Multiparametric MRI for focal dose escalation in prostate cancer radiotherapy

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CHAPTER 1

Introduction

Prostate cancer

Prostate cancer is a common disease that presents primarily in elderly men, with an average age at diagnosis of 66 years (Rawla *et al.* 2019). According to the latest global cancer survey, prostate cancer is responsible for 1.28 million new cases and 359 thousand deaths per year (Ferlay *et al.* 2019). While ranked as the second most common type of male cancer worldwide, in the Netherlands prostate cancer is the leading type of male cancer diagnosed, with an incidence of over 13 thousand cases and almost three thousand deaths per year (NKR 2019).

Prostate cancer is a heterogeneous disease that can present in multiple disease stages and levels of aggressiveness. To a large extent the life expectancy of prostate cancer patients depends on the stage of the disease. The majority of prostate cancers are slow-developing indolent tumors that are confined to the prostate gland. Approximately 15% of the patients present with more aggressive, fast-proliferating tumors that may be accompanied with extracapsular extension or metastatic disease (Chang *et al.* 2014).

Due to screening programs, most new prostate cancer cases are diagnosed without apparent complaints of the patient (Donnelly *et al.* 2019). A blood sample measurement showing an increase of the prostate specific antigen (PSA) may raise suspicion, although nonmalignant conditions as benign prostate enlargement (BPE) or prostatitis can cause similar abnormal PSA scores.

Additional imaging and needle biopsies are recommended to differentiate between cancer and benign conditions (Barentsz *et al.* 2012). Upon imaging any visible tumor tissue is localized and staged. Depending on whether the imaging involves a Digital Rectal Examination (DRE) or an MRI examination, either a clinical or radiological tumor (T-) stage is established. The biopsies reveal tissue pathology at multiple locations in the prostate and are assigned to an ISUP (International Society of Urological Pathology) grade group based on the tissue's cell differentiation (van Leenders *et al.* 2020). While previously ultrasound-guided biopsies were taken and MRI examination was performed in case of positive biopsy cores, current clinical practice involves initial MRI acquisition followed by MRI-targeted biopsies to reduce patient burden and improve the detection of clinically significant prostate cancer (Giganti *et al.* 2017).

The combination of PSA, T-stage and grade group represents the clinical condition of the disease and allows to categorize patients by prostate cancer risk groups. These risk groups represent the chance of developing metastatic disease after primary treatment. In Europe the EAU risk classification is adopted that differentiates between low, intermediate and high-risk patients (Mottet *et al.* 2017). Higher risk is generally associated with poorer survival.

Radiotherapy treatment

Alongside prostatectomy, radiotherapy is a suitable primary treatment option for low to high-risk disease (Kishan *et al.* 2017, Moris *et al.* 2020). Radiotherapy can be delivered internally with brachytherapy, using radiation source tubes or seed implants, or externally with radiation beams, referred to as external beam radiotherapy (EBRT). Treatment with a linear accelerator (linac) is the standard of care for EBRT. To deliver EBRT treatment, an anatomical MRI and a simulation CT are acquired to respectively define anatomical regions of interest and retrieve tissue density information to calculate the attenuation of the radiation dose in the patient. With treatment planning software the beam positions, shape and dose rate are calculated to deliver a homogeneous dose distribution to the entire prostate gland and simultaneously limit the dose to surrounding organs at risk, such as the bladder and rectum. The dosimetrically optimized treatment plan is delivered in multiple fractions, which allows for recovery of benign tissue in between fractions. Radiotherapy is often combined with long-term hormonal therapy in the form of androgen deprivation to reduce metastatic spread and recurrence of the disease (Böhmer *et al.* 2016).

Whole gland dose escalation, in which an elevated radiation dose is prescribed to the entire prostate gland, was found to improve biochemical recurrence free survival rates among low to intermediate risk patients (Pollack *et al.* 2002, Peeters *et al.* 2006, Dearnaley *et al.* 2007). Although further dose escalation may lead to improved recurrence free survival among intermediate to high-risk patients as well (Pollack *et al.* 2002, Peeters *et al.* 2006, Morgan *et al.* 2007), it would also induce unacceptable damage to organs at risk. Interestingly, prostate tumors were found to recur predominantly at the location of the primary tumor site (Cellini *et al.* 2002, Pucar *et al.* 2007). Therefore, focal dose escalation based on tumor tissue presence seems a reasonable approach to increase local control while restricting dose to organs at risk.

Multiparametric MRI

To apply a dose escalation within the prostate gland, soft tissue contrast is required to identify the intraprostatic tumor. MRI is a valuable non-invasive imaging technique to reveal excellent soft tissue contrast (Owrangi *et al.* 2018). A T2-weighted sequence can quickly obtain high-resolution anatomical information from the pelvic region and is therefore the most frequently scanned MRI sequence to localize prostate cancer (Cabarrus *et al.* 2017). The T2-weighted image reflects the T2 relaxation time of tissues relative to each other and visualizes malignant tissue in the prostate as hypointense regions. For delineation purpose the display settings are often adjusted to maximize image contrast.

Although an anatomical T2-weighted MRI gives a good indication on the tumor dimensions, additional biological information greatly contributes to determine the tumor extent and, moreover, reveals physical and physiological characteristics of the tumor (Olsson *et al.* 2019). Imaging of such tumor biology is performed with functional imaging. Functional imaging in prostate cancer primarily focusses on diffusion and perfusion measurements but may also involve measurements of tumor metabolism and hypoxia.

Diffusion weighted imaging (DWI) measures the restricted motion of water molecules in biological tissue and allows to reveal details of the microscopic tissue composition. Since prostate tumors have a higher cell density than healthy prostate tissue, diffusion of water is reduced in the tumor, resulting in a hyperintense region on the diffusion-weighted image. Usually, a series of images with different diffusion weighting is acquired (Maurer *et al.* 2017). From this series a per-voxel apparent diffusion coefficient (ADC) map can be derived that eliminates inherent T2-weighting from the diffusion-weighted images and thereby quantifies the apparent local diffusion within the tissue.

Dynamic contrast enhanced (DCE-) MRI involves the recording of a time series of T1-weighted images of a contrast agent distribution in a region of interest. Several tracer kinetic models exist that apply a cell compartment approximation to estimate the true tissue vascularity (Brix *et al.* 1991, Buckley *et al.* 1994, Tofts 1997, Tofts *et al.* 1999). Among multiple parameters that together model the local tissue perfusion, the volume transfer constant K^{trans} is a commonly investigated parameter in prostate cancer. Increased values of K^{trans} are associated with leaky vascularity which indicates the presence of malignant tissue.

The combination of anatomical and functional MRI is referred to as multiparametric MRI (mp-MRI). Mp-MRI improves the sensitivity of tumor detection considerably. While the sensitivity of clinically detectable tumors on T2-weighted images is 0.73, this value increases to 0.85 – 0.89 when combined with DWI and DCE-imaging (Heijmink *et al.* 2007, Zhang *et al.* 2017, Woo *et al.* 2017).

For prostate cancer detection and staging of the disease, the PI-RADS V2 guidelines recommend a combination of T2-weighted and DWI to be scanned, with optional DCE-MRI (Weinreb *et al.* 2016). Although PI-RADS leads to more consistency in localization of the tumor (Rudolph *et al.* 2020), to date no guidelines exist on the use of mp-MRI to delineate the tumor for treatment purpose. This implies that current institutional practice can only be based on local experience and expertise. Several studies have shown that in the absence of guidelines large inter-observer variability exists when delineating the visible tumor on mp-MRI (Bratan *et al.* 2013, Rischke *et al.* 2013, Anwar *et al.* 2014, Steenbergen *et al.* 2015).

Alternatively, uncertainties introduced by human interpretation can be omitted when manual delineations are replaced by machine learning approaches. In such approach computational models are applied to imaging data and optionally combined with clinical parameters, to calculate a probability distribution of tumor presence in the prostate. The performance of the machine learning model depends on the amount and quality of the data the model has learned from in the training phase. Whenever the training data was labelled, the training phase can be considered as supervised learning. For prostate cancer usually a dataset of patients with ground truth information derived from histopathological data forms the labelled training data.

Quantitative MRI

In line with the PI-RADS V2 guidelines, T2-weighted and DW-MRI sequences are scanned to detect and stage prostate tumors. These are popular sequences for their high spatial resolution, high contrast between tumor and benign tissue, and fast imaging protocols. However, for quantification of the tumor tissue these sequences are not suitable. The dimensionless values that are acquired hamper a comparison of image values between patients or institutions.

MR images that contain values with physical meaning are called quantitative MRI. The physical values of quantitative MRI allow to compare image data from different patients at different scanning devices. It also enables the comparison of consecutive images of the same patient over a period of time. This is specifically interesting for assessing the response of tumor and surrounding tissue to the treatment, which could ultimately lead to improved treatment strategies. Quantitative MRI may also contribute to the development of continuous dose prescription maps that are automatically derived according to and at the resolution of the acquired quantitative images (Bentzen 2005).

T2 and ADC maps are commonly investigated quantitative MRI parameters for dose painting purpose and response assessment of prostate cancer. T2 maps are derived from a series of T2-weighted images, analogous to how ADC maps are derived from diffusion-weighted images. Since the T2 values represent the true transverse relaxation within each voxel in the image, T2 times characterize certain tissues. K^{trans} as a physical quantity may also qualify as quantitative parameter. However, K^{trans} values have a high uncertainty due to the variation within and between investigated patient cohorts (Huang *et al.* 2016), and the actual meaning of those K^{trans} values depends on the tracer kinetic model that was used (Khalifa *et al.* 2014). Therefore, K^{trans} maps are less suitable as quantitative image parameters.

Although quantitative MRI parameters by definition should be equivalent between scanners and institutions, differences in imaging protocol, patient setup and scanner settings are sources of variation in obtained quantitative values. Standardization of these aspects is essential to fully utilize the potential of quantitative MRI in radiotherapy applications (Gurney-Champion *et al.* 2020).

Image-based dose escalation strategies

Using MRI for tumor localization, several studies have demonstrated the feasibility of an image-based focal dose escalation in the prostate while preserving dose constraints to surrounding organs at risk. In a planning study with three patients Singh *et al.* considered delivery of 95 Gy to the dominant intraprostatic lesion using EBRT feasible with acceptable levels of toxicity (Singh *et al.* 2007). The HEIGHT trial demonstrated in 35 patients the feasibility of planning a dose escalation up to 89.3 Gy to the intraprostatic tumor while maintaining strict constraints to organs at risk (Bossart *et al.* 2016). Combining EBRT with concurrent brachytherapy with integrated boost was also found feasible with good outcomes for biochemical control, acute and late toxicities (Gomez-Itturiaga *et al.* 2016, Vigneault *et al.* 2016). In the phase II TARGET trial, 80 patients received 76 Gy from EBRT, combined with either an integrated boost of 95 Gy or a single brachytherapy boost of 10 Gy. Initial results have shown acceptable dosimetry and comparable toxicity and quality of life between both arms of the study (Sanmamed *et al.* 2020).

Focal dose escalation: FLAME

The phase III randomized controlled FLAME trial (Focal Lesion Ablative Microboost in ProstatE, NCT01168479) was performed between 2009 and 2015 to investigate the benefit of an integrated focal boost on 5-year biochemical recurrence free survival in a multi-institutional and single blinded setting (Lips *et al.* 2011). On an institutional level, patients were randomly assigned to either a standard treatment with 77 Gy prescribed to the entire prostate gland, or an experimental treatment with an integrated dose escalation up to 95 Gy to the visible tumor. In four participating institutions in total 571 patients were included.

In addition to the CT scan required for dose calculation purpose, an mp-MRI was acquired to identify the tumor in the prostate and delineate the intraprostatic tumor accordingly. This tumor delineation was defined as gross tumor volume (GTV). Dose painting by contours treatment planning was performed using local treatment planning software. Identical to standard prostate radiotherapy, planning target volume (PTV) coverage was prioritized over dose to organs at risk. For patients in the dose-escalated arm of the trial, objectives were

added to increase the dose to the GTV and preserve the dose to organs at risk. The aim was to achieve a tumor dose of 95 Gy, provided that dose constraints to organs at risk were prioritized.

Due to the integrated boost to an extreme dose in combination with strict constraints to organs at risk, the constitution of a focal dose escalation plan was a complex procedure. Since the optimization function of the treatment planning system was expanded with additional dose objectives, and the iterative manual optimization steps needed to be performed within a reasonable time frame, it is not guaranteed that the GTVs received the highest possible dose that the patient anatomy would allow for.

Recently, the FLAME trial was found to demonstrate a significant increase in 5-year biochemical disease-free survival, from 85% in the standard to 92% in the dose-escalated treatment arm, and a significant GTV dose response relation was observed (Kerkmeijer *et al.* 2021). The nonzero biochemical recurrence rate in the dose-escalated arm of the trial may partially be explained by potential undertreatment of GTVs, suggesting that more consistent treatment planning methods may increase the biochemical recurrence free survival rate even further. A common approach to improve consistency between treatment plans regarding optimal target coverage and organ at risk sparing is knowledge-based planning (KBP) (Wu *et al.* 2009). KBP methods utilize a large dataset of optimized dose distributions for different types of patient anatomy. The achievable doses to target volumes and organs at risk of a new patient are predicted from a subset of similar patient anatomies and corresponding dose distributions from the database (Wu *et al.* 2009, Appenzoller *et al.* 2012, Yuan *et al.* 2012, Wang *et al.* 2013, Wang *et al.* 2017, Wall *et al.* 2018). In standard prostate radiotherapy KBP has led to improved dose distributions and enabled automated plan quality assessment (Janssen *et al.* 2019). In future clinical settings of focal dose escalated treatment, KBP may find similar applications.

Hypofractionated focal dose escalation

Fractionation of the prescribed radiation dose allows for tissue recovery in between consecutive treatment fractions. The sensitivity of tissue to radiation can be described with the linear-quadratic (LQ) model (McMahon *et al.* 2018). The surviving fraction of cells is dependent on the radiation dose D, the intrinsic radiosensitivity parameter α, and the repair capability parameter β. The ratio between α and β describes the fractionation sensitivity of cells and relates to the response time of the cells to radiation.

Evidence was found that the α/β ratio of prostate tumors is lower than the surrounding normal tissue, which is opposite to most other tumor sites (Brenner *et al.* 1999, Vogelius *et al.* 2013). This implies that a sufficiently large dose per fraction will do relatively more damage to tumor

cells than to normal tissue. As a result, patient outcome would benefit from a treatment delivered in fewer treatment fractions with larger fraction doses (Ritter *et al.* 2008, Benjamin *et al.* 2017).

In a recent meta-analysis of 13 randomized trials that studied conventional fractionation with 1.8 – 2.0 per fraction and moderate hypofractionation with 2.4 – 3.4 Gy per fraction, the low α/β ratio was confirmed with a highly significant dose response (Vogelius *et al.* 2018). Indeed, in low to intermediate risk prostate cancer, moderate hypofractionation was shown to be non-inferior and with comparable complication rates as conventional fractionation (Dearnaley *et al.* 2016, Brand *et al.* 2019, Widmark *et al.* 2019). Besides the radiobiological advantage, also practical aspects are in favor of a hypofractionated treatment approach: overall treatment time is reduced, the patient comfort is improved, and resources can be utilized more efficiently.

Based on the aforementioned evidence, recommendation guidelines on the delivery of moderate and even extreme hypofractionation up to 5 Gy per fraction have been published (Morgan *et al.* 2018). As a result, moderate hypofractionation has become the new standard of care for all risk groups. Extreme hypofractionation is considered a save treatment option for low to intermediate risk disease, while intermediate to high-risk patients should only receive such treatment in trial setting. A recent meta-analysis of phase III randomized trials observed similar levels of safety and efficacy in conventional fractionation, moderate hypofractionation and extreme hypofractionation schemes among low to high-risk patients (Lehrer *et al.* 2020).

During enrollment of the FLAME trial, conventional fractionation was delivered with 2.0 Gy per fraction to the prostate, with an optional boost to 2.2 Gy to the delineated tumor. The increasing attention for moderate and extreme hypofractionation over the last years has led to the hypothesis that intermediate to high-risk patients could also benefit from improved treatment outcome and reduced treatment time if such hypofractionated radiation scheme is combined with focal dose escalation. Several studies currently investigate if extreme hypofractionation combined with a focal boost can be safely and effectively delivered to these patients. In the phase II DELINEATE trial, both conventional and moderate hypofractionation were combined with a focal dose escalation (Murray *et al.* 2020). Patients received either 74 Gy in 37 fractions or 60 Gy in 20 fractions, with integrated boost doses of 82 and 67 Gy respectively. In the phase II Hypo-FLAME trial, extreme hypofractionation of 35 Gy in five weekly fractions was delivered with an integrated boost up to 50 Gy (Draulans *et al.* 2020). Similarly, the phase II SPARC trial treated patients in five fractions with 36.25 Gy and up to 47.5 Gy to the intraprostatic tumor (Nicholls *et al.* 2020). While these trials have reported efficacy of the treatment with acceptable toxicity levels, the primary endpoint will eventually

confirm the overall benefit of combined hypofractionation and focal dose escalation for intermediate to high-risk patients.

Dose Painting by Numbers

Dose painting was introduced as a novel planning technique to incorporate both tumor location and characteristics as derived from imaging (Ling *et al.* 2000). Focal dose escalation as performed in the FLAME and hypo-FLAME trials involved a discrete elevated dose prescription to the identified intraprostatic lesion, and is referred to as Dose Painting by Contours. As observed in pathology, the actual prostate tumor boundary is more irregular than delineations suggest (Steenbergen *et al.* 2015). It has been shown that certain types of tumor tissue may be completely missed on mp-MRI (van Houdt *et al.* 2020). Moreover, multiple levels of cell differentiation and aggressiveness may present in the tumor, with different levels of radioresistance. Due to the finite resolution of mp-MRI and the inability to visualize all tumor tissue, delineated tumor boundaries may be inaccurate, and the uniform dose escalation may not always match with the local tumor tissue characteristics.

Dose Painting by Numbers (DPbN) is a treatment strategy that reflects uncertainties of the target definition in terms of boundary irregularities and tumor tissue heterogeneity (Bentzen 2005). DPbN allows to omit manual contouring and instead prescribe dose at the resolution of the mp-MRI. In addition, besides the radiological images DPbN could also be performed on higher order image features that may contain tumor characteristics invisible to the human eye. Often biological heterogeneity is modelled to base the dose prescription on (Vanderstraeten *et al.* 2006, Thorwarth *et al.* 2007, Differding *et al.* 2017, Grönlund *et al.* 2019, Yan *et al.* 2019). Specifically in prostate cancer the modelling of tumor presence is valuable for the purpose of DPbN. Voxel-wise conversion from tumor presence probability to prescription dose is enabled by a calibration function (Bowen *et al.* 2009). In such calibration function dose levels range between a minimum value to guarantee sufficient tumor control and a maximum value that could be delivered safely in performed trials.

Irrespective of the chosen calibration function, the omission of manual contouring and discrete dose levels may lead to propagation of image value uncertainties to the planned dose distribution. Therefore, investigation of the repeatability of image-based dose prescription is essential for the development of DPbN as a robust candidate for dose escalation treatment.

Treatment response monitoring

Not only for treatment planning purpose but also during treatment delivery mp-MRI may potentially further improve current practice. In one of the side studies of the Hypo-FLAME trial (NCT02853110) five weekly mp-MRI were performed to prepare for future MRI-guided treatment. The mp-MRI acquired at each treatment fraction visit allowed to investigate the potential role of mp-MRI for treatment response monitoring and early-adaptive treatment strategies. To achieve such treatment strategies with imaging, an assessment of anatomical, functional or molecular image characteristics, called imaging biomarkers, is required (ESR 2015, Dregely *et al.* 2018). Tracking changes of the tumor appearance in the Hypo-FLAME dataset is a suitable candidate for assessment. In radiotherapy an imaging biomarker, such as tumor intensity change, has a prognostic value if it relates to outcome regardless of the radiation dose. The prognostic value of the imaging biomarker alone, however, will not be suitable to base treatment adaptation on. Imaging biomarkers that do qualify for adaptive treatment need to have predictive value as well (Oldenhuis *et al.* 2008, Gurney-Champion *et al.* 2020). Predictive imaging biomarkers predict patient outcome depending on the radiation dose that was delivered. They allow to relate radiation dose to patient outcome using a calibration curve and act upon early changes during treatment.

Thesis outline

Dose escalation to the intraprostatic tumor has been shown to improve outcome of patients with intermediate to high-risk disease (Kerkmeijer *et al.* 2021). The effectiveness of such novel treatment depends to a large extent on the accuracy of the delivered treatment and the optimal use of available information about the tumor physiology. Over the past decades mp-MRI has found application at all stages of the radiotherapy workflow (Kerkmeijer *et al.* 2018, Olsson *et al.* 2019). This thesis describes mp-MRI applications and models that were specifically developed for, and may play an important role in the evolution of dose escalated treatment of prostate cancer.

Chapters 2 and 3 evaluate to what extent the treatment was realized as intended, and to what extent clinical practice could be further improved. Retrospective analysis of the FLAME dataset was performed to evaluate the quality of tumor delineations and escalated dose levels. Prediction models were applied to demonstrate potential improvements to MRI-based tumor delineations and realized dose escalations on an individual basis. In chapter 2 it was investigated if upon delineation of mp-MRI, besides variation between observers also institutional differences apply. The soundness of individual delineations was verified with an

automatic tumor detection model that may ultimately serve as delineation QA tool in clinical practice. In chapter 3 the realized dose to the tumor was evaluated and compared with the highest achievable dose escalation as predicted by a KBP model to estimate how well the dose escalation to the visible tumor was realized with respect to the prescribed dose and with respect to the patient anatomy.

In chapter 4 and 5, the role for mp-MRI to future dose escalated treatment was investigated. This included DPbN treatment planning and response monitoring. In DPbN, the direct conversion from image parameters to prescription dose, may allow image value uncertainties to propagate into the planned dose distribution. In chapter 4 a test-retest planning study is described to estimate the robustness of DPbN to these uncertainties. In chapter 5 repeated quantitative MRI were analyzed to evaluate if early-responding tissue can be identified during treatment. Such tissue changes would mark the start of establishing predictive imaging biomarkers that could be used in adaptive treatment strategies.

In chapter 6 the findings of this thesis are discussed to answer the main questions: how well can mp-MRI-based focal dose escalation with an extreme dose to the prostate tumor be delivered, how can predictive models assist to improve such dose escalated treatment, and how can potential mp-MRI applications contribute to the evolution of dose painting strategies for prostate cancer.