Automated proton therapy planning: clinical validation for head-and-neck cancer and chordoma

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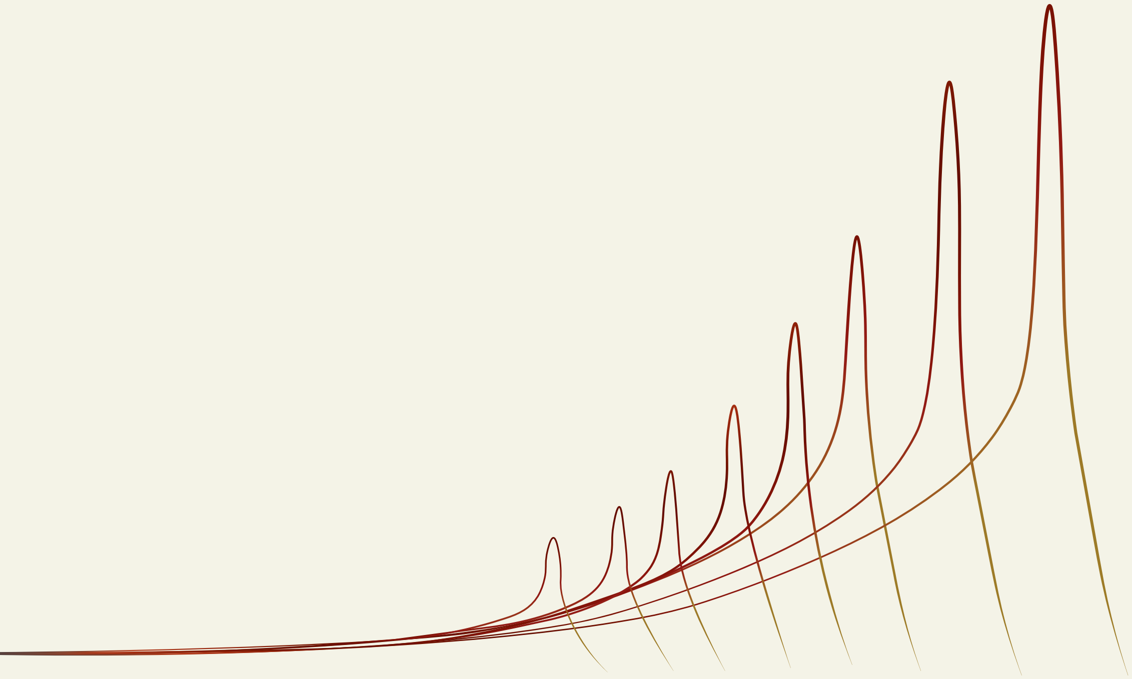

Chapter 8

Summary

This chapter provides a summary of the main findings presented in this thesis. A Dutch summary ('Nederlandse samenvatting') can be found in de Appendices.

Chapter 1: General Introduction

Intensity-modulated proton therapy (IMPT) is a form of radiotherapy that plays a central role in the curative treatment of selected patients with tumors in the head and neck region, including head and neck cancer (HNC) and skull base chordomas. The goal of radiotherapy is to achieve tumor control, while minimizing radiation-induced damage to surrounding organs at risk (OARs). Proton beams exhibit a sharp distal dose fall-off (Bragg peak), resulting in minimal to no exit dose, thereby reducing radiation exposure to healthy tissues while a high radiation dose can be delivered to the target volume.

Prior to treatment, a proton therapy plan with a dose distribution is created. Radiotherapy treatment planning involves several trade-offs between competing clinical objectives and typically requires multiple rounds of optimization, including manual adjustments of objective weights and the addition of supplementary planning goals. This is particularly challenging in HNC, where multiple targets are located close to numerous OARs, and even more so in skull base chordomas, where tumors are adjacent to highly radiosensitive neural and vascular structures. As a result, manual treatment planning is labor intensive, time consuming, and highly dependent on planner expertise. Automated treatment planning offers a potential solution by reducing hands-on planning time while potentially improving plan quality and consistency.

Erasmus-iCycle is such an automated planning approach, guided by a treatment site specific wish-list consisting of a list with prioritized objectives and constraints that reflect the clinical requirements. Before automated IMPT planning solutions can be implemented in clinical practice, their performance must be validated to ensure compliance with these clinical requirements. This thesis therefore focuses on the development and clinical validation of fully automated IMPT planning using Erasmus-iCycle for HNC and skull base chordoma.

The specific objectives of this thesis were to:

1. Develop and clinically validate fully automated IMPT planning through dosimetric and blinded physician comparison (**Chapters 3 and 4**).
2. Evaluate the dosimetric impact of adaptive proton therapy and the addition of transmission beams to IMPT (**Chapters 2 and 5**).
3. Develop and clinically validate fully automated IMPT planning for challenging cases where clinical objectives were not always achieved **(Chapters 5 and 6)**.

Chapter 2: Dosimetric Impact of Adaptive Proton Therapy in Head and Neck Cancer - A Review

One potential application of automated IMPT planning is adaptive proton therapy (APT), in which the treatment plans are adapted to the (daily) anatomy of the patient. Anatomical changes during treatment, such as tumor shrinkage, weight loss or radiotherapy-induced edema, may lead to differences between the planned and delivered dose distribution. However, it remains unclear when and how often proton plan adaptations are required for HNC and how these adaptations affect target coverage and doses to OARs. The dosimetric impact of APT in HNC was therefore examined in Chapter 2 through a review of the literature. It was found that plan adaptations were primarily triggered by deteriorations in target coverage, and that APT restored adequate coverage. In most cases, a single APT intervention was sufficient to restore the target coverage, while additional adaptations improved the target coverage further. OAR doses generally remained similar or decreased slightly after APT. A wide range of adaptation timings and frequencies was reported, and no clear conclusions could be drawn regarding the optimal timing of APT. These findings highlight the clinical need for APT, as well as the potential role for automated planning within APT. Given that the replanning process is time consuming and takes several hours to days before an adapted plan is clinically available, automated IMPT planning tools are essential to reduce workload and support efficient and timely adapted IMPT treatment.

Chapter 3: Validation of Fully Automated Robust Multi-criterial Treatment Planning for Head and Neck Cancer IMPT

Automated robust multicriterial IMPT planning for HNC using Erasmus-iCycle was investigated in Chapter 3. To this purpose, first a treatment site specific wish-list for HNC was developed. Definition of an initial wish-list is based on the clinical planning protocol and discussions with radiation oncologists and planners, whereafter this initial wish-list was applied to a limited number of patients. These are used to guide an iterative wish-list tuning process. During the iterative wish-list tuning, plans were evaluated, and if further enhancements were considered feasible, the wish-list is updated. After the HNC wish-list was developed, automated plans were generated for a total of 30 patients with oropharyngeal of hypopharyngeal cancer, and the resulting IMPT plans were compared to the manually created IMPT plans of these patients. The automatically generated IMPT plans had similar (robust) target coverage, and consistently lower doses to OARs and statistically significant lower normal tissue complication probability (NTCP) for xerostomia and dysphagia as compared to clinical IMPT plans. Importantly, all automated plans met the predefined clinical constraints without requiring manual intervention. This demonstrates that fully automated planning can produce consistent, high-quality IMPT plans for HNC, independent of planner experience, while eliminating hands-on planning time. These results provide the basis for further clinical validation through blinded qualitative assessment in Chapter 4.

Chapter 4: Qualitative Blinded Clinical Assessment of Automated and Manual IMPT Plans for Head and Neck Cancer

While Chapter 3 demonstrated highly favorable dosimetric advantages of automated IMPT planning, clinical acceptability ultimately depends on physician evaluation. In Chapter 4, a qualitative clinical validation of the fully automated IMPT planning approach was performed for HNC. To this purpose, the same cohort of 30 HNC patients from Chapter 3 was used. For each patient, the manually generated clinical IMPT plan and the corresponding fully automated plan were included. Three experienced HNC radiation oncologists (ROs) evaluated these plans independently from each other, in a blinded manner without knowing whether they were generated automatically or manually. The observers assessed plan quality based on target coverage, OAR sparing, and overall clinical acceptability. In addition, they were asked to indicate their preference between the two plans for each patient if any. All automated IMPT plans were considered clinically acceptable, and in the vast majority of the cases, the three ROs unanimously preferred the automated plan. The manual plan was never preferred. Target coverage was considered equivalent, while target conformality and sparing of both serial and parallel OARs were generally rated superior in the automated plans. Overall, this chapter confirms that fully automated IMPT plans are not only dosimetrically comparable or superior, but are also clinically acceptable and preferred according to experienced radiation oncologists. These findings support future clinical implementation and the clinical potential of automated IMPT planning tools.

Chapter 5: Validation of Fully Automated IMPT with and without Transmission Beams for Nasopharyngeal cancer

In Chapter 5, fully automated IMPT planning was further developed and validated for nasopharyngeal cancer (NPC), a particularly challenging subgroup within HNC due to the close proximity of target volumes to critical serial OARs, such as the brainstem and optical system. In these patients, achieving adequate target coverage while respecting OAR constraints is often difficult, and clinical plans may require compromises. To address this, a treatment site-specific wish-list for NPC was developed for use with Erasmus-iCycle, which optimized the target coverage as a heavily weighted objective instead of a constraint. In addition to conventional IMPT, the potential benefit of incorporating transmission beams (TBs) to IMPT was investigated in this study. TBs use high-energy proton beams with the Bragg peak positioned beyond the patient, potentially enabling sharper lateral dose gradients and improved sparing of surrounding tissues. Automated treatment plans were generated using the same wish-list for a cohort of 21 NPC patients using two techniques: 1) IMPT alone and 2) IMPT combined with TBs. The automated plans were compared with manually generated clinical IMPT plans using dosimetric parameters for target coverage and OAR doses, as well as NTCP scores. The results showed that automated IMPT plans achieved target coverage similar to or improved compared to clinical plans, especially in cases with compromised target coverage. However, the addition of TBs did not further improve target coverage. For serial OARs, significant dose reductions were observed, especially in the brainstem and optical system, which were more pronounced with the addition of TBs. Similarly, dose reductions in most parallel OARs were observed. NTCP for dysphagia remained equal, and NTCP for xerostomia was significantly lower in the automated plans. Overall, this chapter demonstrated that automated IMPT planning is able to generate high-quality treatment plans for challenging cases such as NPC, with incorporation of TBs providing additional improvements for dose to serial OARs.

Chapter 6: Validation of Fully Automated IMPT Treatment Planning for Skull Base Chordomas

Finally, fully automated IMPT planning using Erasmus-iCycle was developed and validated for skull base chordomas. These tumors require very high radiation doses to achieve tumor control and are located in close proximity to critical neural and vascular structures, making treatment planning highly challenging. In clinical practice, IMPT planning for these tumors often requires trade-offs with compromises in target coverage and/or violation of serial OAR constraints in consultation with the treating RO. After a skull base chordoma wish-list was developed, automated IMPT planning using Erasmus-iCycle was applied to ten patients. Dose/volume parameters for targets and OARs were compared between automated and manual IMPT plans. In case of inferior target coverage due to OAR constraints, patient-specific wish-list adjustments were applied, permitting limited serial OAR constraint exceedance similar to clinical plans. Overall, automated plans provided similar target coverage to clinical plans with dose reductions in most serial OARs. While manual plans often required concessions leading to OAR constraint exceedance, automated planning consistently maintained these limits. Patient-specific adjustments to the automated planning strategy further enhanced the target coverage in case of target underdosage, while maintaining or lowering OAR doses relative to the clinical plans. These findings demonstrate that automated IMPT planning for this challenging patient cohort results in similar or better plan quality for most patients. However, in individual patients (although few), adjustments to the automated planning strategy are necessary, highlighting the potential of a posteriori MCO to enable patient-specific trade-offs between target coverage and serial OAR constraint exceedance.

Chapter 7: General Discussion

In Chapter 7, the main findings of this thesis are discussed and placed into a broader context. A key motivation for this work is that manual IMPT treatment planning is a time-consuming and resource-intensive process, representing a major bottleneck in the radiotherapy workflow. This is particularly relevant given the increasing number of patients requiring radiotherapy and the ongoing staff shortage. Automated IMPT planning has the potential to substantially reduce workload while maintaining or improving plan quality. The growing clinical interest in APT further emphasizes the need for fast and reliable planning solutions.

The development of fully automated IMPT planning in this thesis was based on treatment site-specific wish-lists. These wish-lists require careful configuration through iterative tuning in collaboration with clinicians and planners, and their quality is crucial for achieving clinically acceptable results. Although this tuning process is time-consuming, once established, a wish-list can be consistently applied across patient cohorts, enabling standardized high-quality plan generation and reducing hands-on planning time.

For clinical implementation, several considerations remain important. Automated planning systems must comply with regulatory requirements, such as the European Medical Device Regulation (MDR). Furthermore, continuous quality assurance and periodic updates of wish-lists are required to ensure that planning strategies remain aligned with evolving clinical protocols and technological developments.

Future developments in automated proton therapy planning include the integration of deep learning-based approaches and further automation of workflow components such as OAR and tumor contouring. While deep learning planning methods offer fast plan generation, they depend on large datasets and the quality of prior plans. In contrast, the Erasmus-iCycle approach used in this thesis is independent of prior datasets, but requires longer optimization times. A combination of both approaches may enable rapid and high-quality automated planning in the future.

In addition, automated planning provides a framework for evaluating advanced treatment techniques such as TBs (as shown in this thesis) and proton arc therapy. These techniques increase planning complexity, highlighting the importance of automation.

In conclusion, this thesis developed and validated automated IMPT planning using Erasmus-iCycle for HNC, NPC and skull base chordomas. Automation plays a key role in improving efficiency, consistency, and scalability of proton therapy and is expected to become an essential component of future adaptive and advanced treatment techniques.