Multiparametric MRI for focal dose escalation in prostate cancer radiotherapy

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CHAPTER 6

General Discussion

In this thesis, the performance of mp-MRI based focal dose escalation to the visible tumor in the prostate was investigated, and potential applications of mp-MRI to further development of dose-escalated treatment were explored. Although intraprostatic lesions may present locally or heterogeneously distributed throughout the prostate, present-day radiotherapy treatment involves irradiation of the entire prostate gland with a uniform dose. Over the past decades, multiple planning studies have demonstrated the feasibility of a focal boost to the intraprostatic tumor (Singh *et al.* 2007, Bossart *et al.* 2016, Garibaldi *et al.* 2016). Recently, the multi-center phase III FLAME trial (NCT01168479) has shown a statistically significant improvement of biochemical disease-free survival in favor of the dose-escalated arm without increased toxicity (Kerkmeijer *et al.* 2021). Focal dose escalation treatment has become a likely candidate for clinical introduction to improve recurrence free survival rates among intermediate to high-risk prostate cancer patients.

The quality of the delivered focal treatment requires accurate contouring of the intraprostatic lesion, and an optimal planned focal dose escalation to achieve the highest local tumor control. By retrospective analysis of the clinically used delineations and focal boost plans in the FLAME study, it was demonstrated that both delineation practice and escalated dose planning could be further improved, and that automated prediction models are valuable tools to realize those improvements. Furthermore, the role for mp-MRI as direct input for dose painting by numbers (DPbN) treatment plans is promising, since treatment plan quality was found robust to noise and day-to-day variation during image acquisition. During the course of treatment on the contrary, quantitative MRI could not detect early responding tissue. Tumor-response driven adaptive strategies for prostate cancer based on interfraction imaging are therefore considered unlikely to be established in the near future.

Delineating on mp-MRI

Detection of the intraprostatic tumor requires both anatomical and functional information. Mp-MRI combines anatomical and functional imaging in a single examination and is therefore an excellent candidate for focal dose escalation strategies. The generally accepted PI-RADS V2 guidelines recommend acquisition of anatomical T2-weighted and functional DWI for the detection and staging of prostate cancer, with a secondary role for DCE MRI (Weinreb *et al.* 2016). These guidelines lead to improved detection rates and more consistent staging (Kasel-Seibert *et al.* 2016, Padhani *et al.* 2019). However, to date no consensus on delineation practice has been established. It has been reported in various studies that in the absence of delineation guidelines significant interobserver variability is observed (Bratan *et al.* 2013, Rischke *et al.* 2013, Anwar *et al.* 2014, Steenbergen *et al.* 2015). Rischke *et al.* observed

substantial agreement between observers on T2-weighted and DCE-MRI and moderate agreement on DWI, which were considered insufficient for radiotherapy purpose. Steenbergen *et al.* found a median interobserver delineation standard deviation of 2.3 mm for intraprostatic lesions delineated on mp-MRI. In this thesis it was demonstrated that in a large multi-institutional patient cohort apart from the observer variability also institutional bias exists regarding relative use of the different MR sequences to delineate the intraprostatic lesions.

Interobserver variability as well as different institutional weighting of mp-MRI suggest that depending on the observer and the institution, the agreement between delineation and actual tumor boundary may vary. Relative large disagreements could result in a suboptimal targeted focal treatment and may affect the expected improvement in biochemical disease free survival. Linking institutional delineation preferences regarding MRI sequence weighting with disease free survival may give evidence to base delineation guidelines on. Unfortunately, for such evaluation institutional confounders as patient cohort, T-stage and treatment plan generation may require a statistical power beyond that of the FLAME dataset.

Consensus guidelines on the use of mp-MRI sequences for delineation of the intraprostatic lesion are hypothesized to minimize interobserver variability and institutional bias. Another approach to improve delineation practice is the introduction of probabilistic models that predict tumor presence. Histopathology based prediction models may reveal hidden patterns and assist to improve contouring consistency. Groenendaal *et al.* observed an area under the receiver operator curve (AUC) value of 0.70 for predicting tumor presence based on ADC and K^{trans} image parameters, using a logistic regression model that was developed based on ground-truth histopathology from prostatectomy patients (Groenendaal *et al.* 2012). Dinh *et al.* extracted higher order image features and cross-validated a logistic regression model on histopathology data from two institutions yielding an AUC value of 0.78 (Dinh *et al.* 2017). They also related per voxel the model predicted tumor probability with the number of observers that included the voxel in the tumor delineation, and found a significant correlation between tumor probability and group consensus (Dinh *et al.* 2016). However due to a large uncertainty range of this correlation no probability threshold could be identified to distinguish tumor from benign tissue and therefore delineations cannot be derived from the probability maps directly.

Over the past years availability of computational power has enabled development of deep learning approaches for the detection and classification of prostate cancer on MRI. Convolutional neural networks (CNNs) are the most commonly investigated deep learning approach and have the potential to outperform classical logistic regression models. To date, according to a recent systematic review on the detection of significant prostate cancer using

computer models, CNNs were found to perform similar to logistic regression approaches (Castillo T. *et al.* 2020).

In this thesis the per-patient tumor probability prediction was determined using an adapted version of the model developed by Dinh *et al.* to check the quality of the manual tumor delineations of the FLAME trial (Dinh *et al*. 2017). Using the AUC score to quantify the agreement with the predicted tumor probability map, clinical delineations with low AUC values were flagged and reviewed retrospectively. It was found that considerable improvements could be realized upon review, suggesting that applying this methodology in clinical routine could be beneficial for delineation practice.

Although these prediction models improve identification of tumor tissue and contribute to more accurate manual tumor delineations, specific parts of the intraprostatic lesion are systematically missed upon delineation on mp-MRI (Rosenkrantz *et al.* 2013, de Visschere *et al.* 2016, Lewis *et al.* 2017). De Visschere *et al.* concluded that the majority of missed tumors were low grade and organ-confined. Van Houdt *et al.* observed a relation between histopathological features and visibility on mp-MRI. The invisibility of tumors on mp-MRI was associated with heterogeneous morphology and low tumor density (van Houdt *et al.* 2020). Since mp-MRI fails to identify certain tumor characteristics, recent studies also investigated the benefit of an additional PSMA-PET scan. Draulans *et al.* proposed optimal tracer-specific window levels for PSMA PET to reduce interobserver delineation variability of the intraprostatic lesion (Draulans *et al.* 2020). In a review study, Zamboglou *et al.* reported that multimodal imaging using PSMA PET and mp-MRI offers complementary information for intraprostatic tumor delineation (Zamboglou *et al.* 2018). The combination of both image modalities results in high sensitivity and specificity. The addition of diagnostic PET to mp-MRI is believed to improve the detection of the intraprostatic tumor, better characterize the tumor biological properties, and ultimately decrease interobserver delineation variability. Although further research is demanded, the combination of PET and mp-MRI better addresses the present-day requirements for identification of intraprostatic lesions and is considered a realistic scenario to improve delineation consistency.

Focal dose escalation

The FLAME trial demonstrated an increase in 5-year biochemical disease-free survival from 85% to 92% with focal boosting of the intraprostatic lesion (Kerkmeijer *et al.* 2021). Post hoc analysis suggests a strong positive correlation between escalated dose level and the 5-year biochemical disease-free survival. The dose response curve suggests there is room for further improvement of focal dose escalation when further increasing the dose to the intraprostatic

lesion. For the remaining 8% of the patients in the dose-escalated arm of the trial, possible explanations of biochemical recurrence could be underdiagnosis of latent metastases, radioresistance, missed tumor tissue in the delineation, or a too low escalated dose to the intraprostatic lesion. For the latter explanation, in this thesis an anatomy-based prediction model was shown to be able to predict an escalated dose in the tumor that could be achieved upon replanning. Since the FLAME trial has demonstrated that focal boosting is relevant to increase biochemical disease-free survival rates, the KBP prediction model that was evaluated in this thesis may be valuable in future clinical setting to optimally target the intraprostatic tumor.

For the treatment plans where unfavorable patient anatomy or tumor location caused an undertreatment of the intraprostatic tumor, solely focal escalated EBRT might not be the most suitable treatment option. Alternative strategies to achieve steeper dose gradients in the unfavorably located tumor may include minimal invasive combined EBRT and brachytherapy boost to the tumor as investigated in the TARGET trial (Sanmamed *et al.* 2020), or MR-based treatment planning and delivery on an MR-Linac, leading to reduced target volume margins (Murray J, *et al.* 2019). Insertion of an endorectal balloon reduces anorectal doses which gives a therapeutic window to increase radiation dose at the dorsal side of the prostate (Smeenk *et al.* 2011). As an alternative to an endorectal balloon, a hydrogel spacer can be simulated between prostate and rectum to separate prostate and rectal wall, and followed by implantation if shown beneficial for the patient (Vanneste *et al.* 2016, van Wijk *et al.* 2017).

The presented KBP model in this thesis was specifically developed to indicate achievable maximum tumor dose in the prostate and was tested on the treatment plans in the dose-escalated arm of the FLAME study. KBP models published so far were developed to predict DVH parameters of OARs surrounding the target volume (Wu *et al.* 2009, Yuan *et al.* 2012, Good *et al.* 2013, Wall *et al.* 2018). Such predictions could guide the clinical planning optimization process to reduce OAR doses. Incorporation of OAR dose DVH parameter prediction in the KBP model presented in this thesis is therefore considered as the next step to produce a plan QA tool dedicated for clinical focal dose escalation in prostate cancer.

Current state-of-the-art automated plan quality optimization approaches rely on KBP, protocol-based automatic iterative optimization, and multi-criteria optimization (MCO) (Hussein *et al.* 2019, Cozzi *et al.* 2019, Ge *et al.* 2019, Moore 2019). In protocol-based automatic iterative optimization, using a predefined protocol, the objectives and constraints are updated for the next iteration (Gintz *et al.* 2016, Kusters *et al.* 2017) In MCO optimization parameters are tuned to optimally balance the target coverage and spare organs at risk. Erasmus-iCycle is a fully automated MCO algorithm that allows to produce Pareto-optimal treatment plans (Breedveld *et al.* 2012). Presently, automated plan optimization is a standard

module of commercial treatment planning systems. Janssen *et al.* reviewed Pinnacle's AutoPlan module to conclude that even commercial auto-plan solutions should be audited with independent KBP methods (Janssen *et al.* 2019). Future automated planning may involve the combination of KBP and MCO, for which higher plan quality in less time was found as compared to both methods separately (Teichert *et al.* 2019).

Dose painting

Delineation guidelines and incorporation of a prediction model are hypothesized to ease clinical delineation practice with the purpose of escalating the radiation dose to a pre-specified region. The resulting manual delineation of the intraprostatic tumor reflects the binary decision of the observer based on the available clinical and image information. To meet closer with the actual tumor biology characteristics, DPbN omits manual contouring and allows to produce a dose prescription at the resolution of the functional images. The direct conversion from image parameters to dose prescription however, potentially allows image value uncertainties to impact the planned dose distribution. In this thesis it was shown that applying a straightforward first or second order polynomial mapping function to image-derived probability maps of repeated mp-MRI examinations, DPbN planning was robust to image value uncertainties and resulted in equivalent dose distributions. This conclusion is a precondition for the further investigation of DPbN and acceptance as an alternative strategy to contour-based dose escalation.

DPbN requires a mapping function between a (composite) image characteristic and prescription dose. Most studies have adopted a linear relationship, inspired by Vanderstraeten *et al.* (2006). Bowel *et al.* presented polynomial and sigmoidal mapping functions (Bowen *et al.* 2009). Such mathematical mapping functions are straightforward to implement and are applicable to image-derived parameter maps or composite parameter maps. On the other hand, these mapping functions are not validated and oversimplify the true dose-response. In addition, the upper dose limit is usually based on prescribed escalation dose levels from clinical trials, which does not necessarily guarantee sufficient tumor control in all tissue.

As an alternative to DPbN, prescription dose could be related to radiobiological tumor characteristics. In biological optimization generally the tumor control probability (TCP) is chosen as target objective to optimize the dose distribution for (Her *et al.* 2020). In addition, biological optimization may simultaneously minimize normal tissue complication probability (NTCP). Most planning studies incorporate a phenomenological TCP model with radiobiological parameter values derived from clinical data (Levegrün *et al.* 2002, Kim *et al.* 2006). Biofocused radiotherapy (BiRT) incorporates histopathology-validated machine

learning methods to derive radiobiological feature maps from imaging and produce a TCP objective map for biological optimization (Haworth *et al.* 2018).

Several studies have reported on the relation between pretreatment ADC values and pathological Gleason score as a predictor of biochemical recurrence. Ghobadi *et al.* postulated a patient-specific dose response with incorporation of the Gleason score in the linear-quadratic model (Ghobadi *et al.* 2016). Casares-Magaz *et al.* inserted cell densities derived from ADC values into a linear-quadratic model to estimate individual tumor control probability (TCP) levels (Casares-Magaz *et al.* 2016). Grönlund *et al.* combined these findings to demonstrate a formalism in which ADC values were related to Gleason score driven dose-responses and dose painted treatment plans were generated that yielded higher TCP and similar dose to normal tissue as compared to homogenous dose prescription (Grönlund *et al.* 2018, Grönlund *et al.* 2021). Although biological optimization is a promising method to yield dose painted treatment plans, uncertainties of radiobiological parameters and models need to be addressed first before considering patient studies.

Both DPbN and biological optimization strategies prescribe a heterogeneous dose distribution to the prostate gland. During treatment anatomical movements may introduce a relative displacement of the delivered dose, which in case of dose painted plans has consequences for the actual received dose by the prostate tissue. Probabilistic planning methods have been developed and evaluated that incorporate optimization uncertainties and perform a robust optimization (Shusharina *et al.* 2018, Miura *et al*. 2019, Bortfeld *et al.* 2021). Thereby image value uncertainties as well as modelling and geometric uncertainties can be accounted for in the generated treatment plan.

DPbN treatment planning in principle could also de-escalate the radiation dose based on image characteristics representing benign prostate tissue. Ultimately such de-escalation to benign tissue below conventional doses is considered beneficial for the patient, but it is challenging to prove this hypothesis without risking insufficient local tumor control. One randomized study for head and neck cancer treatment avoided this risk by defining a dose escalated region first (Heukelom *et al.* 2013). One treatment arm received focal escalated treatment, in the other arm the escalated dose was redistributed based on image characteristics. Thereby the de-escalated part of the escalated dose region still received a dose level above conventional prescription. Such exploratory studies are essential to investigate safe lower limits of radiation dose to tissues considered benign.

Imaging biomarkers

Quantitative imaging biomarkers in prostate radiotherapy are currently primarily used in research on treatment response monitoring and to a smaller extent on dose painting (Gurney-Champion *et al.* 2020). Regarding treatment response monitoring, biomarkers derived from quantitative MRI could prove valuable for image-based adaptive treatment strategies. In order to deliver adaptive therapy, actionable changes occurring early during the course of treatment are required. In this thesis it was investigated if MRI was capable of recording early treatment changes to the tumor and surrounding tissue. In an extreme-hypofractionated setting with an MRI at each of the five fractions, significant early changes to MRI parameters were not observed. Although this study was not powered to detect small or individual changes, results show that adaptive treatment based on the investigated MRI parameters is not evident.

In this thesis imaging biomarkers to evaluate prostate cancer treatment response were investigated in a hypofractionated radiotherapy schedule. In a conventional fractionation schedule primarily ADC has been subject of response monitoring research. Park *et al.* observed significant increase of tumor ADC value at three time points during and after treatment, with respect to the pretreatment ADC value (Park *et al.* 2012). Also, for other tumor sites ADC values were found to change during conventionally fractionated treatment: cervical cancer (Liu *et al.* 2009), rectal cancer (Lambrecht *et al.* 2012), and brain metastases (Mahmood *et al.* 2017). Both the high fraction dose as well as the relative long interval of one week between radiation fraction and MRI examination could be hypothesized to explain why early ADC changes were not observed in this thesis.

Although quantitative imaging for radiotherapy has been studied for decades, multiple issues need to be addressed before clinical introduction is to be considered. Dose response monitoring, timing and optional early treatment adaptation require imaging biomarkers changes that are predictive of patient outcome for a given radiation dose. For dose painting based on quantitative imaging biomarkers, establishing which voxels of the original tumor are related to poor outcome is challenging. In addition, sophisticated trial design is required to prevent unethical dose de-escalation. As long as the imaging biomarker of interest is not proven to be predictive, sub regions in the prostate may receive an unjustified dose de-escalation based on the imaging biomarker with less tumor control as compared to conventional treatment. In order to identify imaging biomarkers for treatment response monitoring or dose painting purpose, large multicenter studies are required to demonstrate clinical applicability (Gurney-Champion *et al.* 2020).

Hypofractionation

In this thesis an assessment of tumor delineations and focal escalated dose distributions was performed on treatment plans that were delivered in 35 fractions. The presented automatic evaluation tools could lead to more consistent delineation practice and higher escalated doses whenever such treatment is delivered in routine clinical practice. Over the past years moderately hypofractionated treatment has become standard of care and extreme hypofractionation with only five treatment fractions is expected to perform even better in terms of patient outcome and clinical workload. Therefore, for patients with intermediate to high-risk disease, trials have been performed that combined extreme hypofractionation and focal dose escalation, and promising preliminary results have been presented (Draulans *et al.* 2020, Murray *et al.* 2020, Nicholls *et al.* 2020). Supposing positive long-term results of these trials, the applicability of the presented work in this thesis to extremely hypofractionated focal dose escalation can already be considered.

The prescribed focal escalated dose distribution is a direct result of the delineation of the intraprostatic lesion. The accuracy of the dose that is actually delivered to the intraprostatic lesion is dependent on the ability of the treatment planning system to realize steep dose gradients and on anatomical changes during treatment. For the latter, the relative high number of treatment fractions with conventional fractionation causes blurring of the planned dose distribution upon treatment delivery and is therefore rather forgiving to small delineation inaccuracies. With fewer treatment fractions, the blurring effect will decrease and delineation inaccuracies will have more impact on the delivered dose. Therefore, precise definition of the tumor boundary is more relevant in an extreme-hypofractionated setting.

The KBP model presented in this thesis was developed using features from planned dose distributions for delivery with conventional fractionation. For application to hypofractionated dose escalation plans, the methodology would remain the same. Anatomical features need to be derived from a new dataset consisting of patients treated with hypofractionated focal dose escalation, and be related to the achieved dose to the tumor. In the FLAME consortium both the Hypo-FLAME (NCT02853110) and the Hypo-FLAME 2.0 (NCT04045717) study would be suitable datasets to build a tumor dose prediction model on. Such model could for example be a valuable tool to explain the discrepancy between the intended dose escalation of 50 Gy to the visible tumor and the realized median dose escalation of 44.7 Gy in the HypoFLAME study (Draulans *et al.* 2020).

The robustness of DPbN treatment plans to image uncertainties was evaluated up to the treatment planning stage and independent from the fractionation scheme. DPbN should therefore be equally applicable to extreme hypofractionated as conventional

hypofractionated focal dose escalation treatments. Since hypofractionated treatment is always preceded by online position verification, setup errors are avoided. Therefore, mainly blurring of the planned dose due to interfraction motion impacts the delivery of the DPbN plan.

The applicability of quantitative MRI for dose response monitoring and potential adaptive strategies in an extreme hypofractionated treatment setting was presented in this thesis. There were no strong indications for a dose response early during treatment on a population basis. Individual early changes were detected but within the uncertainty ranges of the image parameters. Additional research to the outcome of the investigated patients in this study may raise hypotheses on tissue response on an individual level. Further optimization of image protocols is also desired to reduce the uncertainty bandwidth and ease detection of significant early treatment changes.

Conclusions

The FLAME trial has demonstated that mp-MRI can be utilized to define the intraprostatic tumor and deliver a focal dose escalated treatment with improved biochemical disease-free survival. In this thesis it was concluded that delineation guidelines are desired to minimize institutional bias towards interpretation of mp-MRI and ultimately improve delineation consistency and accuracy. Prediction tools for tumor localization and dose escalation were shown to yield potential improvements to clinical cases and are therefore considered valuable tool for future clinical practice of focal dose escalation treatment.

Mp-MRI can furthermore find application in future dose escalation strategies. For DPbN treatment planning it was found that mp-MRI value uncertainties would not significantly impact planned dose distributions and thereby enable further investigation of DPbN as a more sophisticated dose escalation treatment strategy. During the course of extreme-hypofractionated treatment however, repeated MRI did not reveal early responding tumor tissue to potentially adapt treatment to. It is therefore not likely that these will result in actionable imaging biomarkers in the near future to allow for response-based treatment adaptations in hypofractionated radiotherapy of prostate cancer.