Individualizing prostate cancer treatment

Summary

Prostate cancer (PCa) is the second most commonly diagnosed cancer for men, and therefor forms a topic of significant research interest. Especially low-intermediate risk PCa, which forms 40% of the newly diagnosed PCa, has a variety of viable treatment options. The options include passive treatments such as active surveillance, and active treatments such as radiotherapy and prostatectomy. Within treatment types there are still a number of options, such as within radiotherapy the choice exists between brachytherapy or external beam radiotherapy (EBRT), and additional options, such as hormonal therapy or rectum sparing devices can be considered. This, combined with an increasing number of biomarkers make that PCa is an excellent candidate for improvement via personalized medicine.

The importance of personalized medicine has become progressively evident over the past few years, focusing on patient variations, outcome predictions and patient preferences. An important step towards personalized PCa treatment would be a clinical decision support system (DSS), that aids optimizing treatment selection. DSS are typically software applications such as recursive partitioning analyses models, nomograms or websites such as https://www.ai4cancer.ai. A DSS is used to support the groups responsible for deciding on patient treatment, such as the physician, the tumor board and the patient, in making a knowledgeable decision regarding treatment options. The development of such DSS was the primary focus of this thesis.

In **Chapter 3** we provided an overview of existing literature on the topic of DSS in the field of PCa. It was found that a large number of diagnosis and staging DSS are becoming available as well as tools that improve cancer detection, predicting treatment outcome and outcome stratifications. However, limited DSS for treatment selection were found in this literature study, which were mostly centered around EBRT. A lack of DSS for other treatment modalities suggests that the development of new tools are necessary to compare objectively different treatment modalities. Additionally, the field of patient informed decision-making is still in its infancy, but essential for the growth towards individualized medicine.

Other chapters in this work focus on developing, improving and challenging treatment DSS both within the field of EBRT, as well as interdisciplinary comparisons.

Chapter 4 describes the development of a Virtual Implantable Rectum Spacer (V-IRS) that can be used to support the decision for the implantation of an implantable rectum spacer (IRS) for a specified patient or not. An IRS is a device (such as a hydrogel or a biodegradable balloon implant) that is placed between the anorectum wall and the prostate prior to the start of EBRT. This device spares the rectum from high dose levels and reduces the risk of long term treatment related side-effects such as bleeding. The V-IRS uses image deformation on a CT

scan of a patient to render a virtual CT scan of the same patient with a V-IRS. The advantage of this method is that a CT of a patient with an IRS can be generated and made available for treatment planning purposes without the real implantation of the IRS itself. Moreover, we used this method to develop a DSS that, instead of only looking at the improved dose reduction by implanting the IRS, also calculated the toxicity risk reduction and the cost-effectiveness (CE) for comparison. This allows for a decision based not only on dose reduction, but also on the health gain and the costs associated with the health gain. We tested this V-IRS in the following manner: we generated virtual CT scans and performed dose planning on these. We then calculated relevant dose metrics, toxicity risk and performed a CE analysis. This was repeated on CT scans of the same patients with a real IRS, and the results were compared to those of the virtual CTs. The V-IRS resulted in the same classification (place an IRS or don't place an IRS) as the real IRS.

In this study we found that the implantation of an IRS is not cost-effective for all patients, but does provide significant benefit for some, so individual patient assessment could improve the quality of care. We concluded that the V-IRS approach in combination with a toxicity model and a CE analysis can serve as the basis for a decision support system for the implantation of either a hydrogel IRS or a rectum balloon implant.

To expand on the DSS described in the previous chapter, in **Chapter 5** we developed an isotoxic method integrating genetic markers of rectal radio-sensitivity combined to integrate into this DSS. The method calculates the maximum dose per fraction that can be given without exceeding an upfront determined limit for the risk of toxicity, rather than calculating the risk of toxicity resulting from a given dose.

The results show that a higher prescribed dose should be given to improve tumor control, and can be safely administered when combined with an IRS.

The isotoxic model integrating genetic markers for rectal toxicity developed in this study can be used to evaluate a treatment plan, and test how much dose can be given without causing excessive damage to the rectum. Thus sparing the organs at risk at a chosen described level while optimizing the TCP. In combination with the V-IRS, this method can serve as the basis for a DSS for the implantation of an IRS.

One type of IRS is the saline-filled biodegradable balloon implant. **Chapter 6** provides an evaluation of the balloon volume stability that is based on weekly cone-beam CT measurements during the full course of EBRT, because a RBI volume decrease can be expected over time. In this study, we analyzed the dosimetric consequences of this phenomenon and predicted the increase in risk of late rectal bleeding (LRB) resulting from a shrinking balloon implant to assess its potential clinical impact. We concluded that despite that the weekly RBI shrinkage was significant,

neither significant increase in absolute volume or the anorectum receiving at least 75 Gy, nor in predicted LRB risk were observed over the full treatment course. Only when the prostate-rectum distance decreased to under 1 cm a treatment plan adaptation would be advisable. The advantage of this work with relation to the previous chapters is that it shows that the exact shape of the V-IRS is not crucial to proper classification considering treatment advice. This is important as the exact shape and position of both the anorectum and the IRS are difficult to accurately predict from a single CT scan.

In **Chapter 7** we developed an interdisciplinary DSS, which would aid in the treatment selection of either EBRT or radical prostatectomy (RP) and tested this on a synthetic patient dataset. We validated the DSS against published clinical studies and set up an in silico trial for patients between 75 and 80, eligible for both RP and EBRT. We also assessed the CE of a treatment allotment strategy based on the DSS compared to a randomized treatment allotment strategy. Our first hypothesis was that we could accurately replicate results from published studies, which we aimed to confirm by generating synthetic datasets with clinical parameters similar to published trials. The DSS largely replicated the published results accurately. The relative differences between the treatment modalities and fractionation plans were replicated by the model, and the conclusions of the DSS and the studies agreed. We also performed an in silico trial using the DSS, exclusively including elderly patients both without and with prior ED and found that for the first group EBRT was preferred, and for the second RP performed better in terms of QALYs. Additionally, we hypothesized that a treatment selection strategy based on the DSS would improve tumor control, reduce toxicity, and improve CE as opposed to randomized treatment selection. Our CE analyses suggest that not only do the costs of treatment decrease with the application of a DSS, but the number of QALYs also increases, making the integration of a DSS dominantly cost-effective compared to current clinical practice. The expected cost savings within the Netherlands when using a DSS could be as high as EUR 3.8 million over five years, assuming 2400 patients are affected every year. Additionally, the number of patients with recurrence after treatment could be reduced slightly by 2%.

This chapter lays the groundwork for a detailed, personalized treatment DSS that aids in the choice between EBRT and RP for low to intermediate risk PCa patients. This DSS could be used for in silico clinical trials when applied to a synthetic dataset, which would be a valuable precursor to clinical trials.

Chapter 8 provides a general discussion and future perspectives, which is closed with a concluding message. It is discussed that one strength of this thesis is that it lays the groundwork for an extensive DSS for treatment selection for PCa. A variety of methods is presented in this work including the iso-toxic method, incorporating

new biomarkers into existing models, the use of synthetic patient datasets, and in silico clinical trials, all of which could aid in the development of future DSS.

Future works should include the improvement, optimization and validation of the DSS developed in this thesis. It is also advisable to combine the IRS DSS and the EBRT versus RP DSS into a single framework and expand this with other treatment modalities such as watchful waiting and brachytherapy. Finally, the next step towards personalized treatment for PCa would be to combine the DSS framework with a patient decision aid, so that patient preferences would provide valuable input to the DSS and the DSS could be used to customize information for the patient decision aid.