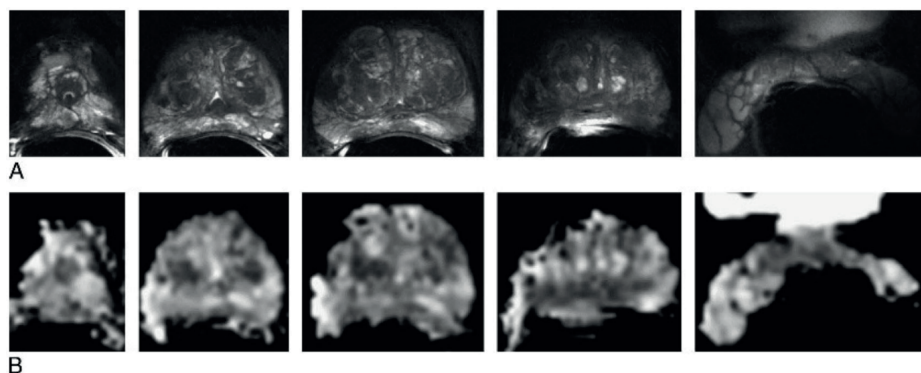


Fig. 2 MRI with an ERC at 7 T of the prostate of a 62-year-old patient with prostate cancer (Gleason score 3 + 3). **a** Five transversal T2w turbo spin-echo images from a series of 23 slices from apex to seminal vesicles, resolution $0.3 \times 0.3 \times 2.0$ mm³. **b** Transversal ADC maps at corresponding locations (5 images from 23 slices), resolution $1.75 \times 1.75 \times 2.0$ mm³. Reprinted with permission from Lagemaat et al. [41]

Dynamic contrast-enhanced MRI of the prostate

While dynamic contrast-enhanced MRI's role in the overall assessment of prostate lesions in PI-RADS version 2 is limited, it remains a continued component of the clinical mpMRI exam for prostate cancer detection [37]. The benefit of 7 T in DCE MRI would be an increase in spatial and/or temporal resolution for improved pharmacokinetic modeling or qualitative assessment of contrast enhancement curves. To date, only limited DCE MRI examinations have been performed in prostate cancer patients at 7 T [49]. To perform these studies, it was important to consider the increased R_2^* ($1/T_2^*$) relaxivity of Gadolinium based contrast agents at 7 T. While the R_1 ($1/T_1$) relaxivity, which gives the desired enhancement for DCE MRI, remains relatively constant with increasing field strength, the R_2^* relaxivity was shown to increase nearly fourfold at 7 T compared to 3 T [50] thus dominating the observed signal changes especially in the blood where the concentrations are the highest. To avoid biasing the interpretations of these data, either the time-varying T_2^* needs to be calculated and corrected for through a multi-TE acquisition, or ultra-short TE acquisitions can be used to mitigate the T_2^* effects [14].

Assessment of metabolite ratios within the prostate with ^1H -MRSI

Proton MRSI of the human prostate has been shown useful at 3 T as healthy and cancerous prostate tissue regions show differences in choline and citrate signal intensities [51]. Different ratios of choline, polyamines, creatine and citrate in combination with anatomical $T_2\text{w}$ MR imaging can identify and localize prostate cancer. Moreover, these ratios can be used to discriminate between different Gleason Grade groups [52], indicating a role for ^1H -MRSI in characterizing prostate cancer. The demand for specific expertise and relatively long acquisition times have prevented this technique to be included in routine mpMRI examinations, as described in the latest PI-RADS version [37]. Since ^1H -MRSI could benefit most from the higher SNR and spatial resolution at 7 T, this was the first MRI technique to be tested for prostate examinations at 7 T. To confirm the potential of prostate ^1H -MRSI, challenges posed by the B_1^+ inhomogeneities and increased chemical shift artifacts had to be overcome for this technique at 7 T.

First, dedicated coil designs for ^1H -MRSI at 7 T were developed. The use of an ERC, if used for RF transmission, can provide high but non-uniform peak B_1^+ fields in the prostate with relatively low RF power [21, 53]. The second challenge, the chemical shift displacement artifact, causes artefactual spatial variations of the citrate to choline ratios and results in contamination of spectra in the volume of interest (VOI) with signals from outside of this VOI. Overcoming both challenges, even in the presence of the large B_1^+ fields generated by the transmit ERC, was done using

adiabatic RF pulses [21]. ^1H -MRSI sequences developed for 7 T are either semi- of fully adiabatic (called semi-LASER or LASER) [21, 54]. The shortest achievable echo time for a semi-LASER sequence including dual-frequency-selective pulses for water and lipid suppression and with an optimal shape of the strongly coupled citrate resonances was 56 ms, which minimizes signal degradation due to T2 relaxation [21]. The addition of chemical shift selective pulses to the semi-LASER sequence to refocus the spermine spins allows obtaining maximum signal of all metabolite of interest in the prostate, albeit at a longer echo time [55].

These dedicated coil designs and pulse sequences were tested in multiple patients. In a study by Luttje et al., five patients with prostate cancer underwent an MRI examination at 7 T with the use of a $^1\text{H}/^{31}\text{P}$ transmit and receive ERC [53]. Two-dimensional ^1H -MRSI was acquired with a composite adiabatic excitation and refocusing pulse [54], taking advantage of the spatial excitation properties of the ERC in the right-left direction of the prostate. At an acquired voxel size of $5 \times 5 \times 5 \text{ mm}^3$ and an acquisition time of 7.46 min, the in vivo spectra showed well-resolved peaks for choline, polyamines, creatine and citrate. The spectra from a tumor region showed an increased total choline peak and decreased polyamine and citrate signals. The sensitivity of the ERC decreased with distance from the coil, resulting in limited coverage in the anterior direction of the prostate.

To allow 3D coverage of the entire prostate, the combination of a body array transmit coil and ERC for reception was tested by Lagemaat et al. [41]. This combination of a transmit surface array coil and receive ERC was able to provide a homogeneous B_1^+ field in the prostate with detection at high SNR [41, 56]. Patients were subjected to an mpMRI examination, consisting of $T_2\text{w}$, DWI, and ^1H -MRSI. As the homogeneous B_1^+ field obviated the need for the LASER sequences, less RF power demanding pulses could be used. Dedicated spectral-spatial refocusing pulses for both spectral and volume selection were developed at 7 T, as a more SAR efficient alternative to the semi-LASER sequence [57]. As these pulses perform frequency selection of the ppm-range of interest next to volume selection, the need for additional water and lipid suppression pulses was eliminated. From 12 patients with prostate cancer, 3D ^1H -MRSI was obtained with this method (real voxel size: 0.6 cm^3 in 7:16 min) [41]. The MRSI quality was rated fair to good in 56% of the acquisitions. Again, signal levels were decreased in spectra more distant from the ERC. Spectra from tumor tissue showed decreased citrate levels compared to the total spermine and choline peak in one patient and an increased choline level compared to healthy prostate tissue in another. Lipid contamination influenced the spectral quality, hindering detection of citrate and indicative

of remaining inhomogeneities in the B_1^+ field. Effort has also been put into the development of parallel transmit-designed adiabatic spectral-spatial refocusing pulses simultaneously providing both spatial localization and signal suppression insensitive to B_0 variations [58].

In a 7 T mpMRI feasibility study by Philips et al. [56], using a $^{31}\text{P}/^1\text{H}$ ERC with an external ^1H transceiver body array and spectral-spatial refocusing pulses, ^1H -MRSI spectra were acquired from three patients. Adequate SNR was seen from apex to base of the prostate resulting in spectra with well distinguishable choline and spermine signals, while citrate in some cases suffered from lipid contamination. Close to the ERC and in the seminal vesicles, the spectral map shows wider peaks because of local B_0 field inhomogeneities. With a corrected voxel size of 1.4 cc, in a patient with Gleason score 4 + 4, an elevated total choline peak was found compared to the contralateral side.

While the studies above show the feasibility of ^1H -MRSI in prostate cancer at 7 T, the potential benefit of spectral-spatial pulses for assessing prostate cancer must be investigated in a larger patient cohort with tumors varying in Gleason scores. Spatial resolution can be improved compared to 3 T due to the high sensitivity at 7 T, which would reduce partial volume effects causing voxels to better represent tumor tissue. Further reductions in voxel size will improve the separate detection of total choline and spermine because this will improve intravoxel B_0 homogeneity, narrowing the linewidths. Ratios including the total choline could then serve to characterize prostate cancer and remove ERC coil profile effects [57]. As the spectral-spatial pulses result in high spermine signals in the ^1H spectra [53, 56], the value of these spermine signals for prostate cancer characterization should be investigated further, as biopsy studies have shown a significant decrease in spermine concentration with increasing tumor grade [59].

Metabolic imaging within the prostate with ^{31}P MRSI

At a magnetic field strength of 7 T, the higher signal-to-noise ratio and increased spectral resolution creates the opportunity to develop ^{31}P spectroscopic imaging of the prostate [10]. Phosphorus spectroscopy enables detection of metabolites with phosphorus atoms, e.g., phosphocreatine (PCr), inorganic phosphate (Pi), the three phosphate groups of adenosine triphosphate (ATP), phosphomonoesters (PME), and phosphodiester (PDE). The increased chemical shift difference between signals, compared to 3 T, might enable detection of individual resonances of PME, phosphoethanolamine (PE) and phosphocholine (PC), and PDE, i.e., glycerophosphoethanolamine (GPE) and glycerophosphocholine (GPC) [10]. As in

vitro studies have shown a significant difference in PE and GPE between cancer and benign prostatic hyperplasia [60] and that ^{31}P profiles discriminate between low-grade and high-grade cancer [61], in vivo ^{31}P MRSI of the prostate could improve the assessment of prostate cancer aggressiveness [11]. Together with the increased SNR, it could be possible to perform localized 3D ^{31}P MRSI at 7 T at a relevant spatial resolution in a clinically acceptable measurement time.

One of the first studies to test the feasibility of ^{31}P MRSI at 7 T in the prostate was performed by Kobus et al. [11]. A ^{31}P endorectal coil was developed and combined with an eight-channel ^1H body array coil to couple metabolic and anatomical information. The combination was submitted to an extensive safety validation, demonstrating that the presence of the ^{31}P endorectal coil had no influence on the SAR levels and temperature distribution of the external eight-channel ^1H array coil. The maximum time-averaged input power of the ^{31}P endorectal coil was determined and used for the first in vivo tests. In a healthy volunteer, using adiabatic excitation, 3D ^{31}P MR spectroscopic imaging produced high-quality spectra from the entire prostate in 18 min with a spatial resolution of 4 cm^3 .

Subsequently, this setup of combined ^{31}P transceiver endorectal and eight-channel ^1H transceiver body coil was tested in an explorative study with 15 patients with biopsy-proven prostate cancer by Lagemaat et al. [62]. The signals of PE and PC were well resolved in most ^{31}P spectra in the prostate, and ^{31}P MRSI at 7 T resulted in distinct features of phospholipid metabolites in the prostate gland and its surrounding structures. The two patients with high Gleason score tumors (GS: $5 + 4$ and $4 + 5$) presented with high PC and GPC levels. Although these ^{31}P PC and GPC levels may be related to prostate cancer aggressiveness, generally, differences in metabolite ratios between prostate cancer and normal-appearing tissue were not observed possibly because of partial volume effects of small tumor foci in large MRSI voxels.

In parallel work by the same group, the ^{31}P MRSI protocol was optimized for the human prostate at 7 T by the evaluation of T_1 relaxation times and the Nuclear Overhauser Effect (NOE) of phosphorus-containing metabolites in 12 patients [63]. T_1 relaxation times of ^{31}P metabolites in the human prostate at 7 T varied between 3.0 and 8.3 s. The relatively long T_1 relaxation times of ^{31}P metabolites, as well as reasonable limitations in total acquisition time, require a tradeoff between TR and accompanying flip angle and matrix size. Sensitivity of ^{31}P MRSI of the prostate at 7 T may be increased by irradiation of water protons, giving rise to NOE enhancement. Positive NOE enhancements were measured for most metabolites, which can improve

fitting accuracy, but the variability in NOE results requires further investigation. With a strongly reduced ^{31}P flip angle ($\leq 45^\circ$), a high-quality ^{31}P MRSI dataset with optimal SNR per unit time can be obtained within 15 min.

A different coil setup for prostate ^{31}P MRSI was developed and tested by Luttje et al. [53], with the aim of acquiring both ^1H and ^{31}P MRSI of the human prostate at 7 T in one scan session. Therefore, a two-element $^1\text{H}/^{31}\text{P}$ transmit and receive ERC was designed. As the endorectal transceiver provides high SNR and strong B_1 fields, detection of the phospholipid metabolites was feasible. Their preliminary in vivo prostate results indicated lower levels of PE in the tumor areas compared to healthy prostate tissue.

As T_2w imaging of the prostate by a transceiver ERC suffers from B_1 inhomogeneities, the combination of an ERC with a ^1H external coil array would be optimal for functional and anatomical imaging. In a study by Philips et al., this strategy was implemented by combining an ERC with a ^{31}P transceiver loop-coil and ^1H receive (Rx) asymmetric microstrip ($^{31}\text{P}/^1\text{H}$ ERC) with an external ^1H transceiver body array coil [56]. After extensive safety testing, the total coil combination allowed acquisition of a multinuclear mpMRI protocol, consisting of high-resolution T_2w imaging and DWI without artifacts and the assessment of ^{31}P and ^1H metabolites of the prostate in three patients with histology proven prostate cancer. In one patient with high-grade prostate cancer (Gleason grade 4 + 4), GPC, GPE, PE and PC levels were identified and elevated in the cancer lesion compared to the healthy contralateral side of the prostate (Fig. 3). In a larger patient population, this combined setup could provide insight in the changes in total choline metabolism in prostate cancer.

The most optimal coil configuration with respect to B_1^+ homogeneity and highest SNR for signal reception would be to separate transmit and receive for both nuclei with a body array capable of transmitting on both the ^1H and ^{31}P frequencies and an endorectal coil to receive the signals from both nuclei.

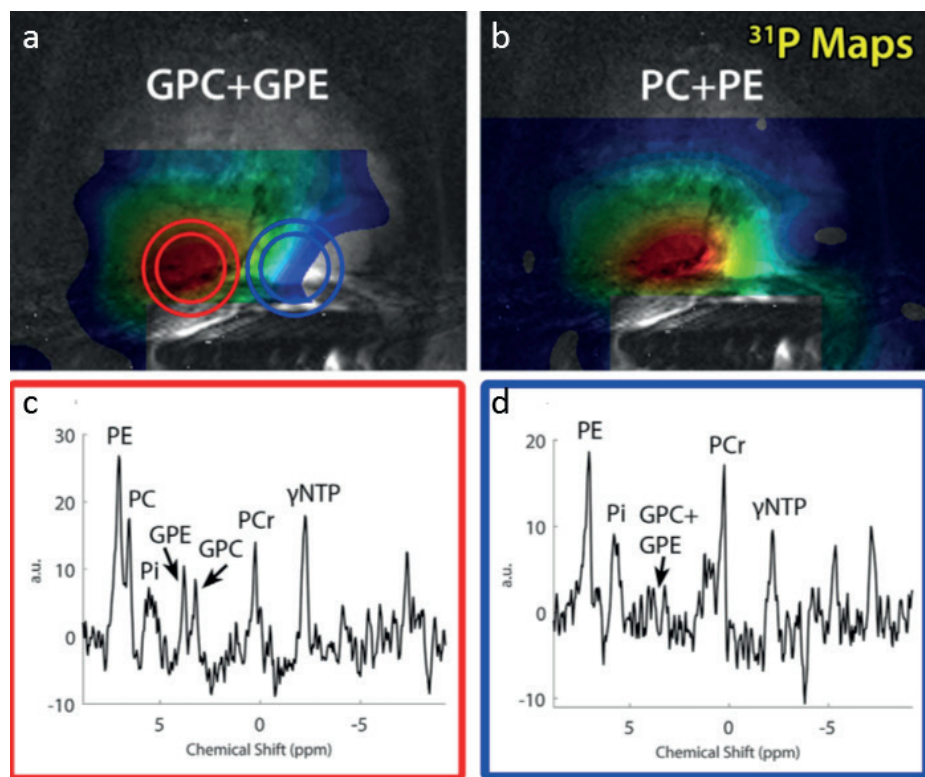


Fig. 3 GPC + GPE and PC + PE, metabolite maps of a 67-year-old patient with metastatic Gleason 4 + 4 prostate cancer (**a**, **b**) overlaid over a T2w image. ^{31}P (**c**, **d**) spectra are shown of the cancer lesion (red circle) as well as a location within healthy tissue (blue circle). Adapted from Philips et al. [56]

Staging lymph nodes at ultra-high magnetic field

Next to imaging and characterization of localized prostate cancer, there is also a potential role of 7 T MRI for the identification of lymph node metastases. There is a great clinical need for precise, reliable and noninvasive N-staging in patients with prostate cancer. The excellent soft-tissue contrast of MRI enables visualization of lymph nodes within the surrounding lipid tissue. Using lipid suppression or water excitation, the contrast between the water containing lymph nodes and lipid tissue can be increased [64]. UHF MRI provides an increased spatial resolution compared to 3 T, which enables the visualization of lymph nodes even smaller than 5 mm. With the large chemical shift dispersion between water and lipids at 7 T, selective excitation of either of the two with short simple rectangular pulses becomes an attractive option. This allows very efficient imaging by short excitations in the order of 1 ms and receiving multiple gradient echoes, using approximately 60% of the repetition time to actually acquire MR signal.

In the work by Philips et al. [65], these advantages of 7 T MRI were used in a multigradient echo sequence combined with TIAMO acquisition. Using a 3D water-selective multigradient echo sequence enabled the quantification of the signal decay of the lymph nodes with its corresponding T_2^* relaxation time. As a consequence, images could be computed at any echo time using all gradient echo signals. This method of high-resolution 3D isotropic pelvic imaging over a large field of view performed robustly in six healthy volunteers with a low SAR. Pelvic lymph nodes were found with a size down to 1.5 mm short axis and a mean short and long axis of 2.2 ± 0.1 and 3.7 ± 0.2 mm, respectively. In another set of 11 young healthy volunteers, 69% of the total amount of 564 pelvic lymph nodes found on the water-selective computed TE images were 2 mm or smaller (mean diameter: 2.3 mm, range 1–7 mm) [66].

Next to small-sized lymph nodes, the 7 T MRI would be able to pick up lymph node morphology in patients, such as heterogeneous signal intensity or irregular border and shape. However, morphological criteria cannot safely differentiate metastatic from nonmetastatic lymph nodes. Using a functional MRI contrast like ferumoxtran-10, currently only available for use in clinical trials, one can discriminate between normal lymphatic tissue that has taken up the ultrasmall superparamagnetic particles of iron oxide (USPIO) and metastatic lymph nodes that have not taken up the particles and preserve high MRI signal on T_2^* -weighted MRI pulse sequences [64].

Performing the same multigradient echo sequence now after USPIO infusion [67], separate scans with either water or lipid excitation provide an anatomical overview while the iron-sensitive signal intensity discriminates between nodes with and without USPIO accumulation. In three patients with rectum cancer and three patients with prostate cancer lymph nodes were identified on computed TE = 0 ms images from water-selective scans in combination with images from lipid-selective scans (Fig. 4). A range of 3–48 lymph nodes without USPIO signal decay was found per patient. This study showed the technical feasibility of USPIO-enhanced MRI at 7 T, enabling the detection of USPIO uptake in normal-sized lymph nodes by the high SNR and unprecedented spatial resolution. The effect of USPIO-enhanced MRI on nodal staging has to be studied as no systematic follow-up or node-to-node pathological data is yet available for prostate cancer. A study by Stijns et al. [68], regarding patients with rectal cancer, revealed challenges to overcome to perform accurate node-to-node matching from clinical USPIO-enhanced MRI to histopathology.

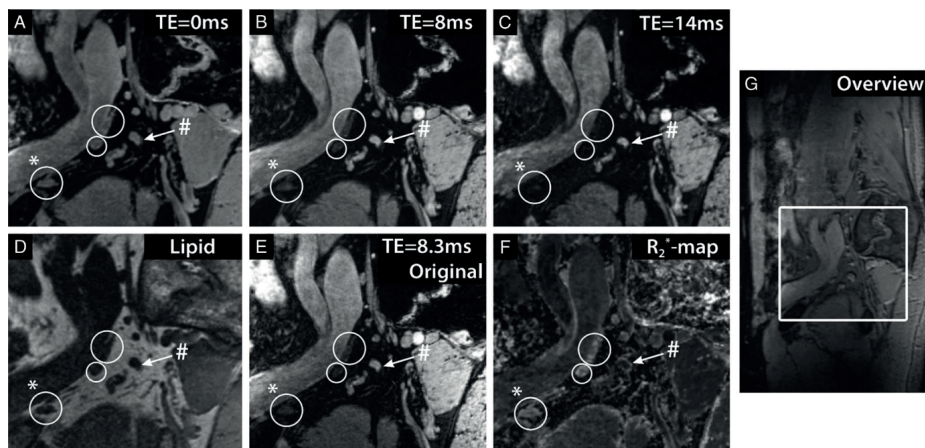


Fig. 4 The effect of USPIO nanoparticles at 7 T in the lymph nodes of a 54-year old patient with prostate cancer metastases. a–c Sagittal images of the same location at different computed echo times (TEs). d Lipid-selective image. e The original TE = 8.3 ms image from the multigradient echo water-selective imaging. f Map of fitted R_2^* relaxation rates. g Sagittal overview image with inset of location of images a–f. Three lymph nodes accumulated USPIO particles and rapidly lost MR signal intensity (white circles), while one suspicious lymph node without USPIOs retained MR signal intensity with increasing TE (white arrow). The lymph node marked with (#) showed a slow signal decay, with an R_2^* value of $80 \pm 6 \text{ s}^{-1}$, whereas the lymph node marked with (*) showed fast signal decay, with an R_2^* value of $247 \pm 25 \text{ s}^{-1}$. Reprinted with permission from Scheenen et al. [64]

Prostate imaging at 10.5 T

The exploration of UHF imaging in the human body extends to 10.5 T where a recent study demonstrated the possibility of imaging targets throughout the torso, including the prostate [69]. In fact, the focus of the first human imaging study ever conducted on the 10.5 T whole-body MRI scanner was the prostate of a healthy male volunteer. At 10.5 T, the proton resonance frequency is 447 MHz with an approximate wavelength of 7 cm in the human body resulting in rapidly varying complex field patterns that need to be managed. Using a 10 channel fractionated dipole as a transceiver [70], subject-dependent RF shimming was performed to mitigate the destructive interferences. Again, the main goal is to generate a sufficiently homogeneous and efficient B_1^+ in the prostate to perform the sequences and obtain the contrasts typical of an mpMRI exam including T_1w , T_2w and DWI acquisitions.

In contrast to prostate studies at 7 T, an RF shimming strategy focusing solely on RF efficiency [15] was not always adequate at 10.5 T. Depending on body geometry and prostate size, a shim optimized for a tradeoff between the two conflicting requirements of homogeneity and efficiency was required to obtain acceptable image quality [71]. As evident from these results and by the contrasts demonstrated

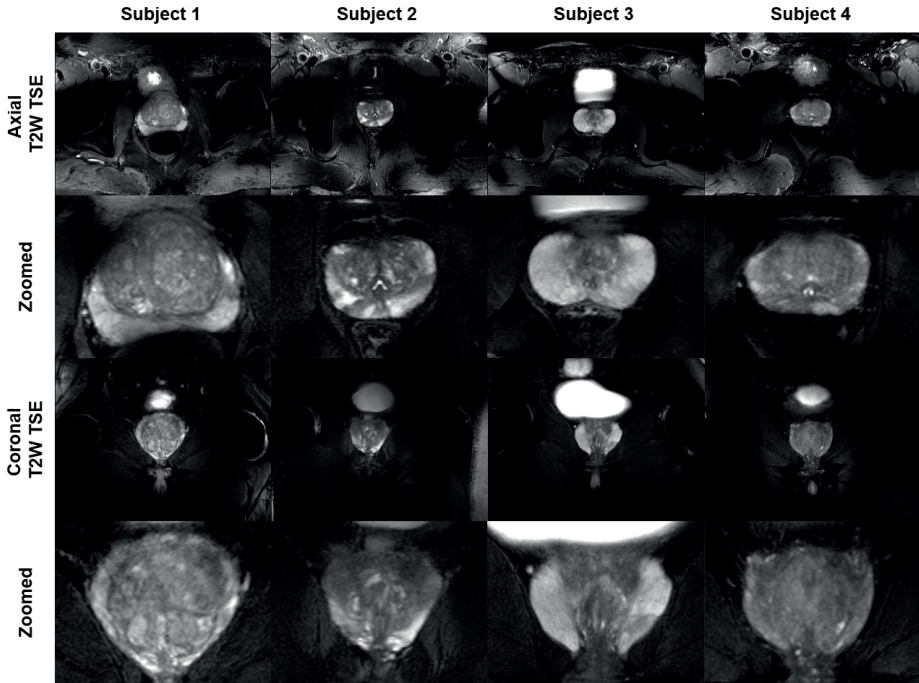


Fig. 5 Full FOV and zoomed-in versions of axial and coronal T2w TSE images of prostates from 4 subjects. Images demonstrate excellent contrast and SNR achieved by phase-only RF shimming. Although providing high peak B_1^+ and reasonable homogeneity over the prostate, the local RF shim resulted in unmanaged RF fields outside the immediate region of the targeted anatomy that caused spatially varying destructive interference patterns as observed in the unzoomed images. Reprinted with permission from He et al. [69]

in axial and coronal T_2w acquisitions acquired across four subjects (Fig. 5), these RF management strategies provided a sufficiently homogeneous and efficient B_1^+ to perform prostate imaging in all volunteers. The average B_1^+ in prostate across all subjects was $10.2 \pm 1.9 \mu T$, and the average coefficient of variations was $13.0 \pm 2.4\%$. Multiparametric mappings in prostate including T_1 , T_2 , ADC and calculated DWI acquired in a subset also demonstrated the feasibility of quantitative imaging at 10.5 T [69].

While standard strategies to minimize power deposition were employed at 10.5 T, such as reduced-flip-angle echo trains for TSE and prolonged repetition times, local SAR limited the number of slices to ≤ 11 of 3 mm while abiding by safety guidelines. This is roughly half that is needed in clinical studies of the prostate to properly cover this anatomy [35]. RF pulses optimized with SAR constraints can be employed to decrease the local peak SAR levels as can RF coil geometries with improved SAR efficiencies to support more time efficient imaging and coverage at 10.5 T [72].

Conclusion

Significant effort has been invested in addressing the technical challenges of UHF imaging of the lower abdomen, specifically the prostate and its surrounding tissue. The culmination of this work clearly demonstrates that multinuclear multiparametric MR(S)I of the prostate at UHF is feasible. With the exploitation of higher spatial resolutions in imaging and in spectroscopy, mpMRI at UHF can yield improved delineation of prostate anatomy and metabolic imaging within the tumor as a biomarker for an assessment of prostate cancer aggressiveness. For clinical detection of primary prostate cancer, a fast, readily available and robust MRI acquisition is needed; current 3 T protocols fulfill these demands. The potential role of prostate imaging at 7 T could be in achieving a better understanding of the development and progression of local prostate cancer, the onset and spatial distribution of metastatic spread, and in characterization of different tumor stages and recurrent disease.

References

1. Hegde JV, Mulkern RV, Panych LP, Fennessy FM, Fedorov A, Maier SE, Tempany CMC (2013) Multiparametric MRI of prostate cancer: An update on state-of-the-art techniques and their performance in detecting and localizing prostate cancer. *J Magn Reson Imaging* 37:1035–1054
2. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, Rouviere O, Logager V, Futterer JJ (2012) ESUR prostate MR guidelines 2012. *Eur Radiol* 22(4):746–757
3. de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM (2016) Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. *Eur Urol* 70(2):233–245
4. Drost FH, Osses D, Nieboer D, Bangma CH, Steyerberg EW, Roobol MJ, Schoots IG (2020) Prostate magnetic resonance imaging, with or without magnetic resonance imaging-targeted biopsy, and systematic biopsy for detecting prostate cancer: a cochrane systematic review and meta-analysis. *Eur Urol* 77(1):78–94
5. Witherspoon L, Breau RH, Lavallée LT (2020) Evidence-based approach to active surveillance of prostate cancer. *World J Urol* 38:555–562
6. Ashrafi AN, Tafuri A, Cacciamani GE, Park D, de Castro Abreu AL, Gill IS (2018) Focal therapy for prostate cancer: concepts and future directions. *Curr Opin Urol* 28(6):536–543
7. Koopman AGMM, Jenniskens SFM, Fütterer JJ (2020) Magnetic resonance imaging assessment after therapy in prostate cancer. *Top Magn Reson Imaging* 29:47–58
8. Smith CP, Harmon SA, Barrett T, Bittencourt LK, Law YM, Shebel H, An JY, Czarniecki M, Mehravivand S, Coskun M, Wood BJ, Pinto PA, Shih JH, Choyke PL, Turkbey B (2019) Intra- and interreader reproducibility of PI-RADSv2: a multireader study. *JMRI* 49(6):1694–1703
9. Lagemaat MW, Scheenen TW (2014) Role of high-field MR in studies of localized prostate cancer. *NMR Biomed* 27(1):67–79
10. Qiao H, Zhang X, Zhu XH, Du F, Chen W (2006) In vivo ³¹P MRS of human brain at high/ultrahigh fields: a quantitative comparison of NMR detection sensitivity and spectral resolution between 4 T and 7 T. *Magn Reson Imaging* 24(10):1281–1286
11. Kobus T, Bitz AK, van Uden MJ, Lagemaat MW, Rothgang E, Orzada S, Heerschap A, Scheenen TWJ (2012) In vivo ³¹P MR spectroscopic imaging of the human prostate at 7 T: safety and feasibility. *Magn Reson Med* 68(6):1683–1695
12. Ladd ME, Bachert P, Meyerspeer M, Moser E, Nagel AM, Norris DG, Schmitter S, Speck O, Straub S, Zaiss M (2018) Pros and cons of ultra-high-field MRI/MRS for human application. *Prog Nucl Magn Reson Spectrosc* 109:1–50
13. Orzada S, Solbach K, Gratz M, Brunheim S, Fiedler TM, Johst S, Bitz AK, Shooshary S, Abuelhajja A, Voelker MN, Rietsch SHG, Kraff O, Maderwald S, Flöser M, Oehmigen M, Quick HH, Ladd ME (2019) A 32-channel parallel transmit system add-on for 7T MRI. *PLoS One* 14(9):e0222452
14. Ertürk MA, Li X, Van de Moortele PF, Uğurbil K, Metzger GJ (2019) Evolution of UHF Body Imaging in the Human Torso at 7T. *Top Magn Reson Imaging* 28(3):101–124
15. Metzger GJ, Snyder C, Akgun C, Vaughan T, Uğurbil K, Van de Moortele PF (2008) Local B1+ shimming for prostate imaging with transceiver arrays at 7T based on subject-dependent transmit phase measurements. *Magn Reson Med* 59(2):396–409
16. Snyder CJ, Delabarre L, Moeller S, Tian J, Akgun C, Van de Moortele PF, Bolan PJ, Ugurbil K, Vaughan JT, Metzger GJ (2012) Comparison between eight- and sixteen-channel TEM transceiver arrays for body imaging at 7 T. *Magn Reson Med* 67(4):954–964

17. Raaijmakers AJ, Ipek O, Klomp DW, Possanzini C, Harvey PR, Lagendijk JJ, van den Berg CA (2011) Design of a radiative surface coil array element at 7 T: the single-side adapted dipole antenna. *Magn Reson Med* 66(5):1488–1497
18. Raaijmakers AJ, Italiaander M, Voogt IJ, Luijten PR, Hoogduin JM, Klomp DW, van den Berg CA (2016) The fractionated dipole antenna: a new antenna for body imaging at 7 tesla. *Magn Reson Med* 75(3):1366–1374
19. Raaijmakers AJ, Luijten PR, van den Berg CA (2016) Dipole antennas for ultrahigh-field body imaging: a comparison with loop coils. *NMR Biomed* 29:1122–1130
20. Orzada S, Quick HH, Ladd ME, Bahr A, Bolz T, Yazdanbakhsh P, Solbach K, Bitz AK. (2009) A flexible 8-channel transmit/ receive body coil for 7 T human imaging. In: proceedings of the 17th annual meeting, international society for magnetic resonance in medicine, Hawaii, USA, p 2999
21. Klomp DW, Bitz AK, Heerschap A, Scheenen TW (2009) Proton spectroscopic imaging of the human prostate at 7 T. *NMR Biomed* 22(5):495–501
22. Arteaga de Castro CS, van den Bergen B, Luijten PR, van der Heide UA, van Vulpen M, Klomp DW (2012) Improving SNR and B1 transmit field for an endorectal coil in 7 T MRI and MRS of prostate cancer. *Magn Reson Med* 68(1):311–318
23. Erturk MA, Tian J, Van de Moortele PF, Adriany G, Metzger GJ (2016) Development and evaluation of a multichannel endorectal RF coil for prostate MRI at 7T in combination with an external surface array. *J Magn Reson Imaging* 43(6):1279–1287
24. Metzger GJ, van de Moortele PF, Akgun C, Snyder CJ, Moeller S, Strupp J, Andersen P, Shrivastava D, Vaughan T, Ugurbil K, Adriany G (2010) Performance of external and internal coil configurations for prostate investigations at 7 T. *Magn Reson Med* 64(6):1625–1639
25. Dieringer MA, Renz W, Lindel T, Seifert F, Frauenrath T, von Knobelsdorff-Brenkenhoff F, Waiczies H, Hoffmann W, Rieger J, Pfeiffer H, Ittermann B, Schulz-Menger J, Niendorf T (2011) Design and application of a four-channel transmit/receive surface coil for functional cardiac imaging at 7T. *J Magn Reason Imaging* 33(3):736–741
26. Erturk MA, Raaijmakers AJ, Adriany G, Uğurbil K, Metzger GJ (2017) A 16-channel combined loop-dipole transceiver array for 7 tesla body MRI. *Magn Reson Med* 77(2):884–894
27. Rietsch SHG, Orzada S, Maderwald S, Brunheim S, Philips BWJ, Scheenen TWJ, Ladd ME, Quick HH (2018) 7T ultra-high field body MR imaging with an 8-channel transmit/32-channel receive radiofrequency coil array. *Med Phys* 45(7):2978–2990
28. Steensma BR, Voogt IJ, Leiner T, Luijten PR, Habets J, Klomp DWJ, van den Berg CAT, Raaijmakers AJE (2018) An 8-channel Tx/Rx dipole array combined with 16 Rx loops for high-resolution functional cardiac imaging at 7 T. *MAGMA* 31(1):7–18
29. Rietsch SHG, Brunheim S, Orzada S, Voelker MN, Maderwald S, Bitz AK, Gratz M, Ladd ME, Quick HH (2019) Development and evaluation of a 16-channel receive-only RF coil to improve 7T ultra-high field body MRI with focus on the spine. *Magn Reson Med* 82(2):796–810
30. International Electrotechnical Commission (2015) Medical electrical equipment. Part 2-33: Particular requirements for the basic safety and essential performance of magnetic resonance equipment for medical diagnosis. IEC 60601-2-33: 33–52
31. Brunheim S, Gratz M, Johst S, Bitz AK, Fiedler TM, Ladd ME, Quick HH, Orzada S (2018) Fast and accurate multi-channel mapping based on the TIAMO technique for 7T UHF body MRI. *Magn Reson Med* 79(5):2652–2664
32. Ipek O, Raaijmakers AJ, Lagendijk JJ, Luijten PR, van den Berg CA (2014) Intersubject local SAR variation for 7T prostate MR imaging with an eight-channel single-side adapted dipole antenna array. *Magn Reson Med* 71(4):1559–1567

33. Meliado EF, van den Berg CAT, Luijten PR, Raaijmakers AJE (2019) Intersubject specific absorption rate variability analysis through construction of 23 realistic body models for prostate imaging at 7T. *Magn Reson Med* 81(3):2106–2119
34. Meliado EF, Raaijmakers AJE, Sbrizzi A, Steensma BR, Maspero M, Savenije MHF, Luijten PR, van den Berg CAT (2020) A deep learning method for image-based subject-specific local SAR assessment. *Magn Reson Med* 83(2):695–711
35. Maas MC, Vos EK, Lagemaat MW, Bitz AK, Orzada S, Kobus T, Kraff O, Maderwald S, Ladd ME, Scheenen TW (2014) Feasibility of T2-weighted turbo spin echo imaging of the human prostate at 7 tesla. *Magn Reson Med* 71(5):1711–1719
36. Gras V, Vignaud A, Amadon A, Le Bihan D, Boulant N (2017) Universal pulses: a new concept for calibration-free parallel transmission. *Magn Reson Med* 77(2):635–643
37. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, Tempany CM, Choyke PL, Cornud F, Margolis DJ, Thoeny HC, Verma S, Barentsz J, Weinreb JC (2019) Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. *Eur Urol* 76:340–351
38. Purysko AS, Rosenkrantz AB, Barentsz JO, Weinreb JC, Macura KJ (2016) PI-RADS version 2: a pictorial update. *Radiographics* 36(5):1354–1372
39. van den Bergen B, Klomp DW, Raaijmakers AJ, de Castro CA, Boer VO, Kroeze H, Luijten PR, Lagendijk JJ, van den Berg CA (2011) Uniform prostate imaging and spectroscopy at 7 T: comparison between a microstrip array and an endorectal coil. *NMR Biomed* 24(4):358–365
40. Vos EK, Lagemaat MW, Barentsz JO, Futterer JJ, Zamecnik P, Roozen H, Orzada S, Bitz AK, Maas MC, Scheenen TW (2014) Image quality and cancer visibility of T2-weighted magnetic resonance imaging of the prostate at 7 Tesla. *Eur Radiol* 24(8):1950–1958
41. Lagemaat MW, Philips BW, Vos EK, van Uden MJ, Futterer JJ, Jenniskens SF, Scheenen TW, Maas MC (2017) Feasibility of multiparametric magnetic resonance imaging of the prostate at 7 T. *Invest Radiol* 52(5):295–301
42. Rosenkrantz AB, Zhang B, Ben-Eliezer N, Le Nobin J, Melamed J, Deng FM, Taneja SS, Wiggins GC (2015) T2-weighted prostate MRI at 7 tesla using a simplified external transmitreceive coil array: correlation with radical prostatectomy findings in two prostate cancer patients. *J Magn Reson Imaging* 41(1):226–232
43. Steensma BR, Luttje M, Voogt IJ, Klomp DWJ, Luijten PR, van den Berg CAT, Raaijmakers AJE (2019) Comparing signal-to-noise ratio for prostate imaging at 7T and 3T. *J Magn Reson Imaging* 49(5):1446–1455
44. Steensma BR, Voogt I, van der Werf AJ, van den Berg CAT, Luijten PR, Klomp DWJ, Raaijmakers AJE (2018) Design of a forward view antenna for prostate imaging at 7 T. *NMR Biomed* 31(9):e3993
45. Solomakha G, Leeuwen CV, Raaijmakers A, Simovski C, Popugaev A, Abdeddaim R, Melchakova I, Glybovski S (2019) The dual-mode dipole: a new array element for 7T body imaging with reduced SAR. *Magn Reson Med* 81(2):1459–1469
46. Zivkovic I, de Castro CA, Webb A (2019) Design and characterization of an eight-element passively fed meander-dipole array with improved specific absorption rate efficiency for 7 T body imaging. *NMR Biomed* 32(8):e4106
47. Sadeghi-Tarakameh A, Adriany G, Metzger GJ, Lagore RL, Jungst S, DelaBarre L, Van de Moortele PF, Ugurbil K, Atalar E, Eryaman Y (2020) Improving radiofrequency power and specific absorption rate management with bumped transmit elements in ultra-high field MRI. *Magn Reson Med* 84(6):3485–3493

48. Vidya Shankar R, Rocchia E, Cruz G, Neji R, Botnar R, Prezzi D, Goh V, Prieto C, Dregely I (2019) Accelerated 3D T(2) w-imaging of the prostate with 1-millimeter isotropic resolution in less than 3 minutes. *Magn Reson Med* 82(2):721–731
49. Metzger GJ, Kalmoe R, Erturk MA, He X, Ramanna S, Leng E, Warlick C, Spilseth B. (2018) Multiparametric MRI methods development for clinical prostate imaging at 7T. In: proceedings of the 26th annual meeting, international society for magnetic resonance in medicine, Paris, France, 2577
50. Kalavagunta C, Michaeli S, Metzger GJ (2014) In vitro Gd- DTPA relaxometry studies in oxygenated venous human blood and aqueous solution at 3 and 7 T. *Contrast Media Mol Imaging* 9(2):169–176
51. Steinseifer IK, van Asten JJA, Weiland E, Scheenen TWJ, Maas MC, Heerschap A (2015) Improved volume selective 1H MR spectroscopic imaging of the prostate with gradient offset independent adiabaticity pulses at 3 tesla. *Magn Reson Med* 74:915–924
52. Maas MC, Litjens GJS, Wright AJ, Attenberger UI, Haider MA, Helbich TH, Kiefer B, Macura KJ, Margolis DJA, Padhani AR, Selnæs KM, Villeirs GM, Fütterer JJ, Scheenen TWJ (2019) A single-arm, multicenter validation study of prostate cancer localization and aggressiveness with a quantitative multiparametric magnetic resonance imaging approach. *Invest Radiol* 54(7):437–447
53. Luttje MP, Italiaander MG, Arteaga de Castro CS, van der Kemp WJ, Luijten PR, van Vulpen M, van der Heide UA, Klomp DW (2014) (31) P MR spectroscopic imaging combined with (1) H MR spectroscopic imaging in the human prostate using a double tuned endorectal coil at 7T. *Magn Reson Med* 72(6):1516–1521
54. Arteaga de Castro CS, Luttje MP, van Vulpen M, Luijten PR, van der Heide UA, Klomp DW (2013) Composite slice-selective adiabatic excitation for prostate MRSI. *NMR Biomed* 26(4):436–442
55. Klomp DWJ, Scheenen TWJ, Arteaga CS, van Asten JJA, Boer VO, Luijten PR (2011) Detection of fully refocused polyamine spins in prostate cancer at 7 T. *NMR Biomed* 24:299–306
56. Philips BWJ, van Uden MJ, Rietsch SHG, Orzada S, Scheenen TWJ (2019) A multitransmit external body array combined with a (1) H and (31) P endorectal coil to enable a multiparametric and multimetabolic MRI examination of the prostate at 7T. *Med Phys* 46(9):3893–3905
57. Lagemaat MW, Breukels V, Vos EK, Kerr AB, van Uden MJ, Orzada S, Bitz AK, Maas MC, Scheenen TW (2016) (1)H MR spectroscopic imaging of the prostate at 7T using spectral-spatial pulses. *Magn Reson Med* 75(3):933–945
58. He X, Auerbach EJ, Garwood M, Kobayashi N, Wu X, Metzger GJ (2021) Parallel transmit optimized 3D composite adiabatic spectral-spatial pulse for spectroscopy. *Magn Reson Med* 86:17–32
59. Giskeødegård GF, Bertilsson H, Selnæs KM, Wright AJ, Bathen TF, Viset T, Halgunset J, Angelsen A, Gribbestad IS, Tessem MB (2013) Spermine and citrate as metabolic biomarkers for assessing prostate cancer aggressiveness. *PLoS One* 8(4):e62375
60. Komoroski RA, Holder JC, Pappas AA, Finkbeiner AE (2011) 31P NMR of phospholipid metabolites in prostate cancer and benign prostatic hyperplasia. *Magn Reson Med* 65:911–913
61. Keshari KR, Tsachres H, Iman R, Delos Santos L, Tabatabai ZL, Shinohara K, Vigneron DB, Kurhanewicz J (2011) Correlation of phospholipid metabolites with prostate cancer pathologic grade, proliferative status and surgical stage—impact of tissue environment. *NMR Biomed* 24(6):691–699
62. Lagemaat MW, Vos EK, Maas MC, Bitz AK, Orzada S, van Uden MJ, Kobus T, Heerschap A, Scheenen TWJ (2014) Phosphorus magnetic resonance spectroscopic imaging at 7 T in patients with prostate cancer. *Investig Radiol* 49(5):363–372
63. Lagemaat MW, Maas MC, Vos EK, Bitz AK, Orzada S, Weiland E, van Uden MJ, Kobus T, Heerschap A, Scheenen TWJ (2015) (31) P MR spectroscopic imaging of the human prostate at 7 T: T1 relaxation times, Nuclear Overhauser Effect, and spectral characterization. *Magn Reson Med* 73(3):909–920

64. Scheenen TWJ, Zamecnik P (2021) The role of magnetic resonance imaging in (future) cancer staging: note the nodes. *Invest Radiol* 56(1):42–49
65. Philips BWJ, Fortuin AS, Orzada S, Scheenen TWJ, Maas MC (2017) High resolution MR imaging of pelvic lymph nodes at 7 Tesla. *Magn Reson Med* 78(3):1020–1028
66. Fortuin AS, Philips BWJ, van der Leest MMG, Ladd ME, Orzada S, Maas MC, Scheenen TWJ (2020) Magnetic resonance imaging at ultra-high magnetic field strength: an in vivo assessment of number, size and distribution of pelvic lymph nodes. *PLoS One* 15(7):e0236884
67. Philips BWJ, Stijns RCH, Rietsch SHG, Brunheim S, Barentsz JO, Fortuin AS, Quick HH, Orzada S, Maas MC, Scheenen TWJ (2019) USPIO-enhanced MRI of pelvic lymph nodes at 7-T: preliminary experience. *Eur Radiol* 29(12):6529–6538
68. Stijns RCH, Philips BWJ, Nagtegaal ID, Polat F, de Wilt JHW, Wauters CAP, Zamecnik P, Fütterer JJ, Scheenen TWJ (2021) USPIO-enhanced MRI of lymph nodes in rectal cancer: a node-to-node comparison with histopathology. *Eur J Radiol* 138:109636
69. He X, Ertürk MA, Grant A, Wu X, Lagore RL, DelaBarre L, Eryaman Y, Adriany G, Auerbach EJ, Van de Moortele P-F, Uğurbil K, Metzger GJ (2020) First in-vivo human imaging at 10.5T: Imaging the body at 447 MHz. *Magn Reson Med* 84(1):289–303
70. Ertürk MA, Wu X, Eryaman Y, Van de Moortele PF, Auerbach EJ, Lagore RL, DelaBarre L, Vaughan JT, Uğurbil K, Adriany G, Metzger GJ (2017) Toward imaging the body at 10.5 tesla. *Magn Reson Med* 77(1):434–443
71. Metzger GJ, Auerbach EJ, Akgun C, Simonson J, Bi X, Uğurbil K, van de Moortele PF (2013) Dynamically applied B1+ shimming solutions for non-contrast enhanced renal angiography at 7.0 Tesla. *Magn Reson Med* 69(1):114–126
72. Steensma B, van de Moortele PF, Erturk A, Grant A, Adriany G, Luijten P, Klomp D, van den Berg N, Metzger G, Raaijmakers A (2020) Introduction of the snake antenna array: geometry optimization of a sinusoidal dipole antenna for 10.5T body imaging with lower peak SAR. *Magn Reson Med* 84(5):2885–2896

Chapter 6

The Potential of Iron Oxide Nanoparticle–Enhanced MRI at 7 T Compared With 3 T for Detecting Small Suspicious Lymph Nodes in Patients With Prostate Cancer

Carlijn J.A. Tenbergen, Ansje S. Fortuin, Jack J.A. van Asten, Andor Veltien, Bart W.J. Philips, Thomas Hambrock, Stephan Orzada, Harald H. Quick, Jelle O. Barentsz, Marnix C. Maas, and Tom W.J. Scheenen

Abstract

Background: Accurate detection of lymph node (LN) metastases in prostate cancer (PCa) is a challenging but crucial step for disease staging. Ultrasmall superparamagnetic iron oxide (USPIO)-enhanced magnetic resonance imaging (MRI) enables distinction between healthy LNs and nodes suspicious for harboring metastases. When combined with MRI at an ultra-high magnetic field, an unprecedented spatial resolution can be exploited to visualize these LNs.

Purpose: The aim of this study was to explore USPIO-enhanced MRI at 7 T in comparison to 3 T for the detection of small suspicious LNs in the same cohort of patients with PCa.

Materials and Methods: Twenty PCa patients with high-risk primary or recurrent disease were referred to our hospital for an investigational USPIO-enhanced 3 T MRI examination with ferumoxtran-10. With consent, they underwent a 7 T MRI on the same day. Three-dimensional anatomical and T2*-weighted images of both examinations were evaluated blinded, with an interval, by 2 readers who annotated LNs suspicious for metastases. Number, size, and level of suspicion (LoS) of LNs were paired within patients and compared between field strengths.

Results: At 7 T, both readers annotated significantly more LNs compared with 3 T (474 and 284 vs 344 and 162), with 116 suspicious LNs on 7 T (range, 1–34 per patient) and 79 suspicious LNs on 3 T (range, 1–14 per patient) in 17 patients. For suspicious LNs, the median short axis diameter was 2.6 mm on 7 T (1.3–9.5 mm) and 2.8 mm for 3 T (1.7–10.4 mm, $P = 0.05$), with large overlap in short axis of annotated LNs between LoS groups. At 7 T, significantly more suspicious LNs had a short axis <2.5 mm compared with 3 T (44% vs 27%). Magnetic resonance imaging at 7 T provided better image quality and structure delineation and a higher LoS score for suspicious nodes.

Conclusions: In the same cohort of patients with PCa, more and more small LNs were detected on 7 T USPIO-enhanced MRI compared with 3 T MRI. Suspicious LNs are generally very small, and increased nodal size was not a good indication of suspicion for the presence of metastases. The high spatial resolution of USPIO-enhanced MRI at 7 T improves structure delineation and the visibility of very small suspicious LNs, potentially expanding the in vivo detection limits of pelvic LN metastases in PCa patients.

Introduction

Detecting lymph node (LN) metastases (LNMs) in patients with prostate cancer (PCa) is very challenging but crucial for accurate staging with important treatment and prognostic implications. An extended pelvic lymph node dissection (ePLND) is still considered the reference standard for nodal staging, whereas the therapeutic value of this invasive procedure is unclear with similar clinical outcomes in patients in whom ePLND was or was not performed.^{1,2} Because LNMs in PCa are often small^{3,4} and can be found outside the surgical resection field in difficult-to-reach anatomical areas,^{5,6} they can be missed. In addition, small LNMs may not be detected in the assessment of histopathological specimens.^{7–10} An accurate noninvasive nodal staging technique is therefore warranted.

Prostate-specific membrane antigen (PSMA)-PET/CT is increasingly used in recent years in clinical practice before initial therapy as it outperforms conventional imaging, which depends on morphological and size criteria. It is noninvasive, which is an advantage over ePLND, avoiding potential significant morbidity of ePLND. Initial results of PSMA-PET/CT are promising for detecting LNMs compared with anatomical imaging¹¹ with good specificity (0.67–1.0, pooled 0.95), although there is a large variation in reported sensitivity (0.23–1.0, pooled 0.58).^{11–13} Sensitivity is hindered by the spatial resolution of PET/CT of 4–5 mm,¹⁴ which makes it difficult to detect small LNMs. In concordance, PET-positive LNMs are reported larger (median, 4.0–13.6 mm) than false PET-negative LNMs (median, 2.5–5.0 mm).¹⁵ Although the sensitivity of PSMA-PET/CT is not yet sufficient to completely replace ePLND for nodal staging, the negative predictive value seems sufficient to safely omit this procedure in men with a low risk of nodal involvement.¹³

Ultrasmall superparamagnetic iron oxide (USPIO)-enhanced magnetic resonance imaging (MRI) is another noninvasive functional imaging technique. Because of the high spatial resolution and superior soft tissue contrast of MRI, it offers promising potential for metastatic LN detection. Intravenously administered USPIO nanoparticles accumulate in phagocytic cells of the immune system (ie, macrophages) in healthy LNs, attenuating their signal on T2*-weighted images, whereas LNs that retain MR signal due to the lack of USPIO nanoparticle accumulation are therefore suspicious for harboring metastases. The lower limit of detectable size is therefore not depending on the accumulated contrast agent, but on the attainable spatial resolution of the images.

Initial USPIO-enhanced MRI studies in PCa were performed at 1.5 T.^{3,16} Magnetic resonance imaging at a higher (3 T) field strength improved the image quality of the technique.¹⁷ In addition, 3D acquisition techniques at 3 T enabled imaging at high isotropic image resolutions (0.85 x 0.85 x 0.85 mm), which was used at the time of the reintroduction of USPIO-enhanced MRI.¹⁸ In a first direct comparison study between USPIO-enhanced MRI at 3 T and PSMA-PET/CT in the same patients, MRI detected more and smaller suspicious LNs than PSMA-PET/CT did.¹⁹

The challenging next step in body MRI is moving to an ultra-high magnetic field strength of 7 T. Exploiting its higher sensitivity by acquiring an even higher spatial resolution than reachable at 3 T, USPIO-enhanced MRI at 7 T could allow improved detection of LNM, which may alter disease management, both in primary PCa and in recurrent disease.^{20,21} The initial technical challenges of previously seen image inhomogeneity with large field of views in the pelvis at 7 T have been overcome,^{22,23} and the feasibility of detecting (suspicious) LNs down to 1.5 mm in size on 7 T has already been demonstrated.^{24–26}

To assess the potential of improved detection of suspicious LNs with USPIO-enhanced MRI at 7 T over 3 T, we compared 7 T USPIO-enhanced MRI with 3 T USPIO-enhanced MRI in a cohort of 20 patients with PCa.

Materials and methods

Participants

This single-center, nonrandomized, prospective trial was approved by the institutional review board (no. 16 7214 BO), and written informed consent was obtained from all participants. The USPIO contrast agent ferumoxtran-10 (Ferrotran; SPL Medical BV, Nijmegen, the Netherlands) was used. This agent is available for clinical studies and in Named Patient Use Programs in the Netherlands and Switzerland. A large phase III international multicenter pivotal trial for EMA approval is ongoing (EudraCT 2018-004310-18). For this study, patients with primary or recurrent PCa, who were referred to our medical center for an investigational USPIO-enhanced 3 T MRI examination due to deemed high risk of LNM (by primary risk classification²⁰ or PSA level after therapy²¹), were included between March 2014 and February 2015. The patients provided written informed consent to undergo a 7 T USPIO-enhanced MRI on the same day as well.

USPIO-Enhanced MRI at 3 T and 7 T

All participants received an intravenous administration of ferumoxtran-10 (dosage 2.6 mg/kg) 24–36 hours before 3 T and 7 T MRI. High-resolution, 3-dimensional anatomical, and T2*-weighted images were acquired at 3 T (MAGNETOM Prisma-fit; Siemens Healthineers, Erlangen, Germany) and within 5 hours on the same day at 7 T (MAGNETOM 7 T; Siemens Healthineers, Erlangen, Germany). Negligible difference in nodal contrast accumulation was to be expected for these 2 scans within this time frame.²⁷ The scanned area included at least the area from the aortic bifurcation to the bladder neck (see Table 1 for scanning parameters).

Table 1: Overview of pulse sequence parameters for 7T and 3T MR acquisitions.

	7T		3T	
	Water selective imaging 3D mGRE – T2*-weighted	Lipid selective imaging 3D GRE - anatomical	Water selective imaging 3D MEDIC - T2*-weighted	VIBE Dixon 3D GRE - anatomical
Voxel size (mm ³)	0.66 x 0.66 x 0.66	0.66 x 0.66 x 0.66	0.85 x 0.85 x 0.85	0.85 x 0.85 x 0.85
FOV	210 x 210 x 169	210 x 210 x 169	328 x 328 x 190	328 x 328 x 204
Matrix	320 x 320 x 256	320 x 320 x 256	384 x 384 x 224	384 x 384 x 240
TE (ms)	2.1, 4.19, 6.21, 8.3, 10.32	2.0	12 (MEDIC 8, 16)	2.5
TR (ms)	14	5.2	21	6.5
Flip angle (deg)	≈15*	≈19*	10	10
Bandwidth (Hz)	625	625	170	350
Acceleration	2x2	2x2	3x1	3x1
Acquisition time (min)	8:24	2:50	10:08	6:55
Excitation	Water selective	Lipid selective	Water and slab selective	Slab selective
Bowel preparation	i.m. dose of 20 mg butylscopolamine just before scan		i.m. dose of 20 mg butylscopolamine just before scan	

The multiple gradient echoes at 7T were reconstructed into one dataset with a computed echo time of 8 ms [1]. *An estimated flip angle over two TRs across the pelvic field of view. MEDIC, multiecho data image combination; VIBE, volumetric interpolated breath-hold examination; mGRE, multiecho gradient echo; FOV, field of view.

Image Evaluation and Annotation

After anonymization, all scans were independently evaluated by 2 experienced abdominal radiologists (A.S.F. with 6.5 years and T.H. with 3 years, R1 and R2, respectively) who were blinded for clinical parameters. First, the 3 T studies were presented to the readers. To avoid recollection, the 7 T scans were assessed in a

blinded random order at least 3 months later. R1 is an abdominal radiologist with initial experience for reading USPIO-enhanced imaging; R2 is an expert in assessing clinical USPIO-enhanced MRI.

Both readers were asked to annotate the LNs suspicious for harboring nodal metastases on the basis of both the anatomical and the T2*-weighted 3D datasets with freedom to scroll in 3 dimensions and with optional maximum intensity projection. The water-selective iron-sensitive T2*-weighted images were used to identify suspicious LNs (3 T: multiecho data image combination, 7 T: computed echo time images from multigradient echo); LNs with a homogeneous residual high signal intensity or those with partial high signal components were deemed suspicious for harboring metastases. The reconstructed water and lipid images (3T: volumetric interpolated breath-hold examination Dixon, 7T: gradient echo) were used for anatomical correlation. The nodes were annotated on T2*-weighted MRI and scored on a 5-point level of suspicion (LoS) scale (metastases very unlikely [1], unlikely [2], equivocal [3], likely [4], and very likely [5]). The readers had the assignment to find all potentially suspicious LNs (defined as LoS ≥ 3). Healthy LNs did not have to be scored, although the scores of LoS 1 and 2 could be used to indicate an LN or other small spherical structure retaining signal on T2*-weighted MRI to deem it benign (eg, a slightly gray LN or a ganglion).

Lymph node annotations from both readers were imported independently into an adapted dedicated viewer (Mevislab; Mevis Medical Solutions, Bremen, Germany). The annotations of both readers could be turned on and off and projected over the patient's images, enabling precise matching between the annotations of both readers. When both readers independently annotated an LN and scored it with LoS 3–5, it was considered “suspicious.” When both readers independently detected an LN with a score of LoS 4–5, it was considered “highly suspicious.” An independent reader (A.V.) performed matching of annotations and nodal size measurements in 3 orthogonal directions (noted as short axis diameter and ellipsoid volume). R1 assessed the image quality of all 3 T and 7 T images (see Supplementary Material).

Statistical Analysis

To compare the detection of suspicious LNs on 3 T and 7 TMRI, the number of suspicious LNs was analyzed per participant by Wilcoxon matched pairs signed rank tests. Mann-Whitney U tests were performed to compare the size of annotated LNs. The LN size is compared between the LoS score groups by Dunn multiple comparison tests after Kruskal-Wallis nonparametric analysis of variance. A subgroup of LNs that were scored on both field strengths by both readers was

analyzed on LoS scores with Wilcoxon matched pairs signed rank tests. A P value <0.05 indicated a statistically significant difference.

Results

Participants

Twenty patients were included with a mean age of 63 years (range, 50–74 years). Participants with primary PCa (n = 7) and patients with recurrent disease (n = 13) had mean serum prostate-specific antigen levels of 33.1 ng/mL and 2.8 ng/mL, respectively (Table 2). In all T2 20 participants, the infusion of the contrast agent was without any adverse events, and they underwent both MRI examinations successfully. The overall image quality and the delineation of anatomical structures on the T2*-weighted images were scored significantly higher on 7 T, with a median score for overall image quality of 4 and 5 for 3 T and 7 T, respectively (P < 0.001) (Fig. 1). For more extensive elaboration of analysis of image quality and a movie comparing 3 T with 7 T data, see the Supplementary Materials.

Table 2: Demographic data of participants.

	Primary PCa	Recurrent PCa
No. participants	7	13
Age, y	61 (50-74)	64 (52-71)
PSA, ng/ml	33.1 (8.2-88)	2.8 (0.2-17.5)
No. suspicious LNs		
7 T	5 (2-34)	4 (0-11)
3 T	3 (0-14)	3 (0-11)

Data for age and PSA are noted as means (range); number of nodes are noted as median per participant with (range). PCa, prostate cancer; PSA, prostate-specific antigen; LN, lymph nodes.

Number of LNs

The total number of annotated LNs by either of the 2 readers was 599 at 7 T and 408 at 3 T (Table 3). The total number of LNs observed per patient (across all levels of suspicion) was higher at 7 T than at 3 T, with a median number (and range) of LNs annotated by at least 1 reader of 23.5 (2–88) versus 17.5 (2–45), P < 0.001 (Fig. 2A). Subgroup analysis showed significant differences in median number of LNs per patient for both primary (7 T: 20 vs 3 T: 17, P = 0.03) and recurrent disease (7 T: 28 vs 3 T: 18, P = 0.009), respectively.

Table 3: Number of annotated LNs on both field strengths, given for each reader separately and divided further on level of suspicion.

	7T				R1&R2	total
	R1		R2			
All nodes	474		284		159	599
LoS 1+2	73	15%	92	32%		
LoS 3	201	42%	54	19%		
LoS 4	146	31%	73	26%	116	477
LoS 5	54	11%	65	23%		

The subset R1 and R2 contains the LNs that were annotated by both readers; the total number encompasses all LNs annotated by either of the 2 readers. LoS, level of suspicion.

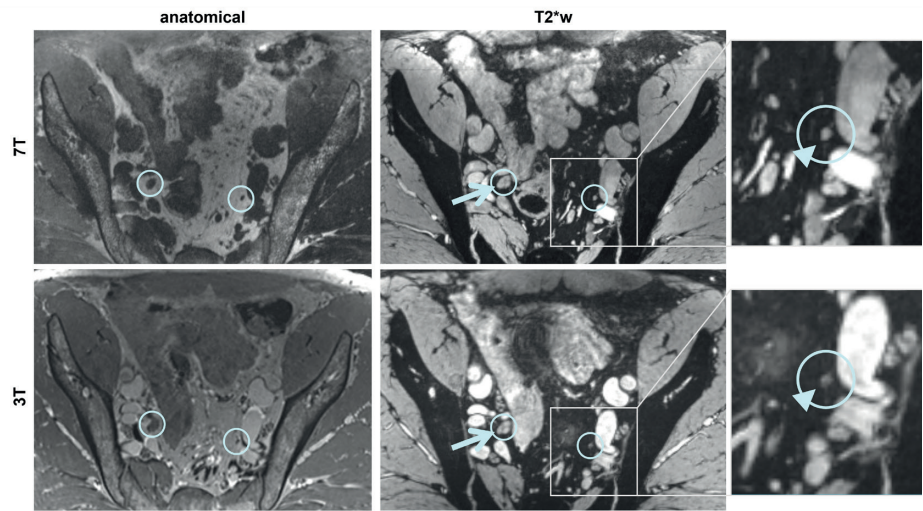


Figure 1. Example of USPIO-enhanced MRI of a patient with advanced prostate cancer at 7 T and 3 T in transversal planes. A big LN(short axis 7.5mm, arrows) was scored by both readers with an LoS of 5 on both 7 T and 3 T. The smaller LN (short axis 3.0 mm, arrowheads) was scored suspicious with LoS 5 by both readers on 7 T. On 3 T, possibly due to its size or appearance, this node was not annotated by either of the readers.

3T				
R1		R2		R1&R2
total				
344		162		98
64	19%	32	20%	
145	42%	62	38%	
98	28%	46	28%	79
37	11%	22	14%	

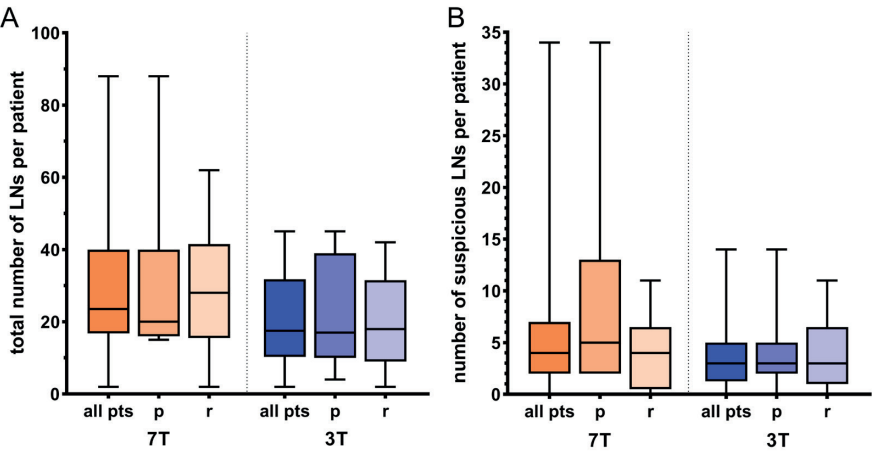


Figure 2. A, All annotated LNs per patient for 7 T and 3 T, with all patients ($n = 20$) and divided into primary ($n = 7$) and recurrent PCa ($n = 13$). **B,** Suspicious LNs (both readers LoS ≥ 3), for 7 T and 3 T. p indicates primary prostate cancer; r, recurrent disease.

Suspicious LNs (ie, LoS 3 or higher indicated by both readers) were found in 17/20 patients at both field strengths (Fig. 2B), with 116 suspicious LNs annotated on 7 T and 79 on 3 T (Table 3). The number of suspicious LNs annotated per patient was higher at 7 T than at 3 T, but the difference was not statistically significant (median [range], 4 [0–34] vs 3 [0–14]; $P = 0.10$). However, the number of highly suspicious LNs per patient (LoS ≥ 4 indicated by both readers) was significantly higher at 7 T ($P = 0.02$). The number of suspicious LNs per patient did not differ significantly between patients with primary and recurrent disease, neither at 7 T (5 [2–34] vs

4 [0–11], $P = 0.30$) nor at 3 T (3 [0–14] vs 3 [0–11], $P = 0.60$) (Table 2). Fifteen percent of suspicious LNs, for both field strengths, were located outside of the standard resection area of ePLND (see Supplemental Materials).

LN Size

Lymph nodes annotated by at least 1 reader (across all levels of suspicion) had a median short axis at 7 T and 3 T of 2.5 and 2.6 mm (Fig. 3), respectively (not significantly different, $P = 0.78$). Subgroup analysis showed no significant differences in median short axis of LNs for primary (7 T: 2.5 vs 3 T: 2.7mm, $P = 0.24$) or recurrent disease (7 T: 2.5 vs 3 T: 2.5 mm, $P = 0.61$), respectively.

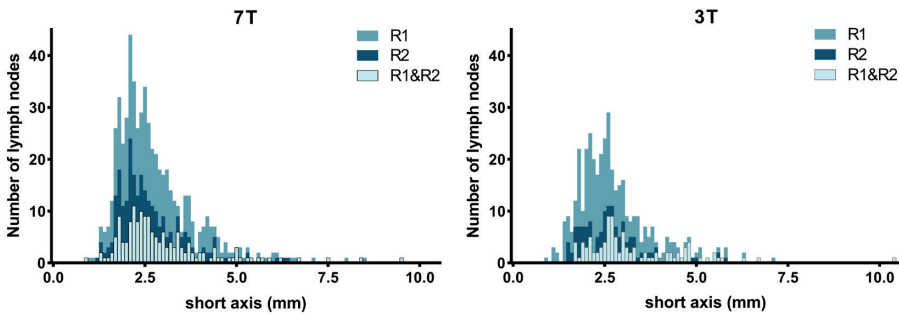


Figure 3. Size distribution of annotated LNs per field strength (all levels of suspicion). Bars are cumulative, showing the LNs with their short axis, split by reader.

For suspicious LNs (7 T: $n = 116$, 3 T: $n = 79$), the median short axis diameters were 2.6 mm (range, 1.3–9.5 mm) and 2.8 mm (range, 1.7–10.4mm) for 7 T and 3 T, respectively (Fig. 4, not significantly different, $P = 0.05$). The volume of suspicious LNs annotated at 7 T was overall significantly smaller compared with 3 T (median, 13.0 vs 19.1 mm³; $P = 0.008$). Also at 7 T, more (44%) suspicious LNs than at 3 T (27%) had a short axis <2.5 mm.

Figure 5 illustrates the size and LoS of all annotated LNs. The short axis diameter shows great overlap between the LoS groups. At 7 T, the median value for LoS 5 shows a significant difference to both LoS 4 ($P = 0.002$) and LoS 3 ($P = 0.02$). At 3 T, the median value for LoS 5 shows a significant difference to LoS 3 ($P < 0.001$).

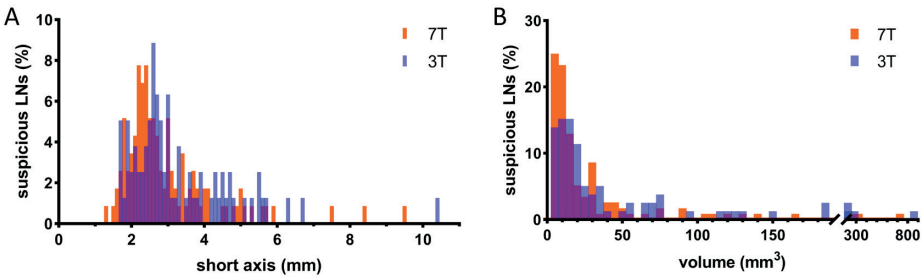


Figure 4. Size distributions of suspicious LNs at 7 T and 3 T, noted as percentage of the total number (116 at 7 T and 79 at 3 T), ordered by short axis (A) and volume (B). 3 T data (semitransparent) is in front of 7 T data, with overlapping bars in purple.

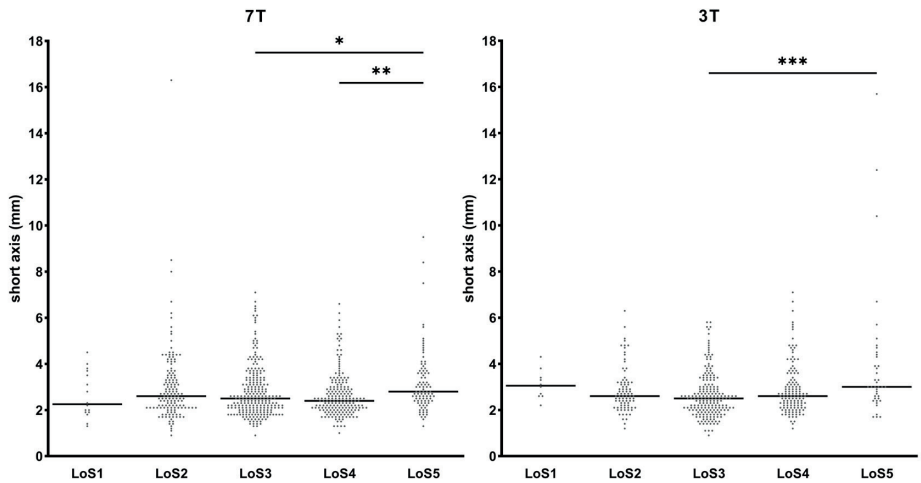


Figure 5. Annotated LNs and their size ordered by LoS, with median value per LoS score group indicated. Scores of 1 and 2 were only given to mark a notable but unsuspicious LN, not incorporating any nodes without signal intensity on T2*-weighted imaging. * $P < 0.05$, ** $P < 0.005$, *** $P < 0.001$.

Table 4: Confusion matrices of inter-reader agreement on 159 from 599 annotated nodes at 7T and on 98 from 408 annotated nodes at 3T.

Confusion matrix 7T					
	R2				
R1	LoS 1	LoS 2	LoS 3	LoS 4	LoS 5
LoS 1	1	0	1	0	0
LoS 2	0	2	0	0	0
LoS 3	0	22	9	9	1
LoS 4	0	15	13	22	25
LoS 5	0	2	2	10	25

Scores of 1 and 2 were only given to mark a notable but unsuspicious LN. LNs with scores $\geq$ LoS3, in bold, were considered suspicious.

Interreader Agreement

R1 and R2 both annotated more LNs on 7 T MRI (474 and 284) compared with 3 T MRI (344 and 162, respectively), see Table 3. Both readers had 98 matching LNs of a total of 408 nodes at 3 T and 159 matching LNs of 599 at 7 T. The individual LoS scores for LNs for both readers can be found in Table 4. R1 gave higher LoS scores for both field strengths ($P < 0.001$ for 7 T and 3 T).

Matched LNs Between Field Strengths

Lymph nodes that were annotated by both readers were matched between field strengths (example in Fig. 1). From the 79 suspicious LNs found on 3 T images, almost all were also annotated on the 7 T images: either by both readers (51) or one of them (21). Of 116 suspicious LNs on 7 T images, 33 were not scored on 3 T images by either of the 2 readers (median short axis of 2.2 mm; range, 1.5–3.0 mm).

Fifty-eight LNs were scored by both readers on both field strengths and therefore further analyzed. There was no difference in size for the matched LNs on both field strengths (short axis mean: 3.64 [7 T], 3.40 [3 T]; $P = 0.11$). The interpretation of one reader did differ between field strengths in these matched LNs, as R2 gave significantly higher LoS scores for the same LNs on 7 T images compared with 3 T ($P < 0.001$, R1: $P = 0.60$).

Confusion matrix 3T					
	R2				
R1	LoS 1	LoS 2	LoS 3	LoS 4	LoS 5
LoS 1	0	1	0	0	0
LoS 2	0	1	1	0	0
LoS 3	0	3	6	10	1
LoS 4	0	13	18	10	4
LoS 5	0	0	6	11	13

Discussion

This is the first study in which 7 T USPIO-enhanced MRI is compared with 3 T USPIO-enhanced MRI to detect LNs suspicious of metastases in the same patients with PCa. At 7 T, high-quality images allow the detection of more and especially more small (<2.5 mm) suspicious LNs. More highly suspicious LNs (LoS 4/5) were found per patient on 7 T compared with 3 T ($P = 0.02$). We showed that suspicious nodes in PCa are generally very small, with 44% of the suspicious LNs found on 7 T measuring <2.5 mm in short axis.

With different radiofrequency coils and pulse sequence possibilities at both field strengths, pulse sequences and sequence parameters were not the same for this comparison between 7 T and 3 T, but optimized to imaging on either 7 T or 3 T to exploit the advantages of that specific field strength. Examinations at 7 T with its substantially higher spatial resolution (voxel size being a factor 2.14 higher than 3 T: 0.29 mm^3 vs 0.61 mm^3) enabled us to detect more LNs with a short axis diameter below 2 mm. Although the short axis diameters of suspicious nodes did not differ significantly between 7 and 3 T, incorporating 3 spatial dimensions by measuring nodal volumes did reveal a significant difference in size between suspicious nodes detected at 7 T versus 3 T. Matching annotated LNs between field strengths showed that many of these very small LNs were not annotated on 3 T, possibly just due to their small size or due to being closely adjacent to and thereby indistinguishable from neighboring structures. As matched LNs did not show a difference in measured short axis diameter between field strengths, this indicates that there is no consistent measurement error due to the image quality or resolution.

The high number of suspicious LNs per patient is not unexpected, as the pelvis is known to hold many LNs (range, 19–91 LNs per healthy volunteer on 7 TMRI).²⁴ The large variability in the number of annotated LNs per patient in this work represents the actual differences in patients at high risk for metastatic disease: 3 participants had more than 10 suspicious LNs, 3 patients had none, and in the remaining participants, the number of suspicious LNs ranged from 1 to 7. The number of annotated LNs located (partly) outside the standard ePLND resection field is in line with previous work¹⁹ and underlines the diagnostic and therapeutic challenges of ePLND.

As a large proportion of suspicious LNs in PCa were very small, the ability to identify these LNs could have important clinical implications. As a comparison, in breast cancer, direct ultrasound-guided fine-needle aspiration or core biopsy is recommended in axillary LNs with a cutoff point of maximum cortex thickness as small as 2.3 mm to achieve a high sensitivity of 95% and accepting a limited specificity of 44%.²⁸ A positive result directly changes further diagnostics.²⁹ In our study, there was a large overlap in short axis of annotated LNs between LoS groups. The idea that large LNs are suspicious and small LNs are not suspicious might no longer be valid in PCa, as most suspicious LNs were very small. The benefit for the patient in detecting more and more small suspicious LNs will most probably not be found in extending pelvic LN dissections, as its current impact on overall survival is already under debate,^{1,2} and removal of all small suspicious nodes will be very challenging. The combination of high-resolution MRI and functional USPIO contrast could introduce a new approach to personalized image-guided LNM-targeted therapy by enabling primary radiotherapy of these small LNMs.^{30–32} Although PSMA-PET/CT is of increasing clinical benefit for image-guided therapy and has the advantage of simultaneous assessment of distant (bone) metastases, its spatial resolution for LN detection is limited compared with the spatial resolution of 7 T USPIO-enhanced MRI.

R1 annotated many more LNs on both 7 T and 3 T examinations compared with R2, possibly because of the difference in experience with USPIO-enhanced MRI in combination with a continuous scale of nodal signal intensity. Annotating and scoring LNs based on the presence or absence of USPIO contrast-loaded macrophages enable a functional assessment that is no longer based on size and morphological characteristics. This requires, however, a different approach to “reading” images. The interpretation of USPIO accumulation with its different shades of gray without quantifying signal intensity requires a learning process. Of note is the increased confidence of the experienced USPIO-MRI reader R2 in scoring

field strength-matched suspicious nodes, presumably because of the improved image quality at 7 T. Recently, Driessen et al^{33,34} have described a new paradigm for evaluating USPIO-enhanced MRI of the head and neck region, incorporating differences in retained signal intensity of nodes. Aided by an extensive workflow for node-to-node matching of in vivo detected LNs with histopathology of resected nodes,³⁴ a new reading algorithm was designed incorporating the signal intensity of LNs compared with the surrounding fat, improving discrimination between metastatic and nonmetastatic LNs.^{33,34} This algorithm potentially also improves the agreement between readers in future studies if lipid tissue is not fully suppressed (not excited) in the multiecho gradient echo pulse sequence.

An important limitation of this study is that there is no histopathological reference standard for the suspicious LNs. Four of the 20 participants underwent ePLND after USPIO-enhanced imaging, but without a dedicated workflow for node-to-node matching of surgical specimens to pathological review of nodes.^{26,34} On a patient level, the USPIO-enhanced MRI results corresponded to the histopathological outcome: 3 patients with suspicious LNs on 3 T and 7 T MRI had LNMs on histopathology; the other patient who had no suspicious LNs on 7 T imaging and 1 suspicious LN on 3 T had no LNMs on histopathology. In absence of matched histopathology, we have chosen to deem LNs suspicious in case both readers annotated the LN with a high LoS. The sensitivity and specificity of 7 T USPIO-enhanced MRI to detect especially small LNMs in PCa remain to be investigated, this study however gives an indication of what to expect of high field strength MRI.

In conclusion, this first comparison of 7 T USPIO-enhanced MRI with 3 T USPIO-enhanced MRI in the same cohort of PCa patients reveals an increased detection of small LNs suspicious for harboring metastases on 7 T MRI. The high resolution of USPIO-enhanced 7 T MRI potentially expands the in vivo detection limits of pelvic LNM in PCa patients and can offer insight in pelvic LNM distributions. This may provide a new gateway to personalized image-guided therapy.

References

1. Fossati N, Willemse PM, Van den Broeck T, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. *Eur Urol.* 2017;72:84–109.
2. Preisser F, van den Bergh RCN, Gandaglia G, et al. Effect of extended pelvic lymph node dissection on oncologic outcomes in patients with D'Amico intermediate and high risk prostate cancer treated with radical prostatectomy: a multi-institutional study. *J Urol.* 2020;203:338–343.
3. Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med.* 2003; 348:2491–2499.
4. Fortuin AS, Deserno WM, Meijer HJ, et al. Value of PET/CT and MR lymphography in treatment of prostate cancer patients with lymph node metastases. *Int J Radiat Oncol Biol Phys.* 2012;84:712–718.
5. Heesakkers RAM, Jager GJ, Hovels AM, et al. Prostate cancer: detection of lymph node metastases outside the routine surgical area with ferumoxtran-10-enhanced MR imaging. *Radiology.* 2009;251:408–414.
6. Schilham MGM, Küsters-Vandeveld H, Somford DM, et al. How image-guided pathology can improve the detection lymph node metastases in prostate cancer. *Clin Nucl Med.* 2022;47:559–561.
7. Engvad B, Poulsen MH, Staun PW, et al. Histological step sectioning of pelvic lymph nodes increases the number of identified lymph node metastases. *Virchows Arch.* 2014;464:45–52.
8. Montironi R, Scarpelli M, Galosi AB, et al. Total submission of lymphadenectomy tissues removed during radical prostatectomy for prostate cancer: possible clinical significance of large-format histology. *Hum Pathol.* 2014;45:2059–2062.
9. Prendeville S, van der Kwast TH. Lymph node staging in prostate cancer: perspective for the pathologist. *J Clin Pathol.* 2016;69:1039–1045.
10. Conti A, Santoni M, Burattini L, et al. Update on histopathological evaluation of lymph node specimens from prostate cancer patients. *World J Urol.* 2017;35: 517–526. doi:10.1007/s00345-015-1752-8.
11. Petersen LJ, Zacho HD. PSMA PET for primary lymph node staging of intermediate and high-risk prostate cancer: an expedited systematic review. *Cancer Imaging.* 2020;20:10. doi:10.1186/s40644-020-0290-9.
12. Abrams-Pompe RS, Fanti S, Schoots IG, et al. The role of magnetic resonance imaging and positron emission tomography/computed tomography in the primary staging of newly diagnosed prostate cancer: a systematic review of the literature. *Eur Urol Oncol.* 2021;4:370–395.
13. Stabile A, Pellegrino A, Mazzone E, et al. Can negative prostate-specific membrane antigen positron emission tomography/computed tomography avoid the need for pelvic lymph node dissection in newly diagnosed prostate cancer patients? A systematic review and meta-analysis with backup histology as reference standard. *Eur Urol Oncol.* 2022;5:1–17.
14. Wang K. Feasibility of high spatial resolution working modes for clinical PET scanner. *Int J Med Phys Clin Eng Radiat Oncol.* 2018;7:539–552.
15. Hernes E, Revheim M-E, Hole KH, et al. Prostate-specific membrane antigen PET for assessment of primary and recurrent prostate cancer with histopathology as reference standard: a systematic review and meta-analysis. *PET Clinics.* 2021; 16:147–165.
16. Heesakkers RA, Hövels AM, Jager GJ, et al. MRI with a lymph-node-specific contrast agent as an alternative to CT-scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study. *Lancet Oncol.* 2008;9:850–856.

17. Heesakkers RAM, Fütterer JJ, Hövels AM, et al. Prostate cancer evaluated with ferumoxtran-10-enhanced T2*-weighted MR imaging at 1.5 and 3.0 T: early experience. *Radiology*. 2006;239:481–487.
18. Fortuin AS, Brüggemann R, van der Linden J, et al. Ultra-small superparamagnetic iron oxides for metastatic lymph node detection: back on the block. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2018;10:e1471. doi:10.1002/wnan.1471. PubMed PMID: 28382713; PubMed Central PMCID: 5763341.
19. Schilham MGM, Zamecnik P, Privé BM, et al. Head-to-head comparison of (68) Ga-prostate-specific membrane antigen PET/CT and ferumoxtran-10-enhanced MRI for the diagnosis of lymph node metastases in prostate cancer patients. *J NuclMed*. 2021;62:1258–1263.
20. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESURSIOG guidelines on prostate cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2021;79:243–262.
21. Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESURSIOG guidelines on prostate cancer. Part II-2020 update: treatment of relapsing and metastatic prostate cancer. *Eur Urol*. 2021;79:263–282.
22. Orzada S, Maderwald S, Poser BA, et al. RF excitation using time interleaved acquisition of modes (TIAMO) to address B1 inhomogeneity in high-field MRI. *Magn Reson Med*. 2010;64:327–333.
23. Orzada S, Maderwald S, Poser BA, et al. Time-interleaved acquisition of modes: an analysis of SAR and image contrast implications. *Magn Reson Med*. 2012;67: 1033–1041.
24. Fortuin AS, Philips BWJ, van der Leest MMG, et al. Magnetic resonance imaging at ultra-high magnetic field strength: an in vivo assessment of number, size and distribution of pelvic lymph nodes. *PloS One*. 2020;15:e0236884.
25. Philips BWJ, Stijns RCH, Rietsch SHG, et al. USPIO-enhanced MRI of pelvic lymph nodes at 7-T: preliminary experience. *Eur Radiol*. 2019;29:6529–6538.
26. Fortuin AS, van Asten J, Veltien A, et al. Small suspicious lymph nodes detected on ultrahigh-field magnetic resonance imaging (MRI) in patients with prostate cancer with high risk of nodal metastases: the first in-patient study on ultrasmall superparamagnetic iron oxide-enhanced 7 T MRI. *Eur Urol*. 2023; 83:375–377.
27. Hudgins PA, Anzai Y, Morris MR, et al. Ferumoxtran-10, a superparamagnetic iron oxide as a magnetic resonance enhancement agent for imaging lymph nodes: a phase 2 dose study. *Am J Neuroradiol*. 2002;23:649–656.
28. Deurloo EE, Tanis PJ, Gilhuijs KGA, et al. Reduction in the number of sentinel lymph node procedures by preoperative ultrasonography of the axilla in breast cancer. *Eur J Cancer*. 2003;39:1068–1073.
29. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019;30: 1194–1220.
30. Hölscher T, Baumann M, Kotzerke J, et al. Toxicity and efficacy of local ablative, image-guided radiotherapy in gallium-68 prostate-specific membrane antigen targeted positron emission tomography-staged, castration-sensitive oligometastatic prostate cancer: the OLI-P phase 2 clinical trial. *Eur Urol Oncol*. 2022;5:44–51.
31. Zamagni A, Bonetti M, Buwenge M, et al. Stereotactic radiotherapy of nodal oligometastases from prostate cancer: a prisma-compliant systematic review. *Clin Exp Metastasis*. 2022;39:845–863.

32. Shiota M, Blas L, Eto M. Current status and future perspective on the management of lymph node-positive prostate cancer after radical prostatectomy. *Cancer*. 2022; 14:2696.
33. Driessen DAJJ, Zámecnik P, Dijkema T, et al. High-accuracy nodal staging of head and neck cancer with USPIO-enhanced MRI: a new reading algorithm based on node-to-node matched histopathology. *Invest Radiol*. 2022;57: 810–818.
34. Driessen DAJJ, de Gouw DJJM, Stijns RCH, et al. Validation of in vivo nodal assessment of solid malignancies with USPIO-enhanced MRI: a workflow protocol. *Methods Protoc*. 2022;5:24.

Supplemental material



Video: via Investigative Radiology 59(7):p 519-525

Direct comparison of image quality. Transversal 2 mm maximum intensity projection images of the same patient at 3T (left) and 7T (right). Depiction of anatomical structures is sharper at 7T, due to the higher spatial resolution of the reconstructed dataset (0.68 mm isotropic at 7T vs. 0.85 mm isotropic at 3T).

6

Image quality

Image quality was scored by reader R1 for all 7T and 3T MRI studies. In the supplementary movie the T2*-weighted USPIO-enhanced MRI datasets from 1 patient at 3T and 7T are visualized. Overall diagnostic image quality and visibility of structures on all image sets were scored on a 5-point Likert scale: very poor (1), poor (2), adequate (3), good (4) and very good (5). The presence of artifacts was also scored on a 5-point scale, with, similarly, a higher score indicating less artifacts and therefore better image quality (artifacts pronounced (1), considerable (2), moderate (3), minimal (4), absent (5)). Specific artifacts were scored separately, with motion artifacts were defined as image artifacts in the region of the vessels or presacral due to patient or bowel motion, causing disturbed images (with or without ghosting, in the phase-encoding direction). Aliasing encompassed wrap-around artifacts in the image. Susceptibility artefacts were defined as image distortion, together with signal voids caused by susceptibility differences between lymph nodes and their environment, resulting in signal loss influencing interpretability. Noise was specified as a subjective impression of a low signal-to-noise ratio.

Table S1: Image quality score for 7T and 3T images, as scored by reader R1.

	7T		3T		p-value
	Mean	Median	Mean	Median	
Overall image quality (usefulness for nano-MRI)	5.00	5	4.11	4	<0.001*
Visibility of structures					
Lymph node border delineation - T2*w	4.35	4	4.37	5	0.93
Nerves/ganglia / Vessels delineation - T2*w	4.61	5	4.37	5	0.47
Lymph node border delineation - anatomical	4.63	5	4.16	4	0.03*
Nerves/ganglia / Vessels delineation - anatomical	4.68	5	4.12	4	0.01*
Presence of artifacts					
Motion artifact of bowels	3.89	4	3.26	3	0.04*
Motion artifact of LN	4.44	4	4.00	4	0.17
aliasing	4.68	5	4.89	5	0.79
susceptibility around bowels	4.26	4	3.82	4	0.07
susceptibility around lymph nodes	4.22	4	3.40	3	0.002*
Noise	3.88	4	4.75	5	0.002*
Other	4.58	5	4.78	5	0.60

* indicates significant difference

Mean and median scores of all 20 subjects for 7T and 3T images are shown in Table S1. Mann-Whitney-U-test were used to test for significant differences between 7T and 3T images. Some missing score values prevented the pairing of images per subjects. The 7T images showed a significant better quality overall and of the anatomical images for delineation of lymph nodes and surrounding structures. Significant less susceptibility artifacts around the lymph nodes were seen on 7T images compared with 3T images. However, at the higher field strength, more noise was perceived.

Location of lymph nodes

Most suspicious lymph nodes were detected along the internal iliac arteria (7T: 31%, 3T: 20%), external iliac artery (7T: 15%, 3T: 24%) and in the obturator space (7T: 26%, 3T: 24%), but also in the perirectal (7T: 12%, 3T: 10%) region suspicious nodes were detected. Table S2 shows the complete distribution of lymph nodes over the pelvic area. A total of 15% of all suspicious lymph nodes, on both field strengths, was located outside of the standard area of ePLND.

Table S2: distribution of the annotated suspicious lymph nodes over the pelvic regions.

	7T	3T
All	36 (31%)	16 (20%)
Obturator	30 (26%)	19 (24%)
AIE	17 (15%)	19 (24%)
AIC	12 (10%)	12 (15%)
Presacral	4 (3%)	1 (1%)
Perirectal	14 (12%)	8 (10%)
Perivesical	2 (2%)	1 (1%)
Para-aortal*	1 (1%)	3 (4%)

The standard areas included in ePLND in bold. AIC= common iliac artery, All= internal iliac artery, AIE= external iliac artery. *The para-aortal region was not a region of interest. However, as the field of view contained at least the area from the aorta bifurcation, the para-aortal lymph nodes that were within the field of view and suspicious were taken into account.

1. Philips BWJ, Stijns RCH, Rietsch SHG, Brunheim S, Barentsz JO, Fortuin AS, et al. USPIO-enhanced MRI of pelvic lymph nodes at 7-T: preliminary experience. European radiology 2019;29(12):6529-38.

Chapter 7

Discussion and future perspectives



With prostate cancer incidence rising and options for personalized treatment upcoming, accurate staging of the disease is vital. Multiparametric MRI of the prostate at clinical magnetic field strengths has emerged as a reliable noninvasive imaging modality for identifying clinically significant cancer, enabling selective sampling of high-risk regions with MRI-targeted biopsies, and enabling minimally-invasive focal treatment options. Clinical guidelines have incorporated the mpMRI pathway with PI-RADs as standardized interpretation and reporting of MR images^{1,2}. While the MRI pathway can reduce the number of performed biopsies and reduce the detection of clinically insignificant cancers, the inter-reader variance is high. An efficient MRI pathway can benefit from further optimized imaging, which could minimize variance in MRI data acquisitions and improve image quality and interpretations. This can decrease the number of diagnostic steps to identify clinically significant cancer, matching the increasing demand for mpMRI diagnostics.

This thesis has covered several studies to optimize technical aspects of MRI of the prostate, aiming to facilitate the quantitative assessment of the aggressiveness of prostate cancer and initial metastatic spread of the disease to lymph nodes. The first section covers two studies that were performed in public-private partnerships with two companies. With Siemens Healthineers the focus was a clinical evaluation of an automated MR acquisition protocol. Together with a small company, MR Shim GmbH, new MR hardware to improve the magnetic field homogeneity in the prostate was developed and tested. This direct link to the industry can help in enabling the translation of results from the performed studies to the clinic, achieving a short route to immediate impact on patient care.

Robust ¹H-MRSI and DWI to quantify the prostate cancer lesion

The first study in section one mainly focuses on MRSI, a technique that has proven additional value for the assessment of prostate cancer lesions as it can correlate metabolite ratios to tumor aggressiveness³. As MRSI can provide quantitative parameters of prostate cancer lesions, adding this sequence to the mpMRI exam has the potential to decrease inter-reader variability and provide a reliable follow-up measure in a repeat setting. This technique, however, is not included in the latest PI-RADS versions, as it required rather long examination times while being less robust than the other pulse sequences in an mpMRI examination. MRSI is therefore difficult to deploy successfully in clinical routine, particularly if no significant in-house expertise is available.

For easy set-up, requiring minimal experience and minimizing the time used for setting-up, a semi-automatic workflow was created for mpMRI of the prostate. This workflow is based on initial automatic segmentation of the prostate, which is used for positioning and alignment of subsequent pulse sequences. Upon testing, we found that overall segmentation went well, and the prostate is nicely contoured at the mid-section. With a quick check of the segmentation result, one could easily see which areas could be causing difficulties in subsequent steps of the protocol and needed more attention. In some subjects (8 out of 40) the segmentation algorithm resulted in large errors and we proposed to do a rerun of the segmentation based on the diagnostic T2w images. In 32 out of the 40 cases, the workflow performed well with only small manual adjustments needed for positioning of the imaging series and setting up the MRSI. This resulted in a high amount of good quality voxels (84%) found in most subjects. We proposed recommendations to balance manual input and automatization for optimal personalization and set-up time. As the set-up of the MRSI pulse sequence can be done during the acquisition of other sequences, the addition of MRSI to an mpMRI exam would cost only the additional time of acquisition. For MRSI to be used in the clinic, at a time where shorter examinations are investigated (biparametric mpMRI⁴ or acceleration methods⁵), next to facilitating the acquisition, we focused on improvements to be made on robustness and interpretability to establish the additional value of MRSI.

Improved shimming, and thereby increased robustness of DWI and ¹H-MRSI, was the aim of the presented add-on hardware for mpMRI of the prostate in chapter 3, the second study in section one. To address main magnetic field (B₀) distortions in the prostate, increasing the quality of DWI and ¹H-MRSI, the proposed methodology involved calculating the optimal combination of 1st-order shim values of the MR scanner and add-on coil's shimming settings, which were compared with conventional scanner shimming in seven healthy volunteers. In ¹H-MRSI, citrate linewidths improved significantly, decreasing from 8.3 ± 5.7 Hz with conventional shimming to 7.9 ± 3.6 Hz with the add-on shim coil.

A clear difference in magnetic field homogeneity in the prostate was visible between patients, with the differences between patients persisting for both shim methods. This consistency underscores the correlation between the achievable magnetic field homogeneity in the prostate and various physiological characteristics of an individual subject, with factors such as subject size, pelvic anatomy, prostate size, and bowel motion playing a big role. As robust shimming over all subjects was not yet achieved, a first recommendation would be to learn from this inter-subject variety and check with an initial scan if problems with shimming are to be expected,

based on anatomy and gas presence, and then apply the add-on shim in this subset of subjects. Secondly, the shim software of the add-on coil could be further improved. A feedback control system could be implemented to continuously monitor shim quality between consecutive acquisitions. Such a system would enable prompt re-shimming if a decline in quality is detected, related to bowel or patient movement, making the method even more personalized.

After automated planning of MRSI and homogenizing the magnetic field within the prostate, post-processing methods can further improve MRSI quality. Without increasing the acquisition time from current three-dimensional ^1H -MRSI acquisition methods, a 3D overdiscretized reconstruction method in Chapter 4 is aimed at improving the localization of metabolite signals in the prostate without compromising on SNR. In phantom measurements, this ODR method resulted in an SNR increase of 45% of the main metabolite present in the phantom, which was creatine. While it is more difficult to assess SNR in volunteers, within the same acquisition time and without loss of SNR compared with weighted k-space sampling and Hamming filtering, we achieved increased spatial resolution and improved localization in metabolite maps. Subsequent testing of the ODR method in patients with prostate cancer showed the effect of improved signal localization and SNR on tumor characterization. With expected differences in prostate sizes and larger prostate VOIs in older subjects, the acquisition time for MRSI might become longer than the acquisition time of 11 mins required for our healthy (young) volunteers. For subsequent testing in patients, a combination of complete k-space sampling and ODR with accelerated read-outs, e.g., EPI or spiral read-out methods is recommended to not exceed a clinically acceptable acquisition time below 10 minutes.

Besides MRSI, DWI can also profit from improved shimming, which was also investigated in Chapter 3. The choice for EPI-based sequences to routinely acquire DWI in the clinic is due to its acquisition efficiency, speed, and robustness to patient motion. This sequence, however, is very sensitive to B_0 field inhomogeneities, visible as geometric distortions in resulting images. While other DWI acquisition approaches exist, each of them comes with different pros and cons for routine clinical use⁶. While DWI is a crucial MRI sequence in disease detection and characterization, there are no universally accepted quality criteria⁷. Image quality in DWI is impacted by susceptibility differences between air and tissue, attributed to bowel gas and amplified by motion, that impose a longstanding issue of complex B_0 field distortions. The additional hardware in Chapter 3 is aimed to ensure a robust quality of DWI by minimizing the resulting artifacts, visible as geometric

distortions, from B0 field distortions. The proposed shimming method and regular shimming on the scanner were compared by analyzing the shape of the prostate on DWI image sets resulting from both shim methods and assessing the match with the T2w image series as the anatomical reference. With the add-on shim coil and shim method, an overall significant improvement in geometric resemblance to the reference T2w image, expressed as the Dice similarity coefficient, was observed. Improved shimming and resulting B0 field homogeneity were also reflected in B0-maps of the volume of interest, which was closely fit around the prostate, by a reduction in off-resonance frequencies. In future studies, the interaction of the shim coils with the scanner's receive coil arrays needs to be minimized, as the presence of the shim coil array now imposed a decrease in SNR of 20%. Our volunteers did not take any antispasmodic agents to reduce bowel motion, as patients in the clinic would do to prepare for an MRI. The effects of these agents on bowel motion last up to 15-20 minutes⁸, which can significantly improve T2w images. However, they are not translated into improvements in DWI quality^{9,10}. The effect of the add-on shim coil array on dynamic changes in B0 field homogeneity from bowel or patient motion, despite the use of antispasmodic agents, should therefore be studied next in patients. Ideally for this subsequent testing, the shim method should be improved by a feedback system to monitor the shim quality for each acquisition and immediately start re-shimming in case motion deteriorates the shim quality. Another application of the proposed shimming method would be in patients with metallic hip implants, as these implants can create pronounced distortions and regions of signal dropout on DWI, preventing adequate visualization of the prostate and potentially rendering the images non-diagnostic¹¹. Enhanced shimming flexibility could offer substantial benefits to this group, leading to increased precision in DWI and, as described earlier, enabling MRSI as part of the multi-parametric MRI.

Ultra-high magnetic field strength for lymph node assessment

In the second part of this thesis, we move away from clinical 3 T MRI scanners and focus on the application of ultra-high magnetic field strength for MR imaging of prostate cancer. With increased sensitivity and spectral resolution, ultra-high-field MRI (≥ 7 Tesla) holds the promise of MR imaging and spectroscopy of the prostate with exceptional detail. However, exploiting the advantages of the ultra-high magnetic field is challenging due to the inhomogeneity of the radiofrequency field and high local specific absorption rates, with local heating in the body as a safety

concern. Various coil designs and acquisition strategies have been studied over the past years to overcome these challenges and demonstrate the potential of UHF MRI in anatomical, functional, and metabolic imaging of the prostate and pelvic lymph nodes.

Anatomical T2w imaging of the prostate is feasible and with various coil designs a significant increase in SNR from 3 T can be reached at 7 T^{12,13}, albeit often not robustly over the entire prostate^{14,15}. The advantage of higher SNR at 7 T is counteracted by SAR limitations and available transmit power, resulting in limitations for in-plane resolution, total number of slices, or repetition times. Further studies should continue the development of optimal receiver arrays, RF management strategies, and acquisition techniques, with a specific focus on the strength of MRI at ultra-high field: large field-of-view and low-flip-angle anatomical 3D imaging at high isotropic resolution. New acquisition strategies consisting of low-flip-angle excitations with gradient echo readouts prepared with T2w modules could, for example, provide 3D high isotropic resolution with low SAR demands. Similar to T2w preparation modules, diffusion-preparation modules could be combined with low-flip-angle excitations and gradient echo readouts for DWI of the prostate at 7 T. This remains challenging as increasing the magnetic field strength from clinical 3 T to experimental 7 T comes with an increase in magnetic susceptibility differences within tissue or at tissue-air interfaces.

For ¹H-MRSI, high sensitivity at 7 T can be used to improve spatial resolution, which would reduce partial volume effects, causing voxels to better represent the imaged tissue. Dedicated coil designs for ¹H-MRSI at 7 T, combining a transmit surface array coil and receive endorectal coil, have been able to obtain high SNR with a voxel size of 0.6 cm³, though with a distinct signal level decrease in spectra more distant from the endorectal coil¹⁵. Thereby, acquisition with dedicated spectral-spatial refocusing pulses for both spectral and volume selection at 7 T have been able to provide a more homogeneous B₁⁺ field in the prostate with detection at adequate SNR, in ¹H-MRSI voxels of 1.4 cm³¹⁶. As lipid contamination influenced the spectral quality, hindering the detection of citrate and indicating remaining inhomogeneities in the B₁⁺ field, effort has also been put into the development of parallel transmit-designed adiabatic spectral-spatial refocusing pulses¹⁷. These pulses could simultaneously provide both spatial localization and signal suppression insensitive to B₀ variations. Further reductions in voxel size will improve the intravoxel B₀ homogeneity, leading to narrow metabolite linewidths and thereby improved separate detection of total choline and spermine. Ratios including the total choline and spermine signals could then be used to characterize

prostate cancer. While the feasibility of ^1H -MRSI in prostate cancer at 7 T has been shown, the potential benefit of spectral-spatial pulses and choline/spermine ratios for assessing prostate cancer must be investigated in a larger patient cohort with tumors varying in Gleason scores.

The higher SNR at 7T allows us to also assess metabolites containing phosphorus atoms (^{31}P), with ^{31}P spectroscopic imaging of the prostate. The first studies showed that acquiring signals was possible, though differences in metabolite ratios between prostate cancer and normal-appearing tissue were not observed, possibly because of partial volume effects of small tumor foci in large MRSI voxels¹⁸. Subsequent studies did show further improvements and the feasibility of this technique to measure phospholipid metabolites in prostate cancer lesions. However, results for one metabolite, namely phosphoethanolamine, were contradicting as both lower and higher levels were seen in comparison to healthy prostate tissue^{16,19}. It is therefore clear that *In vivo* ^{31}P -MRSI of the prostate should be studied more extensively to establish ^{31}P profiles of low and high-grade cancer and to live up to the expectation to improve the assessment of prostate cancer aggressiveness²⁰, with localized 3D ^{31}P -MRSI at 7 T performed at a relevant spatial resolution in a clinically acceptable measurement time. As for the pulse sequence, with a strongly reduced ^{31}P flip angle ($\leq 45^\circ$), a high-quality ^{31}P MRSI dataset with optimal SNR per unit time can be obtained within 15 min²¹. The most optimal coil configuration, regarding B_1^+ homogeneity and highest SNR for signal reception, would be to separate transmit and receive for both nuclei with a body array capable of transmitting on both the ^1H and ^{31}P frequencies and an endorectal coil to receive the signals from both nuclei. In a large patient population, this combined setup could provide insight into the changes in total choline metabolism in prostate cancer.

Next to imaging and characterization of the primary prostate cancer lesion, there is a clinical need for precise, reliable, and noninvasive N-staging, a potential application of 7 T MRI. USPIO-enhanced MRI at 7 T could allow improved identification of lymph node metastases, exploiting its higher sensitivity by acquiring an even higher spatial resolution than reachable at 3 T. The large chemical shift dispersion between water and lipids at 7 T enables selective excitation of either of the two with short simple rectangular pulses, allowing very efficient imaging by short excitations in the order of 1 ms and receiving multiple gradient echoes in approximately 60% of the repetition time. Separate scans with either water or lipid excitation then provide an anatomical overview while the iron-sensitive signal intensity from the USPIO-contrast discriminates between nodes with and without USPIO accumulation. The initial technical challenges of previously seen RF transmit inhomogeneities with

large field of views in the pelvis at 7 T have been overcome²², and the feasibility of detecting (suspicious) lymph nodes on 7 T was demonstrated earlier^{23,24}. Based on this experience, in Chapter 6 of this thesis, we have acquired USPIO-enhanced MRI of 20 patients with prostate cancer at 7 T, and compared the detection of suspicious LNs with USPIO-enhanced MRI at 7 T and 3 T in this cohort.

Our study, as the first study in which 7 T and 3 T USPIO-enhanced MRI are compared in the same patients with prostate cancer, showed that more highly suspicious lymph nodes were found per patient on 7 T compared to 3 T. At 7 T, high-quality images allow the detection of more and especially more small (<2.5 mm) suspicious lymph nodes. An important limitation of our study is that there is no histopathological reference standard for the suspicious lymph nodes. The sensitivity and specificity of 7 T USPIO-enhanced MRI to detect especially small lymph node metastases in prostate cancer remains to be investigated, while a node-to-node match with pelvic lymph node dissection specimens is very difficult to achieve. Without available pathological assessment, we chose to deem lymph nodes suspicious if both readers scored them with a Level of Suspicion ≥ 3 . There was a lot of variance in the scores from both readers. These inter-reader differences are probably caused by differences in the experience for reading USPIO-enhanced images, regarding the number of scans reported in a clinical or a research setting, and come as a consequence of using a qualitative grey-scale instead of quantitative parameters. Previous research of USPIO-enhanced MRI, though from other lymph node regions allowing pathological matching, has shown that experience in interpretation could translate into a higher sensitivity in finding lymph node metastases^{25,26}. Our study contributes to the scientific field with another interesting finding; the experienced reader scored with more confidence on the 7 T images. This result indicates that imaging at 7 T, with its higher resolution, improves the detection of suspicious lymph nodes.

As we showed that suspicious nodes in prostate cancer are generally very small, the idea that large lymph nodes are suspicious and small lymph nodes are not might no longer be valid. The ability to identify very small suspicious lymph nodes in prostate cancer could have important clinical implications. Currently, PSMA-PET/CT is used in clinical practice for detecting metastases in the lymph nodes and subsequent treatment planning. While PSMA-PET/CT shows good specificity (0.67–1.0, pooled 0.95) for detecting lymph node metastases, the sensitivity is hindered by the spatial resolution of PET/CT of 4–5 mm²⁷, which makes it difficult to detect small lymph nodes. Although PSMA-PET/CT is of increasing clinical benefit for image-guided therapy and has the advantage of simultaneous assessment of distant (bone)

metastases, its spatial resolution for lymph node detection is limited compared with the spatial resolution of 7 T USPIO-enhanced MRI. While we did not directly compare USPIO-enhanced MRI to PSMA-PET/CT in our work, this comparison was made by Schilham et al. in a retrospective study²⁸. In 45 patients, USPIO-enhanced MRI at 3 T identified a significantly greater number of suspicious lymph nodes per patient (mean: 3.6) than ⁶⁸Ga-PSMA PET/CT (mean: 1.6), with a significantly smaller mean size of lymph nodes detected by nano-MRI compared to ⁶⁸Ga-PSMA PET/CT (mean: 5.3 mm vs 6.0 mm, respectively). As the two modalities have a different pathophysiologic target (lymphatic invasion of tumor tissue vs. PSMA expression), this could explain that different lymph nodes were found by both modalities, as tumor lesions without PSMA expression will be missed on PSMA-PET/CT and USPIO-enhanced MRI is not able to discriminate metastatic lymph nodes from lymph nodes with fibrosis disturbing the USPIO-accumulation. An important limitation of both the aforementioned and our work is that there is no histopathological reference standard for the suspicious lymph nodes. Accuracy of either PSMA-PET/CT or USPIO-enhanced MRI for prostate cancer nodal metastases should ideally be assessed by an extensive node-to-node matching of in vivo detected LNs with histopathology of resected nodes²⁹, validating the suspiciousness of lymph nodes and clarifying false positive lymph nodes without USPIO-accumulation. In practice, matching nodes as small as 2 to 5 mm from in vivo imaging to the histopathological slide is sheer impossible, so alternative validation methods are needed. One could consider initially following up on the size of small suspicious lymph nodes in patients with unexpected rising PSA after prostatectomy or local prostate lesion treatment, with increasing lymph node size as a sign of metastatic growth. After stereotactic radiotherapy treatment of suspicious lymph nodes in these patients, a decrease in PSA level could validate the reduction of prostate cancer disease burden as a result of targeting these lymph nodes.

Future perspectives

High-quality ¹H-MRSI spectra could be of additional value in the clinical management of prostate cancer. Although accelerated acquisition and an automated post-processing workflow might still be prerequisites for clinical implementation, MRSI can provide complementary quantitative parameters of prostate cancer lesions. Adding this sequence to the mpMRI exam has the potential to decrease inter-reader variability. Especially in repeated examinations per patient, as in active surveillance, we believe acquiring quantitative MRSI data can provide a reliable follow-up measure and maximize the non-invasively acquired information on the prostate.

MRSI enables direct comparison between scans and could therefore pick up on progression more accurately than a PSA value and possibly at an earlier time point than when any changes are distinguishable on T2w MRI or DWI.

Robust quality of acquisition is another prerequisite for clinical application of MRSI. With an aging population, we have to secure the robustness and short acquisition time of mpMRI examinations to keep up with a possible growing demand for these exams. In prostate MRI, improving image quality is still a focus with PI-RADS that set out minimum technical requirements to acquire a good quality scan¹, followed by the PI-QUAL dedicated standardized scoring system³⁰, to evaluate the diagnostic quality of prostate mpMRI by assessing the ability to clearly visualize anatomic landmarks and the presence of artifacts. Our work could contribute to robust quality of DWI and MRSI of prostate exams by applying the advanced shim method in certain cases. After a short initial B0map 'localizer' acquisition that would indicate if there are challenges for shimming to be expected, we would ideally apply a further improved version of the add-on shim coil and shimming method to ensure robust DWI and MRSI acquisitions. Applying this advanced shimming as default in patients with hip implants could increase the quality and value of the mpMRI exam in these patients.

A different development in the acquisition of prostate mpMRI is the recent testing of a bi-parametric MRI exam (bpMRI), consisting of T2w and DWI and discarding the dynamic contrast-enhanced sequence^{1,4}. The aim of such a scan protocol is to keep up with the increasing number of prostate scans by optimization of scan time without sacrificing on diagnostic quality. While the DCE sequence can be especially useful in cases where DWI is hampered by artifacts, and is referred to as a 'safety-net' sequence, studies have assessed the value of bi-parametric MRI for detection of clinically significant prostate cancer⁴ and conclusive results of prospective multi-center trials are awaited to support this scan strategy³¹. For an efficient bi-parametric protocol, a quick and robust DWI, with advanced shimming to prevent low-quality or repeated acquisition, is essential. If a bpMRI protocol becomes the standard protocol for initial diagnosis of prostate cancer, there is still a possible role for MRSI within this diagnostic setting. If an AI-assisted real-time assessment of the acquired bi-parametric MRI images is able to indicate a possible prostate cancer lesion, automated MRSI acquisition could be performed subsequently within the same exam. This would imply acquiring a quick bi-parametric scan routinely and only an additional MRSI when needed, thereby optimizing acquired (quantitative) information and scan time without administration of a contrast agent. Choices in this diagnostic setting would be driven by acquisition time and sensitivity for

prostate cancer detection, whereas in an active surveillance setting, with several MRI scans over time, MRSI could become a default sequence. Since MRSI enables a reproducible quantitative assessment, repeated results could easily be compared without reader-effects, thereby preventing unnecessary invasive biopsies to be taken in cases where readers would doubt.

This quantitative information from MRSI, as we match it with underlying anatomical structures as found on clinical prostate MR imaging, may improve the metabolic characterization of small prostate cancer lesions. With precise localization of the signals, MRSI could indicate the most aggressive part of a prostate cancer lesion as a biopsy target. If future work can further establish the link between the metabolic characterization with MRSI and the metastatic potential of a prostate cancer lesion, the invasive biopsy might lose its importance in tumor staging and assessment of the lymph nodes might be the direct subsequent focus after initial mpMRI. Besides MRSI, the increased role of mpMRI in the diagnosis of prostate cancer over the last years might advocate a revision of the EAU risk groups from 2020. Practical suggestions have been made for changing this classification with information acquired with mpMRI, either based on MRI-targeted biopsies³² or characteristics of the prostate cancer lesion MR images^{33,34}.

To further characterize different tumor stages and help explain the onset and spatial distribution of metastatic spread, MRI of the prostate at a field strength of 7 T can be used in its full strength, together with large field-of-view and low-flip-angle anatomical 3D imaging. While 7 T MRI of the prostate will not be a routine clinical exam within the near future, characterization of different tumor stages and recurrent disease can be performed already when difficulties with power deposition of many refocusing pulses are overcome and the full potential of metabolic spectroscopic imaging is used. With detailed visualization of prostate cancer lesions, increased imaging quality could be reached with an increased accuracy in the detection of extra-prostatic extension. This improvement in staging could lead to accurate and personalized treatment for each patient at an early time point of the disease.

As we have seen in this work, imaging at 7 T is beneficial for the visualization of lymph nodes that might harbor metastases. Future research is needed to validate that the lymph nodes now stated as suspicious on USPIO-enhanced MRI indeed show metastatic cells on pathological assessment, and USPIO-enhanced MRI can be used to guide metastasis-directed therapy. As we will be able to detect more and smaller lymph node metastases with 7 T, the definition of oligometastatic

disease might change toward a larger number of small lymph nodes for which metastases-directed therapies might even be given with curative intent. In the short term, as USPIO-enhanced MRI has the potential to pick up on smaller lymph node metastases than PSMA-PET/CT can, an USPIO-enhanced MRI might already be indicated as follow-up scan in the case of rising PSA and negative PSMA-PET/CT scan. Whereas PSMA-PET/CT has a higher sensitivity with higher PSA, a patient would not have to wait for the next PSMA-PET/CT scan as an USPIO-enhanced MRI can detect the metastatic spread of the disease earlier on, with the corresponding possible benefits for treatment to be established. The benefit of undergoing USPIO-enhanced MRI for the patient will most probably not be found in extending pelvic lymph node dissections, as removal of all small suspicious nodes will be very challenging and its current impact on overall survival is already under debate. The combination of high-resolution MRI and functional USPIO contrast could introduce a new approach to personalized image-guided targeted therapy by enabling primary radiotherapy of these small lymph node metastases. Future research should provide an indication of what size of lymph nodes can be accurately treated with radiotherapy and what this form of therapy entails for patient prognosis.

References

- 1 Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *European Urology* 2019;Sep(76):340-51.
- 2 Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2021;79(2):243-62.
- 3 Maas MC, Litjens GJS, Wright AJ, Attenberger UI, Haider MA, Helbich TH, et al. A Single-Arm, Multicenter Validation Study of Prostate Cancer Localization and Aggressiveness With a Quantitative Multiparametric Magnetic Resonance Imaging Approach. *Invest Radiol* 2019;54(7):437-47.
- 4 Belue MJ, Yilmaz EC, Daryanani A, Turkbey B. Current Status of Biparametric MRI in Prostate Cancer Diagnosis: Literature Analysis. *Life (Basel)* 2022;12(6).
- 5 Mir N, Fransen SJ, Wolterink JM, Fütterer JJ, Simonis FFJ. Recent Developments in Speeding up Prostate MRI. *J Magn Reson Imaging* 2023.
- 6 Tamada T, Ueda Y, Ueno Y, Kojima Y, Kido A, Yamamoto A. Diffusion-weighted imaging in prostate cancer. *Magnetic Resonance Materials in Physics, Biology and Medicine* 2022;35(4):533-47.
- 7 Padhani AR, Barentsz J, Villeirs G, Rosenkrantz AB, Margolis DJ, Turkbey B, et al. PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway. *Radiology* 2019;292(2):464-74.
- 8 Engels RRM, Israel B, Padhani AR, Barentsz JO. Multiparametric Magnetic Resonance Imaging for the Detection of Clinically Significant Prostate Cancer: What Urologists Need to Know. Part 1: Acquisition. *Eur Urol* 2020;77(4):457-68.
- 9 Roethke MC, Kuru TH, Radbruch A, Hadaschik B, Schlemmer HP. Prostate magnetic resonance imaging at 3 Tesla: Is administration of hyoscine-N-butyl-bromide mandatory? *World J Radiol* 2013;5(7):259-63.
- 10 Slough RA, Caglic I, Hansen NL, Patterson AJ, Barrett T. Effect of hyoscine butylbromide on prostate multiparametric MRI anatomical and functional image quality. *Clin Radiol* 2018;73(2):216.e9-e14.
- 11 Nakai H, Takahashi H, Adamo DA, LeGout JD, Kawashima A, Thomas JV, et al. Decreased prostate MRI cancer detection rate due to moderate to severe susceptibility artifacts from hip prosthesis. *European radiology* 2024;34(5):3387-99.
- 12 Steensma BR, Luttje M, Voogt IJ, Klomp DWJ, Luijten PR, van den Berg CAT, et al. Comparing signal-to-noise ratio for prostate imaging at 7T and 3T. *Journal of magnetic resonance imaging: JMIR* 2019;49(5):1446-55.
- 13 Steensma BR, Voogt I, van der Werf AJ, van den Berg CAT, Luijten PR, Klomp DWJ, et al. Design of a forward view antenna for prostate imaging at 7 T. *NMR in biomedicine* 2018;31(9):e3993.
- 14 Rosenkrantz AB, Zhang B, Ben-Eliezer N, Le Nobin J, Melamed J, Deng FM, et al. T2-weighted prostate MRI at 7 Tesla using a simplified external transmit-receive coil array: correlation with radical prostatectomy findings in two prostate cancer patients. *Journal of magnetic resonance imaging: JMIR* 2015;41(1):226-32.
- 15 Lagemaat MW, Philips BW, Vos EK, van Uden MJ, Fütterer JJ, Jenniskens SF, et al. Feasibility of Multiparametric Magnetic Resonance Imaging of the Prostate at 7 T. *Invest Radiol* 2017;52(5):295-301.

- 16 Philips BWJ, van Uden MJ, Rietsch SHG, Orzada S, Scheenen TWJ. A multitransmit external body array combined with a (1) H and (31) P endorectal coil to enable a multiparametric and multimetabolic MRI examination of the prostate at 7T. *Medical physics* 2019;46(9):3893-905.
- 17 He X, Auerbach EJ, Garwood M, Kobayashi N, Wu X, Metzger GJ. Parallel transmit optimized 3D composite adiabatic spectral-spatial pulse for spectroscopy. *Magnetic resonance in medicine* 2021;86(1):17-32.
- 18 Lagemaat MW, Vos EK, Maas MC, Bitz AK, Orzada S, Uden MJv, et al. Phosphorus Magnetic Resonance Spectroscopic Imaging at 7 T in Patients With Prostate Cancer. *Investigative Radiology* 2014;49(Number 5).
- 19 Luttje MP, Italiaander MG, Arteaga de Castro CS, van der Kemp WJ, Luijten PR, van Vulpen M, et al. (31) P MR spectroscopic imaging combined with (1) H MR spectroscopic imaging in the human prostate using a double tuned endorectal coil at 7T. *Magnetic resonance in medicine* 2014;72(6):1516-21.
- 20 Kobus T, Bitz AK, van Uden MJ, Lagemaat MW, Rothgang E, Orzada S, et al. In vivo 31P MR spectroscopic imaging of the human prostate at 7 T: safety and feasibility. *Magnetic resonance in medicine* 2012;68(6):1683-95.
- 21 Lagemaat MW, Maas MC, Vos EK, Bitz AK, Orzada S, Weiland E, et al. (31) P MR spectroscopic imaging of the human prostate at 7 T: T1 relaxation times, Nuclear Overhauser Effect, and spectral characterization. *Magnetic resonance in medicine* 2015;73(3):909-20.
- 22 Orzada S, Maderwald S, Poser BA, Johst S, Kannengiesser S, Ladd ME, et al. Time-interleaved acquisition of modes: an analysis of SAR and image contrast implications. *Magnetic resonance in medicine* 2012;67(4):1033-41.
- 23 Fortuin AS, Philips BWJ, Leest MMGvd, Ladd ME, Orzada S, Maas MC, et al. Magnetic resonance imaging at ultra-high magnetic field strength: An in vivo assessment of number, size and distribution of pelvic lymph nodes. *PloS one* 2020;15(7).
- 24 Philips BWJ, Stijns RCH, Rietsch SHG, Brunheim S, Barentsz JO, Fortuin AS, et al. USPIO-enhanced MRI of pelvic lymph nodes at 7-T: preliminary experience. *European radiology* 2019;29(12):6529-38.
- 25 Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tabatabaei S, van de Kaa CH, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med* 2003;348(25):2491-9.
- 26 Heesakkers RA, Hövels AM, Jager GJ, van den Bosch HC, Witjes JA, Raat HP, et al. MRI with a lymph-node-specific contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study. *Lancet Oncol* 2008;9(9):850-6.
- 27 Wang K. Feasibility of High Spatial Resolution Working Modes for Clinical PET Scanner. *International Journal of Medical Physics, Clinical Engineering and Radiation Oncology* 2018;7:539-52.
- 28 Schilham MGM, Zamecnik P, Privé BM, Israël B, Rijpkema M, Scheenen T, et al. Head-to-Head Comparison of (68)Ga-Prostate-Specific Membrane Antigen PET/CT and Ferumoxtran-10-Enhanced MRI for the Diagnosis of Lymph Node Metastases in Prostate Cancer Patients. *Journal of nuclear medicine: official publication, Society of Nuclear Medicine* 2021;62(9):1258-63.
- 29 Driessen DAJJ, de Gouw DJJM, Stijns RCH, Litjens G, Israël B, Philips BWJ, et al. Validation of In Vivo Nodal Assessment of Solid Malignancies with USPIO-Enhanced MRI: A Workflow Protocol. *Methods and Protocols* 2022;5(2):24.
- 30 Giganti F, Allen C, Emberton M, Moore CM, Kasivisvanathan V. Prostate Imaging Quality (PI-QUAL): A New Quality Control Scoring System for Multiparametric Magnetic Resonance Imaging of the Prostate from the PRECISION trial. *Eur Urol Oncol* 2020;3(5):615-9.

- 31 Asif A, Nathan A, Ng A, Khetrpal P, Chan VW, Giganti F, et al. Comparing biparametric to multiparametric MRI in the diagnosis of clinically significant prostate cancer in biopsy-naïve men (PRIME): a prospective, international, multicentre, non-inferiority within-patient, diagnostic yield trial protocol. *BMJ Open* 2023;13(4):e070280.
- 32 Ploussard G, Manceau C, Beauval JB, Lesourd M, Almeras C, Gautier JR, et al. Decreased accuracy of the prostate cancer EAU risk group classification in the era of imaging-guided diagnostic pathway: proposal for a new classification based on MRI-targeted biopsies and early oncologic outcomes after surgery. *World J Urol.* 2020 Oct;38(10):2493-2500.
- 33 Roumiguie M, Lesourd M, Zgheib J, Tollon C, Salin A, Alméras C, et al. Improvement of the intermediate risk prostate cancer sub-classification by integrating MRI and fusion biopsy features. *Urologic Oncology: Seminars and Original Investigations*, 2020;38(5):386-392,
- 34 Boschheidgen M, Schimmöller L, Radtke JP, Kastl R, Jannusch K, Lakes J, et al. MRI characteristics predict risk of pathological upgrade in patients with ISUP grade group 1 prostate cancer. *Eur Radiol.* 2024 Sep 13.

Chapter 8

Summary



Multi-parametric magnetic resonance imaging (mpMRI) of the prostate has become an essential tool in diagnosing prostate cancer. Research over the past decade has stimulated and supported the routine use of mpMRI as a reliable and sensitive noninvasive imaging modality for detecting and characterizing focal regions within the prostate. Clinical guidelines have incorporated the mpMRI pathway as part of the diagnostic process, using the standardized interpretation system called PI-RADS. The mpMRI exam is currently used in men who are suspected of having clinically significant disease and is performed before and to direct biopsy. The MRI-pathway can reduce the number of men who need a prostate biopsy, reduce the number of diagnoses of clinically insignificant cancers, and improve the detection and localization of significant cancer. However, there can be variations in interpretation due to the expertise of the radiologist. An efficient MRI-pathway can benefit from further optimized imaging, minimizing variance in MRI data acquisitions, image quality, and interpretations and a decrease in the number of diagnostic steps to identify clinically significant cancer, to match an increasing demand for mpMRI in prostate cancer diagnostics. This thesis has covered several studies to optimize technical aspects of MRI of the prostate, aiming to facilitate the quantitative assessment of the aggressiveness of prostate cancer and the spread of the disease to lymph nodes.

The first section of the thesis mainly focuses on MRSI, a technique that has proven additional value for the assessment of prostate cancer lesions as it can correlate metabolite ratios to tumor grade. This technique is not included in the latest PI-RADS versions though. This decision was made at that time as the technique required rather long examination times while being less robust than the rest of the mpMRI sequences. MRSI was difficult to apply successfully in clinical routine, particularly if no significant in-house expertise was available. As MRSI can provide quantitative parameters of prostate cancer lesions, adding this sequence to the mpMRI exam has the potential to decrease inter-reader variability and provide a reliable follow-up measure in a repeat setting. For MRSI to fulfill this potential, we have to improve this technique on robustness so it can be more easily applied again in the clinic, as in previous PI-RADS.

For a more easy and standardized acquisition of MRSI, in **Chapter 2** we evaluated a scanning workflow from Siemens, in which initial automatic segmentation of the prostate aids in setting up subsequent sequences. This workflow is aimed at enabling easy performing MRSI next to the clinical mpMRI sequences, improving usability as setting up can be done while scanning previous sequences. We provided feedback to Siemens on two versions of their semi-automated acquisition protocol

based on scanning 34 subjects in the Radboudumc and another six that were scanned in the University Hospital in Trondheim. Initial automatic segmentation of the prostate went well in 32 out of the 40 cases, which sets up the rest of the protocol accurately; MRSI settings need only small manual adjustments and result in overall good quality spectra. This workflow enabled easy setup with minimized additional preparation time, only the additional time of acquisition would be added to an mpMRI scan. We provided recommendations for the perfect balance of manual input and automatization.

Next to facilitating MRSI acquisition, robust MRSI is also dependent on the quality of shimming. In **Chapter 3**, we collaborated with the company MRShim to develop and analyze an add-on local shim array to ensure a homogeneous main magnetic field over the prostate. MR modalities require optimal magnetic field homogeneity for high-quality acquisitions. The prostate presents challenges due to susceptibility differences induced by bowel gas and motion, resulting in complex B0 field distortions. This study introduced a customized add-on local external shim array coil to improve B0 field homogeneity in prostate applications. To address B0 field distortions in the prostate, the proposed methodology involved calculating the optimal combination of 1st order shim values of the MR scanner and add-on coil's shimming settings, which were compared with conventional scanner shimming in seven healthy volunteers. In DWI, an overall significant improvement in the Dice similarity coefficient was observed with the add-on shim coil, which was also reflected in the B0 maps by a reduction in off-resonance frequencies. In ¹H-MRSI, citrate linewidth exhibited improvement, significantly decreasing from 8.3 ± 5.7 Hz with conventional shimming to 7.9 ± 3.6 Hz with the add-on shim coil. While effectiveness varied between subjects, the overall results showed that an external add-on shim array coil can improve B0 homogeneity in the prostate. With improved robustness, this method can lead to improved image quality, reduced artifacts, and enhanced precision in DWI and MRSI.

Besides solutions for fast and robust acquisition of MRSI, software improvements can also be applied to the elaborate processing of acquired MRSI data. In **Chapter 4**, we have successfully implemented a post-processing method for MRSI data, aimed at increasing the quality of spectra and the spatial resolution of metabolite maps and hence their match to underlying anatomical structures. In in vivo ¹H-MRSI of the prostate, small matrix sizes can cause voxel bleeding extending to regions far from a voxel, dispersing a signal of interest outside that voxel and mixing extra-prostatic residual lipid signals into the prostate. To resolve this problem, we developed a three-dimensional overdiscretized reconstruction method. Without

increasing the acquisition time from current 3D MRSI acquisition methods, this method is aimed at improving the localization of metabolite signals in the prostate without compromising on SNR. The proposed method consists of a 3D spatial overdiscretization of the MRSI grid, followed by noise decorrelation with small random spectral shifts and weighted spatial averaging to reach a final target spatial resolution. We successfully applied the three-dimensional overdiscretized reconstruction method to 3D prostate ^1H -MRSI data at 3 T. Both in phantom and in vivo, the method proved to be superior to conventional weighted sampling with Hamming filtering of k-space. Compared with the latter, the overdiscretized reconstructed data with a smaller voxel size showed up to 10% less voxel bleed while maintaining higher SNR by a factor of 1.87 and 1.45 in phantom measurements. For in vivo measurements, within the same acquisition time and without loss of SNR compared with weighted k-space sampling and Hamming filtering, we achieved increased spatial resolution and improved localization in metabolite maps.

While all data in the chapters in the first section was acquired with the clinical 3 T MR systems at the Radboudumc, the second section of this thesis covered ultra-high field, 7 T, MRI. At this higher magnetic field strength, research scanners with increased sensitivity and spectral resolution hold the promise of imaging and spectroscopy of the prostate with unprecedented detail, which can be used for assessing the lymph node status. Chapter 5 gives an overview of the challenges that come with this field strength and solutions that were found over the years for body imaging on 7 T. Significant efforts have been invested in addressing the technical challenges of UHF imaging of the lower abdomen, specifically for the prostate and its surrounding tissue. The culmination of this work demonstrates that multinuclear multiparametric MR(S)I of the prostate at UHF is feasible. With the exploitation of higher spatial resolutions in imaging and spectroscopy, mpMRI at UHF can yield improved delineation of prostate anatomy and metabolic imaging within the tumor as a biomarker for an assessment of prostate cancer aggressiveness. For clinical detection of primary prostate cancer, a fast, readily available, and robust MRI acquisition is needed; current 3 T protocols fulfill these demands. The potential role of prostate imaging at 7 T could be in achieving a better understanding of the development and progression of local prostate cancer, the onset and spatial distribution of metastatic spread, and in characterization of different tumor stages and recurrent disease.

One application in this ultra-high field, the detection of lymph nodes suspicious for metastases, is described in **Chapter 6**. Accurate detection of lymph node metastases in prostate cancer is a challenging but crucial step for disease staging.

Ultrasmall super-paramagnetic iron oxide nanoparticles (USPIO)-enhanced MRI enables distinction between healthy lymph nodes and nodes suspicious for harboring metastases. When combined with MRI at an ultra-high magnetic field of 7 T, an unprecedented spatial resolution can be exploited to visualize these lymph nodes. To explore USPIO-enhanced MRI at 7 T in comparison to 3 T for the detection of small suspicious LNs, the same cohort of patients with PCa was scanned on both field strengths. Results show that in the same cohort of patients with prostate cancer, more and more small LNs were detected on 7 T USPIO-enhanced MRI compared with 3 T MRI. Suspicious LNs are generally very small and increased nodal size was not a good indication of suspicion for the presence of metastases. The high spatial resolution of USPIO-enhanced MRI at 7 T improved structure delineation and the visibility of very small suspicious LNs, potentially expanding the in vivo detection limits of pelvic LN metastases in PCa patients.

In **Chapter 7** an overall discussion and outlook towards the future is presented. With robust acquisition, high-quality ^1H -MRSI spectra could be of additional value in the clinical management of prostate cancer. Since MRSI enables a reproducible quantitative assessment, in an active surveillance setting, repeated results could easily be compared without reader-effects. A robust and high quality MRSI sequence can thereby prevent unnecessary invasive biopsies to be taken in cases where readers would doubt. By acquiring mpMRI at an ultra-high field strength with detailed visualization of prostate cancer lesions, increased imaging quality could be reached with an increased accuracy in the detection of extra-prostatic extension. This improvement in staging could lead to accurate and personalized treatment for each patient at an early time point of the disease. The combination of 7 T high-resolution MRI and functional USPIO contrast could enable primary radiotherapy of small lymph node metastases and thereby introduce a new approach to personalized image-guided targeted therapy of prostate cancer.

Chapter 9

Nederlandse samenvatting

Nederlandse samenvatting

Het multi-parametisch MRI onderzoek (mpMRI) is een belangrijk onderdeel geworden van het diagnosticeren van prostaatkanker. Wetenschappelijk onderzoek in de afgelopen tien jaar heeft ervoor gezorgd dat routinematig klinisch gebruik van mpMRI mogelijk is; studies hebben aangetoond dat mpMRI een betrouwbare en gevoelige niet-invasieve beeldvormingsmodaliteit is voor het detecteren en karakteriseren van focale gebieden verdacht voor kanker in de prostaat. Het mpMRI onderzoek van de prostaat is daarom opgenomen in klinische richtlijnen, met een gestandaardiseerde methode van interpretatie van de verkregen beelden (genaamd PI-RAD'S). Het mpMRI-onderzoek wordt momenteel standaard gebruikt bij mannen bij wie wordt vermoed dat ze een klinisch significante prostaatkanker hebben en wordt uitgevoerd vóór en ter voorbereiding van een biopsie. Deze zogenoemde mpMRI-route kan zorgen voor het verminderen van het aantal mannen dat een prostaatbiopsie moet ondergaan, het verminderen van het aantal diagnoses van klinisch onbeduidende kankers en het verbeteren van de detectie en lokalisatie van significante kankers. Het expertiseniveau van de radioloog veroorzaakt verschillen in de interpretatie van het mpMRI-onderzoek, wat resulteert in een hoge variatie tussen radiologen. Om tegemoet te komen aan de toenemende vraag naar mpMRI bij de diagnostiek van prostaatkanker is een efficiënte mpMRI-route nodig. Met een verder geoptimaliseerde beeldvorming wordt de variantie in MRI-gegevensverzamelingen, beeldkwaliteit en interpretaties geminimaliseerd en kan het aantal diagnostische stappen om klinisch significante kanker te identificeren worden verminderd. In dit proefschrift zijn verschillende studies beschreven om de technische aspecten van MRI van de prostaat te optimaliseren, met als doel de kwantitatieve beoordeling van de agressiviteit van prostaatkanker en de verspreiding van de ziekte naar de lymfeklieren te vergemakkelijken.

Het eerste deel van het proefschrift richt zich voornamelijk op MR spectroscopic imaging (MRSI), een techniek met bewezen toegevoegde waarde voor de beoordeling van prostaatkankerlaesies, door het correleren van de gemeten metabolietenverhoudingen met de tumorgraad. Deze techniek is echter niet opgenomen in de meest recente PI-RADS-versies. Deze beslissing werd destijds genomen omdat de techniek tamelijk lange onderzoekstijden vereiste, terwijl deze minder robuust was dan de rest van de mpMRI-sequenties. MRSI was daarom moeilijk succesvol toe te passen in de klinische routine, vooral als er geen expertise ter plekke beschikbaar was. Omdat MRSI als resultaat kwantitatieve parameters van prostaatkankerlaesies verschaft, kan het toevoegen van deze sequentie aan het mpMRI-onderzoek de variabiliteit tussen lezers verminderen en een betrouwbare

maat bieden, die te volgen is over meerdere opvolgende controles. Om MRSI gemakkelijker opnieuw in de kliniek toe te passen, zoals in eerdere versies van PI-RADS, moeten we deze techniek verbeteren wat betreft de robuustheid.

Voor een eenvoudigere en gestandaardiseerde acquisitie van MRSI hebben we in **hoofdstuk 2** een scan workflow van Siemens geëvalueerd, waarbij een automatische segmentatie van de prostaat op de eerste beelden helpt bij het instellen van daaropvolgende sequenties. Deze workflow heeft als doel om MRSI eenvoudig in te stellen en uit te voeren naast de klinische mpMRI-sequenties, waardoor de bruikbaarheid in de kliniek wordt vergroot. We hebben Siemens feedback gegeven op twee versies van hun werkpakket, gebaseerd op onze ervaring met het scannen van 34 proefpersonen in het Radboudumc en nog eens zes die waren gescand in het Universitair Ziekenhuis in Trondheim. De initiële automatische segmentatie van de prostaat verliep goed in 32 van de 40 gevallen, waardoor de rest van het protocol nauwkeurig werd opgezet; MRSI-instellingen vereisen slechts kleine handmatige aanpassingen en resulteren in spectra van goede kwaliteit. Deze workflow maakt daarmee de MRSI puls-sequentie eenvoudig in te stellen, waardoor de benodigde installatietijd tot een minimum wordt beperkt en het instellen van de MRSI opname kan worden gedaan terwijl eerdere sequenties worden gescand. Daarom is er geen extra insteltijd vereist en wordt alleen de extra acquisitietijd aan een mpMRI-scan toegevoegd. We hebben aanbevelingen gedaan voor het perfect evenwicht tussen handmatige invoer en automatisering, waardoor de acquisitie is geoptimaliseerd voor elke patiënt.

Naast het faciliteren van MRSI-acquisitie, is robuuste MRSI ook afhankelijk van de kwaliteit van de shimming, het homogeniseren van het magneetveld (B0-veld) van de scanner. In **hoofdstuk 3** hebben we samengewerkt met het bedrijf MRShim om een lokale shim-spoel te ontwikkelen en analyseren om een homogeen magnetisch hoofdveld over de prostaat te garanderen. Deze shim-spoel kan worden toegevoegd en bevestigd aan de conventionele shim-opstelling van de scanner. MR-sequenties vereisen optimale homogeniteit van het magnetische veld voor acquisities met hoge kwaliteit. Het scannen van de prostaatregio biedt uitdagingen. Dit wordt veroorzaakt door de aanwezigheid van gas in de darmen en de beweging daarvan, wat resulteert in complexe vervormingen van het B0-veld. Deze studie introduceerde een op maat gemaakte, lokale externe shim-array-spoel om de homogeniteit van het B0-veld bij prostaattoepassingen te verbeteren. De voorgestelde methode omvatte het berekenen van de optimale combinatie van eerste orde shim-waarden van de MR-scanner en de shim-instellingen van de add-on-spoel, en het vergelijken met conventionele scanner-

shims bij zeven gezonde vrijwilligers. In DWI acquisities werd een algehele significante verbetering in de Dice-gelijkeniscoëfficiënt waargenomen met de add-on shim-spoel, wat ook tot uiting kwam in de B0-mappen als een vermindering van de afwijkingen in resonantiefrequenties. In ^1H -MRSI vertoonde de lijnbreedte van citraat een verbetering, die aanzienlijk afnam van $8,3 \pm 5,7$ Hz met conventionele scanner-shims tot $7,9 \pm 3,6$ Hz met de add-on shim-spoel. Hoewel de effectiviteit per proefpersoon varieerde, toonde het algehele resultaat aan dat een externe add-on shim-spoel de B0-homogeniteit in de prostaat kan verbeteren. Met verder verbeterde robuustheid kan deze methode leiden tot verbeterde beeldkwaliteit, minder artefacten en verbeterde precisie bij DWI en MRSI.

Naast oplossingen voor het snel en robuust verkrijgen van MRSI opnames kunnen softwareverbeteringen ook worden toegepast op de verwerking van verkregen MRSI-gegevens. In **hoofdstuk 4** hebben we met succes een nabewerkingsmethode voor MRSI-gegevens geïmplementeerd, gericht op het verhogen van de kwaliteit van de spectra en de ruimtelijke resolutie van metabolietenmappen en daarmee de overeenkomst met onderliggende anatomische structuren vergroten. Bij in vivo ^1H -MRSI van de prostaat kunnen de relatief kleine matrixafmetingen ervoor zorgen dat signaal afkomstig van één voxel zich uitstrekt naar omliggende voxels, waardoor een signaal van interesse buiten die voxel wordt verspreid en lipidensignalen van buiten de prostaat zich mengen in het gebied van interesse. Om dit probleem op te lossen, hebben we een drie-dimensionale, overgediscretiseerde reconstructiemethode ontwikkeld. Zonder daarbij de acquisitietijd van de huidige 3D-MRSI-acquisitiemethoden te verlengen, richt deze methode zich op het verbeteren van de lokalisatie van metabolietensignalen in de prostaat zonder concessies te doen aan de SNR. De voorgestelde methode bestaat uit een 3D ruimtelijke overdiscretisatie van het MRSI-raster, gevolgd door ruisdecorrelatie met kleine willekeurige spectrale verschuivingen en gewogen ruimtelijke middeling om een uiteindelijke ruimtelijke doelresolutie te bereiken. We hebben met succes de driedimensionale, overgediscretiseerde reconstructiemethode toegepast op 3D- ^1H -MRSI-gegevens van de prostaat op 3 T. Zowel in een fantoom als in vivo bleek de methode superieur te zijn aan conventionele gewogen filteren met een Hamming-filter van de k-ruimte. Vergeleken met laatstgenoemde lieten de overgediscretiseerde gereconstrueerde gegevens met kleinere voxelgrootte tot 10% minder verspreiding van signaal zien, terwijl een hogere SNR met een factor 1,87 en 1,45 werd gehandhaafd bij fantoommetingen. Voor in vivo metingen bereikten we binnen dezelfde acquisitietijd en zonder verlies van SNR een verhoogde ruimtelijke resolutie en verbeterde lokalisatie in metabolietmappen, vergeleken met Hamming-filtering.

Terwijl alle data in de hoofdstukken in het eerste deel werden verkregen met de klinische 3 T MR-systemen in het Radboudumc, bestreek het tweede deel van dit proefschrift ultrahoogveld, 7 T, MRI. Bij deze hogere magnetische veldsterkte houden onderzoeksscanners met verhoogde gevoeligheid en spectrale resolutie de belofte in van beeldvorming en spectroscopie van de prostaat met ongekeende details, die kunnen worden gebruikt voor het beoordelen van de status van de lymfeklieren. **Hoofdstuk 5** geeft een overzicht van de uitdagingen die deze veldsterkte met zich meebrengt en oplossingen die door de jaren heen zijn gevonden voor lichaamsbeeldvorming op 7 T. Er zijn aanzienlijke inspanningen geleverd om de technische uitdagingen van UHF-beeldvorming van de onderbuik aan te pakken, met name voor de prostaat en het omliggende weefsel. Het hoogtepunt van dit werk toont duidelijk aan dat multinucleaire multiparametrische MR(S)I van de prostaat bij UHF haalbaar is. Met de exploitatie van hogere ruimtelijke resoluties bij beeldvorming en bij spectroscopie kan mpMRI bij UHF een betere afbakening van de prostaatanatomie en metabolische beeldvorming binnen de tumor opleveren als een biomarker voor een beoordeling van de agressiviteit van prostaatkanker. Voor de klinische detectie van primaire prostaatkanker is een snelle, gemakkelijk beschikbare en robuuste MRI-acquisitie nodig; huidige 3 T-protocollen voldoen aan deze eisen. De potentiële rol van prostaatbeeldvorming bij 7 T zou kunnen liggen in het verkrijgen van een beter begrip van de ontwikkeling en progressie van lokale prostaatkanker en het begin en de ruimtelijke distributie van metastatische verspreiding. Daarnaast kan het inzicht geven in de karakterisering van verschillende tumorstadia en recidiverende ziekten.

Eén toepassing op dit ultrahoge veld, de detectie van lymfeklieren die verdacht zijn op metastasen, wordt beschreven in **hoofdstuk 6**. Nauwkeurige detectie van lymfekliermetastasen bij prostaatkanker is een uitdagende maar cruciale stap voor het stadiëren van de ziekte. MRI met gebruik van ultrakleine superparamagnetische ijzeroxide nanodeeltjes (USPIO-MRI) maakt het mogelijk om onderscheid te maken tussen gezonde lymfeklieren en klieren die verdacht zijn op uitzaaiingen. In combinatie met MRI bij een ultrahoog magnetisch veld van 7 T kan een ongekeende ruimtelijke resolutie worden benut om deze lymfeklieren zichtbaar te maken. Om USPIO-MRI op 7 T in vergelijking met 3 T te onderzoeken voor de detectie van kleine verdachte lymfeklieren werd hetzelfde cohort patiënten met prostaatkanker gescand op beide veldsterktes. De resultaten laten zien dat in hetzelfde cohort patiënten met prostaatkanker meer kleine lymfeklieren werden gedetecteerd op 7 T USPIO-MRI vergeleken met 3 T MRI. Verdachte lymfeklieren zijn over het algemeen erg klein en een grotere omvang van de klieren was geen goede indicatie voor verdenking op de aanwezigheid van metastasen. De hoge ruimtelijke

resolutie van USPIO-MRI op 7 T verbeterde de afbakening van structuren en de zichtbaarheid van zeer kleine verdachte lymfeklieren, waardoor mogelijk de in vivo detectielimieten van lymfekliermetastasen in het bekken bij patiënten met prostaatkanker werden vergroot.

Hoofdstuk 7 geeft een discussie over het geheel en een vooruitblik naar de toekomst. Samenvattend geeft dit proefschrift methodes weer voor robuuste acquisitie van ^1H -MRSI spectra van hoge kwaliteit. Deze zouden van toegevoegde waarde kunnen zijn bij het klinisch opvolgen van prostaatkanker. Aangezien MRSI een reproduceerbare kwantitatieve beoordeling mogelijk maakt, zouden herhaalde resultaten in een actieve surveillance setting gemakkelijk vergeleken kunnen worden zonder effect van verschillende beoordelaars. Een robuuste MRSI-sequentie van hoge kwaliteit kan zo voorkomen dat er onnodige invasieve biopsieën moeten worden genomen in bepaalde gevallen waarin radiologen onzeker zijn over de noodzaak hiervan. Wanneer we daarnaast mpMRI acquisitie uitvoeren op een ultrahoge veldsterkte met gedetailleerde visualisatie van prostaatkankerlaesies, kunnen we een hogere beeldvormingskwaliteit bereiken en daarmee nauwkeuriger detecteren of de prostaatkanker zich heeft uitgebreid tot buiten de prostaat. Dit kan leiden tot een nauwkeurige en gepersonaliseerde behandeling voor elke patiënt in een vroeg stadium van de ziekte. De combinatie van 7 T-MRI en functioneel USPIO-contrast kan mogelijk helpen bij het detecteren van kleine uitzaaiingen. Doelgerichte radiotherapie op deze lymfekliermetastasen is daardoor mogelijk een nieuwe benadering van gepersonaliseerde en beeldgeleide therapie voor prostaatkanker.

Appendices

Data Management

This thesis is based on the results of research involving human participants (or existing data from published papers), which were conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct and Radboudumc policy. The recognized Medical Ethics Review Committee 'METC Oost-Nederland' has given approval to conduct these studies (file numbers: NL58944.091.16). The institutional ethical review committee CMO Radboudumc, Nijmegen, the Netherlands has given approval to conduct the studies in Chapter 2-4 (dossier number: CMO 2016-2774). The research in Chapter 6 is conducted under approval of the Ethics Committee of the University of Duisburg-Essen (no. 16 7214 BO).

According to Dutch legislation, data collection from electronic patient files was performed by personnel with a treatment relationship with the patient and by the researcher(s) upon consent by the study participant. The privacy of the participants in these studies was warranted by the use of pseudonymization. The pseudonymization key was stored on a secured network drive that was only accessible to members of the project who needed access to it because of their role within the project: coordinating and principle investigator, and trial coordinator of the Department of Medical Imaging, Radboudumc. The pseudonymization key was stored separately from the research data (\\UMCfs097\radngdata\$\Research-codelists\18046_SpectroDotEngine and \\UMCfs097\radngdata\$\Research-codelists\17032_BioMR). Informed consent was obtained from participants to collect and process their data for this research project. Consent was also obtained for sharing the (pseudonymized) data after research.

Subject data for Chapter 2 was collected through electronic Case Report Forms (eCRF) using CASTOR EDC. From Castor EDC data were exported to SPSS (SPSS Inc., Chicago, Illinois, USA). All study data and pseudonymized data were stored on the server of the Department of Medical Imaging, Radboudumc (\\UMCfs097\radngdata\$\Research\BioMR\Carlijn) and in Castor EDC and are only accessible by project members working at the Radboudumc. Paper (hardcopy) data is stored in the Trial Master Files in cabinets in the department of Medical Imaging, Radboudumc. Pseudonymized MRI data (Chapters 2-4 and 6) are stored securely on the local Radboudumc server (for raw data: \\rdscience.umcn.nl\mrs_data5\CarTen and for processed data: \\umcsanfscpl01\radng_biomr\ biomr\Carlijn.Tenbergen) of the Medical Imaging Department.

All studies are published open access. The research data will be stored for a period of 15 years after completion of the studies. Using these patient data in future research is only possible if explicit permission by the participants is given in the informed consent or after a renewed permission by the patient as recorded in the informed consent. Requests for access will be checked by the data manager of the department, against the conditions for sharing the data as described in the signed Informed Consent.

List of journal publications

Tenbergen CJA, Metzger GJ, Scheenen TWJ. Ultra-high-field MR in Prostate cancer: Feasibility and Potential. *Magnetic Resonance Materials in Physics, biology and Medicine*. 2022 Aug;35(4):631-644.

Tenbergen CJA, Ruhm L, Ypma S, Heerschap A, Henning A, Scheenen TWJ. Improving the Effective Spatial Resolution in ¹H-MRSI of the Prostate with Three-Dimensional Overdiscretized Reconstructions. *Life (Basel)*. 2023 Jan 19;13(2):282.

Tenbergen CJA*, Fortuin AS*, van Asten JJA, Veltien A, Philips BWJ, Hambrock T, Orzada S, Quick HH, Barentsz JO, Maas MC, Scheenen TWJ. The Potential of Iron Oxide Nanoparticle-Enhanced MRI at 7 T Compared With 3 T for Detecting Small Suspicious Lymph Nodes in Patients With Prostate Cancer. *Investigative Radiology*. 2024 Jul 1;59(7):519-525. *shared first authors

Stamatelatou A, **Tenbergen CJA**, Nassirpour S, Chang P, van Asten JJ, Heerschap A, Scheenen TWJ. Improving magnetic field homogeneity in prostate MR imaging and spectroscopy using an add-on local external shim array coil. *Magnetic Resonance Materials in Physics, biology and Medicine*, under submission

List of conference abstracts

Tenbergen CJA, Weiland E, Heerschap A, Scheenen TWJ. Evaluation of an Automated Acquisition Workflow for Multiparametric MR (Spectroscopic) Imaging of the Prostate. Proceedings of the ISMRM workshop on advances in Multiscale Cancer Detection 2018; Dublin, Ireland. Poster presentation

Tenbergen CJA, Weiland E, Heerschap A, Scheenen TWJ. Evaluation of an automated acquisition workflow for multiparametric MR (spectroscopic) imaging of the prostate. RIHS PHD Retreat 2018; Den Bosch, the Netherlands. Oral presentation

Tenbergen CJA, Weiland E, Selnaes KM, Bathen TF, Heerschap A, Scheenen TWJ. Initial evaluation of an automated acquisition workflow for multiparametric MR (spectroscopic) imaging of the prostate. ISMRM Benelux 2019 Chapter Meeting; Leiden, the Netherlands. Oral presentation

Tenbergen CJA, Weiland E, Selnaes KM, Bathen TF, Heerschap A, Scheenen TWJ.. Initial evaluation of an automated acquisition workflow for multiparametric MR (spectroscopic) imaging of the prostate. Proceedings of the 27th Annual Meeting of ISMRM 2019; Montreal, Canada. Poster presentation

Tenbergen CJA, Ruhm L, Heerschap A, Henning A, Scheenen TWJ. Overdiscrete reconstruction to correct for B0 inhomogeneities in 1H-MRSI of the prostate – RIHS PhD Retreat 2019; Den Bosch, the Netherlands. Oral presentation - **awarded with 'Best 4-minute short talk'**

Tenbergen CJA, Ruhm L, Heerschap A, Henning A, Scheenen TWJ. Over-discretized reconstruction to correct for B0 inhomogeneity and improve localization in 1H-MRSI of the prostate. ISMRM Benelux 2020 Chapter Meeting; Arnhem, the Netherlands. Poster presentation

Tenbergen CJA, Ruhm L, Heerschap A, Henning A, Scheenen TWJ. Over-discretized reconstruction to correct for B0 inhomogeneity and improve localization in 1H-MRSI of the prostate. Proceedings of the 28th Annual Meeting of ISMRM 2020; Virtual conference. Poster presentation

Tenbergen CJA, Ruhm L, Heerschap A, Henning A, Scheenen TWJ. 3D over-discretized reconstruction in 1H-MRSI of the prostate to improve metabolite

resolution. ISMRM Benelux 2021 Chapter Meeting; virtual conference. Oral presentation

Tenbergen CJA, Stamatelatou A, Nassirpour S, Chang P, Scheenen TWJ. An add-on local external shim array to improve the main magnetic field homogeneity in the prostate. ISMRM Benelux 2023 Chapter Meeting; Brussels, Belgium. Oral presentation

Tenbergen CJA, Stamatelatou A, Nassirpour S, Chang P, Scheenen TWJ. An add-on local external shim array to improve the main magnetic field homogeneity in the prostate. Proceedings of the 32nd Annual Meeting of ISMRM 2023; Toronto, Canada. Poster presentation

PhD portfolio

Department: **Medical Imaging**
 PhD period: **09/04/2018 – 01/07/2023**
 PhD Supervisor(s): **Prof. dr. ir. T.W.J. Scheenen, Prof. dr. M.J.P. Sedelaar**

Training activities	Hours
Courses	
• BROK (2018)	42.0
• Introduction day Radboudumc (2018)	14.0
• RIHS - Introduction course for PhD candidates (2018)	15.0
• Basic Life Support (2018)	4.2
• 15th PhD in vivo NMR course (2018)	49.0
• Achieving your Goals and performing more successfully in your PhD (2019)	42.0
• NVvO Basiscursus Oncologie 2019 (2019)	49.0
• Statistiek voor promovendi met SPSS (opfriscursus) (2019)	56.0
• Scientific Integrity for PhD candidates (2019)	28.0
• Presentation Skills (2020)	42.0
• Design and Illustration (2020)	28.0
• Scientific Writing for PhD candidates (2021)	84.0
• Radboudumc - Re-registration BROK (2022)	5.0
• Career development workshop "The next step in my career" (2022)	24.0
• Radboudumc - Scientific integrity (2023)	0.0
Seminars	
• Departmental Research meeting, weekly attendance, 2 oral presentations (2018 - 2023)	128.0
• BioMR group research meeting, weekly attendance, 8 oral presentations (2018 - 2023)	168.0
• BioMR group literature meeting, 2 oral presentations (2018-2020)	16.8
Conferences	
• ISMRM workshop on Multiscale Cancer Detection (poster presentation) (2018)	42.0
• RIHS PHD Retreat (including oral presentation) (2018)	21.0
• ISMRM Benelux 2019 Chapter Meeting (including oral presentation) (2019)	21.0
• ISMRM 2019 Annual Meeting (including poster presentation) (2019)	56.0
• Radboud Research Round (2019)	2.8
• RIHS PhD Retreat (including oral presentation) (2019)	21.0
• ISMRM Benelux 2020 Chapter Meeting (including poster presentation) (2020)	21.0
• ISMRM 2020 Annual Meeting virtual conference (digital poster presentation) (2020)	56.0
• ISMRM Benelux 2021 virtual Chapter Meeting (including oral presentation) (2021)	21.0
• Radboudumc Research Integrity Round (2021)	16.0
• 3rd Nijmegen Prostate Cancer Prospects (2022)	56.0
• Radboudumc Cancer Research Retreat (2022)	1.5
• ISMRM Benelux 2023 Chapter Meeting (including oral presentation) (2023)	13.0
• ISMRM 2023 Annual Meeting (including poster presentation) (2023)	11.0
Other	
• Committee Departmental Research Meeting (2020)	14.0
• ISMRM Benelux organizing committee (2020)	70.0
Teaching activities	
Lecturing	
• MR imaging, minor course, workgroup (2018)	22.4
• In vivo NMR course, practical lesson (2019)	11.2
Total	1,271.9

Dankwoord

Eindelijk is het zover, het boekje is af! Ik wil graag iedereen bedanken die heeft bijgedragen om tot dit eindresultaat te komen en die mijn jaren in het Radboudumc tot zo'n leuke tijd heeft gemaakt.

Allereerst bedankt aan alle patiënten die voor mij wat langer in de MRI scanner hebben willen liggen, en in het bijzonder de patiënten die de belevenis van de scanner in Essen hebben aangedurfd. Alle mede-auteurs wil ik bedanken voor hun inhoudelijke bijdrage en tekstuele feedback op de verschillende hoofdstukken in dit boekje.

Natuurlijk mijn promotoren, Tom en Michiel, bedankt voor het initiëren van dit promotieproject en mij begeleiden naar dit resultaat! Tom, bedankt voor het overbrengen van jouw kennis en vooral ook jouw manier van aanpakken. Waar onze tempo's niet altijd overeen kwamen, heb ik mij aardig weten te herpakken dankzij jouw begeleiding en motivatie. Dank voor jouw eerlijke en open communicatie, enthousiasme om dingen uit te proberen, gevoel om tot de kern van een tekst te komen, en achievements te vieren. Michiel, bedankt voor jouw klinische blik op ons MRI werk, aan het begin van mijn traject voor het kader en klinische wensen en aan het einde voor de toegevoegde waarde aan mijn manuscript.

De leden van de manuscriptcommissie, Prof. Schalken, Evita en Prof. De Visschere, dank voor het lezen en beoordelen van dit werk.

De BioMR groep, wat een fijne groep mensen om mee te werken, te kletsen, taart voor te bakken en mee op te eten, en die altijd bereid zijn om als vrijwilligers voor elkaar een momentje in de MRI scanner te liggen. Ten eerste de vaste mannen: Arend dank voor jou inzichten, altijd terechte vragen en opmerkingen en relativeren van onze problemen met verhalen uit het verleden. Sjaak, dank voor de vaste complimentjes op nieuwe kleding, de eeuwige hulp bij ICT en MRSI vragen, en dat er bij jou ook altijd ruimte is voor het bespreken van emoties. Andor, vaste steun voor praktische MRI vragen en koffie pauzes, dank voor de MRI introductie met cherrytomaten, het vaste enthousiasme voor het organiseren van activiteiten en cadeaus en jouw vrolijke positieve aanwezigheid. Marnix, dank voor jou voorbeeld van hard werken en kennis delen, jouw interesse en behulpzaamheid. Mark dank voor jouw creativiteit, Joannes met jouw gestructureerde methodologie van toegevoegde waarde voor het team en Donny, dank voor jouw humor.

Dank aan alle BioMR PhDs en studenten (Linda, Evita, Tom, Frits, BartP, Rutger, Didi, Daphne, Geke, Ivo, Sjoerd, Elina, Kirsten, Gijs, Roël, Colette, Tijmen, Rik, Luka, Camille, Mike) voor het delen van hoogtepunten, tips, ervaringen en uitdagingen op de kamer, tijdens alle pauzes, of bij leuke activiteiten buiten het werk.

Evita en Tom, dank voor het zetten van de hoge standaard als voorbeelden van promoveren. Linda, ik heb veel aan jou gehad als kamergenootje in het begin van mijn PhD, dank voor alle antwoorden en ervaringen tijdens thee momenten. Een hele gezellig afsluiting van de tijd met jou was mijn eerste ISMRM in Montreal, deze maakte alle verwachtingen waar. Dank Linda, Andor, Wendelien en Rutger voor deze gezellige trip naar de walvissen.

Ivo, dank voor jouw oprechte open blik en nieuwsgierigheid, waar ik iets van probeer mee te nemen. Elina, unfortunate that we didn't connect on a deep level from the beginning, it took some shared challenges for us to bond. Thank you for your example of self-motivation and hard work, your non-Dutch view to the group and your help with my Greek pronunciation. We had some great (small) trips and a trip to Greece with you as a tour guide still to follow. Samen met ook Kirsten, Gijs en Roël was ISMRM Toronto een hoogtepunt, met onze trip langs de watervallen, muggen en elanden.

Dank aan het hele ELH Essen team, voor de inspirerende pionierende omgeving. Jenni, dank voor jou ervaring met het 7T systeem. Ansje, dank voor het toevertrouwen van jouw werk en de fijne samenwerking om die goede resultaten in een mooi paper te vormen.

Paul and Sahar, thank you for your trips to Nijmegen and your teamwork behind the scanner for our creative, though hard to write down, project.

ISMRM Benelux 2020 team, dank voor gezellige tijd waarin we echt een goed congres hebben neergezet waar de collega's in Nijmegen het nog steeds over hebben! Een van de hoogtepunten van mijn PhD tijd.

Ik wil alle MR laboranten bedanken voor hun hulp tijdens het scannen van onze patiënten, voor hun geduld als de scanner vastliep of niet lang genoeg voor het programma klaar waren. Marijke, bedankt voor de hulp vooral tijdens mijn eerste studie en het beantwoorden van alle vragen ook daarna samen met het trialbureau. Marjolein, dank voor jou hulp voor alles wat je ook maar kan bedenken.

Lieve LDM'ers van het Máxima, met al onze verschillende achtergronden. 1.5 Jaar werk ik nu alweer in Utrecht en ik voel me echt op mijn plek. Bedankt voor de fijne sfeer en gezelligheid op onze kamer, tijdens lunchwandelingen en voor de interesse in mijn onderzoek.

Lieve familie en vrienden, dank voor de interesse in en al het fijns naast het werk. Ineke, dank voor alle gezellige bijkletsmomentjes, onze gemeenschappelijke interesses die ons tot in Peru hebben geleid en nu weer terug op onze eigen nestjes in de Liemers.

Walter en Claudia, dank voor het fijne schoongezin dat we vormen met Tom, Jeremy, Guus en Cheyenne. En Claudia, ik hoop dat je nu begrijpt wat een PhD ongeveer inhoudt.

Lieve papa en mama, dank voor jullie altijd aanwezige steun en hulp bij van alles, voor het doorgeven van jullie brede interesse in de levende natuur, de nieuwsgierigheid om te blijven leren en de motivatie om iets bij te dragen voor anderen. Dankjewel Jorieke voor de mooie omslag en jouw creativiteit die altijd tot uiting komt en ik heel graag gebruik van maak, vooral op de meest belangrijke momenten in mijn leven.

Lieve Bart, zonder jou had ik dit proefschrift niet tot een goed einde kunnen brengen. Dank voor alle motiverende woorden en jouw stabiliteit, altijd en ook tijdens mijn meest labiele momenten. Dankjewel dat je mij laat lachen en we zo'n goed team vormen. Dank voor het bewaken van onze planning, en het op tijd reserveren voor vakanties of andere vrije dagen. Toch krijg ik het voor elkaar dat privé en werk pieken snel op elkaar volgen. Ik hou ervan om samen met jou deze mooie dingen te mogen beleven en ik kijk uit naar nog veel meer momenten om te vieren op ons nieuwe plekje.

Curriculum Vitae

Carlijn Tenbergen was born on February 8th, 1992, in Zevenaar, the Netherlands. After completing her secondary education at the Liemers College in Zevenaar, she started the bachelor program of Technical Medicine at the University of Twente in 2010. She obtained her bachelor's degree after finishing her bachelor's thesis, titled 'Collateral and recanalization measurements for ischemic stroke treatment'.



She continued her education with the master's program of technical medicine, with the Imaging and Interventions track. This program included four 10-week internships, which she spent at the departments of Nuclear Medicine at Isala Zwolle, Lung diseases at Radboudumc Nijmegen, Vascular surgery at Rijnstate Arnhem, and Radiotherapy group Deventer. In her last Master's year, Carlijn conducted research at the Nuclear medicine department of the Leiden University Medical Center, resulting in her master thesis titled: 'Quantification of amyloid PET imaging in early detection of Alzheimer's disease'.

In 2018, Carlijn started her PhD research at Radboudumc in Nijmegen within the medical imaging department, in collaboration with Urology, under the supervision of prof Tom Scheenen and prof Michiel Sedelaar. This research included the initiation and execution of research projects on 3T and 7T MRI and MRSI, comprising patient studies, technical implementations, and processing of data on local prostate cancer lesions and regional lymph node metastases. During this time, she also enjoyed being part of the Organizing Committee of the ISMRM Benelux 2020 chapter meeting, welcoming 350 participants at the Burgers Zoo in Arnhem.

Since December 2023, Carlijn has been working at the Trial and Data Center of the Princess Maxima Center for Pediatric Oncology in Utrecht, where she enjoys working as a local data manager.



9 789465 151021 >