Multiparametric MRI for focal dose escalation in prostate cancer radiotherapy

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Summary

For patients with intermediate to high-risk prostate cancer, focal dose escalation to the intraprostatic lesion has been hypothesized to improve local control with no additional normal tissue complications as compared to conventional uniform dose prescription. Recently, the FLAME trial demonstrated that focal dose escalation significantly improves 5-year biochemical disease-free survival rates, without increased toxicities or reduced quality of life. Since a clinical benefit of focal dose-escalated treatment was found, a technical analysis of the FLAME dataset is useful for the further optimization of focal dose escalation strategies. In Chapter 2 and 3 of this thesis the FLAME dataset is analyzed and prediction models are applied to evaluate the soundness of tumor delineations and escalated dose levels. Chapter 4 and 5 of this thesis describe the applicability of multiparametric (mp-)MRI for dose painted treatment, and the value for early response-based adaptive treatment.

In **Chapter 2** the soundness of **clinical delineations** of the intraprostatic tumor in the FLAME trial is evaluated. It was found that besides interobserver variability, significant institutional bias exists regarding the weighting of T2-weighted, DWI and DCE-MRI sequences to delineate the intraprostatic lesion. It is therefore recommended to involve weighting of MRI sequences in the development of delineation guidelines for intraprostatic lesions on mp-MRI. In addition, a tumor prediction model was shown to be capable of identifying manual delineations that needed to be corrected. This demonstrates the added benefit of prediction models in the clinical workflow.

The realized level of dose escalation during treatment planning depends to a large extent on the anatomy of the patient and the complexity of the dose optimization process. In **Chapter 3** dose volume histogram (DVH) parameters of the **planned dose distributions** of the FLAME trial are reported, showing how well a focal dose escalation up to 95 Gy could be planned. In the dose-escalated arm of the trial, a median $D_{98\%}$ of 84.7 Gy was observed, and 99% of the patients received a significant dose escalation above 82.4 Gy. During treatment planning, an unfavorable tumor location with respect to healthy surrounding organs results in a lower than intended planned dose escalation. To assist during the treatment planning procedure, a regression model was developed that estimates the achievable dose escalation to the tumor as a function of patient anatomy. To validate the model, a random subset of dose-escalated treatment plans was replanned. For this subset a strong correlation ($r = 0.89$) was found between predicted increase in tumor $D_{98\%}$ and replanned tumor $D_{98\%}$. It was concluded that the model may assist future clinical dose escalated treatment planning to reach the highest achievable dose to the tumor.

With mp-MRI both anatomical and functional information is acquired. For this reason, an mp-MRI examination is recommended for identifying the intraprostatic lesion and for defining the target for focal dose escalation. Currently, most research on mp-MRI focusses on improved identification of the intraprostatic lesion. With the positive outcome of the FLAME trial, new applications of mp-MRI can be considered for further development of focal dose escalation for prostate cancer.

While in the FLAME trial a uniform escalated dose was prescribed to the delineated intraprostatic lesion, in reality the tumor can be spatially heterogeneous and the boundary is not discrete. Circumventing the binary process of manual contouring and to reflect the biological characteristics of the tumor, dose painting by numbers (DPbN) prescribes a heterogeneous dose distribution to the prostate gland and is directly related to imaging features. The omission of manual interaction however potentially allows measurement uncertainties in image data to impact the planned dose distribution. In **Chapter 4**, a repeatability analysis is performed to quantify the applicability of **dose painting by numbers**. The intra-class correlation (ICC) coefficients used as repeatability measure, improved from 0.84 to 0.93 from acquired imaging data towards planned dose distributions. It was concluded that variation in imaging data had a minimal impact on the realized planned dose distributions, which suggests that DPbN treatment planning is a realistic alternative to contour-based dose painting.

While mp-MRI has proven its use for focal dose escalated treatment and was shown suitable for DPbN treatment planning as well, during the delivery of the treatment, mp-MRI may also record radiation response of the tumor. In **Chapter 5** the value of **quantitative MRI biomarkers during radiotherapy** for the purpose of image-based treatment adaptation was investigated. T2 and ADC maps of six MRI examinations during hypofractionated treatment were analyzed. No early treatment-induced changes to the tumor on a population basis were found. It is therefore unlikely that in the near future actionable imaging biomarkers will be discovered for early-treatment adaptations in hypofractionated prostate radiotherapy.

In this thesis a technical evaluation of focal dose escalation of prostate cancer was performed and the role of mp-MRI for future optimization of this treatment strategy was investigated. The technical evaluation demonstrates the need for MRI-based delineation guidelines of the intraprostatic tumor, and that models could contribute to more consistent tumor delineations and optimization of the escalated dose to the tumor. The presented findings with respect to future optimization of this treatment strategy show that mp-MRI is applicable in the planning stage of the treatment for the purpose of dose painting, and leave little room for early adaptive treatment based on mp-MRI.