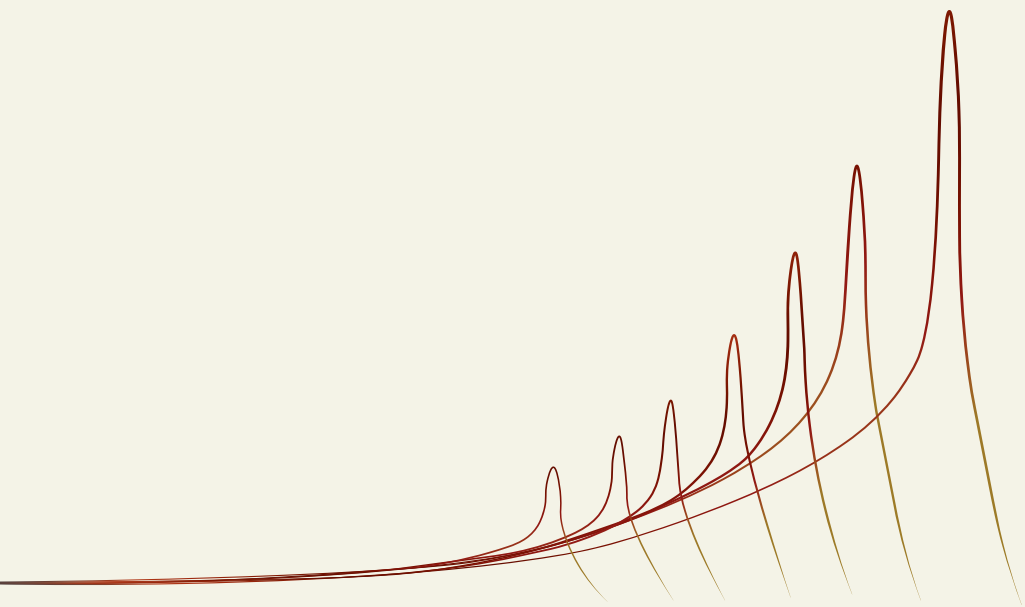
Automated proton therapy planning: clinical validation for head-and-neck cancer and chordoma

Huiskes, M.



Chapter 7

General Discussion

RATIONALE FOR AUTOMATION IN PROTON THERAPY

The proton therapy workflow typically involves several sequential steps, from patient consultation and image acquisition to delineation of targets and OARs, treatment planning, quality assurance, and finally treatment delivery. Among these steps, manual treatment planning, including contouring, dose optimization and plan verification, is often the most time-consuming and resource-intensive phase, representing a major bottleneck in clinical practice. This becomes increasingly relevant given the growing number of cancer patients requiring radiotherapy, coupled with ongoing staff shortages in radiotherapy departments. Automated IMPT planning can substantially reduce the workload currently required for manual treatment plan generation.

Moreover, the increasing clinical interest in adaptive proton therapy highlights the urgency for rapid, consistent, and reliable planning solutions, as frequent plan adaptations are necessary to maintain target coverage while minimizing toxicity, and manual replanning can not meet these time constraints. In this context, automation is not only an important means to improve efficiency but also a prerequisite for implementations of technological advancements, such as adaptive workflows. However, before such solutions can be adopted in clinical practice, the performance of automated IMPT planning must be validated to ensure it meets clinical requirements. Additionally, automated planning methods must be time-efficient, ideally minimizing or eliminating the need for hands-on planning. This thesis therefore aimed to develop and clinically validate fully automated IMPT planning for different treatment sites.

CLINICAL NEED FOR ADAPTIVE PROTON THERAPY

Plan adaptations during IMPT for HNC are regularly required, often at least once during the treatment. Since the optimal timing for adaptive proton therapy remains uncertain, frequent imaging and reassessment of the original plan quality on the patient's current anatomy are necessary. Previous studies, summarized in **Chapter 2**, showed that proton plan adaptations were primarily triggered by deteriorating target coverage, and adaptation typically restored or improved this coverage, often with additional OAR dose reductions and thus potential toxicity reductions. Compared to photon therapy, this need arises less frequently from OAR constraint violations in IMPT, which can be explained due to its inherently lower normal tissue doses. However, re-imaging, re-contouring, and re-optimization and re-assessment make IMPT plan adaptations both workload- and resource-intensive, requiring several hours to days before an adapted plan is clinically available.

Automated IMPT planning tools are therefore essential to significantly reduce the ongoing workload associated with plan adaptations and support efficient timely treatment delivery, particularly in the context of rising patient numbers. As adaptive workflows evolve toward daily online adaptation, automation will become indispensable to ensure that replanning occurs within clinically acceptable timescales, maintain high plan quality, and allow the potential for reduced treatment margins. Automation for IMPT thus should be seen not only as a means to increase efficiency, but as an integral component for maintaining high treatment standards in a resource constrained clinical environment.

DEVELOPMENT AND CONFIGURATION OF AUTOMATED IMPT PLANNING

Automated treatment planning systems typically require input from experienced planners for initial configuration to ensure clinically acceptable plan quality. In Erasmus-iCycle, fully automated IMPT plan generation is enabled through the development of a treatment site specific wish-list. The wish-list includes a list of objectives and constraints, each assigned a specific priority order for sequential optimization. Its development relies on close collaboration between radiation oncologists and planners to identify treatment site specific clinical requirements. Through iterative tuning on a subset of representative patients, the wish-list is refined until the resulting automated IMPT plans reproduce or improve upon clinical IMPT plans **(Chapters 3, 5 and 6).**

A suboptimal configuration can systematically compromise plan quality across all patients within a treatment site, emphasizing the importance of careful tuning and inclusion of anatomically diverse patient cohorts. Therefore, it is important to include patients with diverse anatomical characteristics during this tuning phase, such as patients with small and large tumor volumes or with and without metal implants. The tuning process is the most time-consuming yet critical component of the automated IMPT planning workflow, and its duration should be considered when preparing implementation timelines.

Ideally, one wish-list is developed per treatment site. Although initial development may be time-intensive, particularly for complex sites such as HNC with numerous OARs, once robust and validated, the wish-list can be applied consistently across larger patient cohorts, reducing hands-on planning time, and enabling rapid adaptation to new dose prescriptions or anatomical sub-sites. This facilitates efficient extension across treatment sites while keeping plan quality updated with clinical insights and protocol improvements.

For clinically complex treatment sites that require specific planning strategies, tailored automated planning approaches are necessary. An example is NPC, where the close proximity of serial OARs to the target volumes makes achieving adequate target coverage while respecting dose constraints for critical structures (e.g., brainstem, spinal cord) particularly complex. A modified optimization strategy was integrated in the automated planning method, which treated target coverage, unlike in the standard Erasmus-iCycle approach, not as a hard constraint but as a heavily weighted objective. This approach enables a better balance in situations where strict constraint-based optimization could not yield a feasible solution due to conflicting requirements between targets and serial OARs (**Chapter 5)**. Such adjustments illustrate that for anatomically complex sites, customization of treatment (sub)site-specific optimization strategies is sometimes required.

Once developed, these strategies can also be applied to less complex cases. For the clinical validation of automated IMPT planning, however, it is advisable to begin with less complex cases. In these cases, the effect of parameter adjustments during the tuning process can be more easily assessed, providing clearer insight into the behavior of the algorithm. Starting directly with highly complex cases risks generating suboptimal plans, without the ability to determine whether this results from limitations of the automated planning optimization method itself or from insufficient tuning. Demonstrating feasibility in less complex cases therefore provides a solid basis before extending automated planning to more challenging scenarios, as performed in this thesis.

CLINICAL VALIDATION ACROSS TREATMENT SITES

Automated IMPT planning was clinically validated across various treatment sites (**Chapters 3, 4, 5, and 6**), each with different levels of planning complexity:

1. Cases where the clinical desired goals are achieved;
2. More complex cases with clinically trade offs in target coverage while respecting toxicity constraints;
3. Challenging cases, where both target coverage and toxicity constraints are compromised in clinical practice.

In cases where clinically the desired target coverage could always be obtained, the automated IMPT approach was able to achieve similar target coverage, while consistently reducing the dose to OARs, and thereby lowering the probability of toxicity **(Chapter 3)**. Especially in more complex cases were clinically target coverage concessions were made to respect constrains to serial OARs, the automated plans

improved the target coverage, while still adhering to all critical dose constraints **(Chapter 5)**. These results demonstrate that automated IMPT planning is highly suitable for generating high-quality treatment plans for the first two sort of cases, while requiring no hands-on planning time.

Importantly, all the automatically generated IMPT plans for HNC from Chapter 3 were clinically approved and preferred over their manual counterparts by experienced radiation oncologists (**Chapter 4**). These outcomes are highly important, as clinical implementation of automated planning relies on the confidence and approval of the treating radiation oncologists, since they are end-responsible for the patient its treatment. Their acceptance is thus crucial and confirm that automated IMPT plans can meet or exceed clinical standards and are suitable for integration into routine clinical workflows. Moreover, with the improvement in plan quality using automated planning, patients may benefit from lower expected treatment related toxicities. Furthermore, successful clinical implementation requires the involvement of both manual treatment planners and radiation oncologists as end users, enabling them to build trust in automated planning systems, contribute to their ongoing refinement, and adapt to the evolving role of automation within radiotherapy workflows.

In challenging cases, where both target coverage and toxicity constraints are clinically compromised, automated IMPT planning was able to achieve mostly similar or improved target coverage while respecting these constraints (**Chapter 6**). However, for a subset of patients, strict adherence to OAR constraints reduced target coverage, whereas clinicians occasionally exceed constraints intentionally to improve outcomes. This highlights that a single, site-specific wish-list can not fully capture the nuanced decision-making of clinicians, indicating a need for alternative automated strategies in particularly complex cases.

MANAGING CHALLENGING CASES

To address this limitation, an alternative wish-list that permitted selective exceedance of specific dose constraints is proposed **(Chapter 6)**. This enables the automated generation of IMPT plans with target coverage similar to the clinical plans, while achieving similar to reduced toxicity. In clinical practice, it is not known in advance which patients require exploration of this 'grey area'. Therefore, for particularly complex cases, the development of an alternative automated planning strategy capable of identifying and exploring this region of trade-offs between TCP and risk of toxicity is necessary, where limited constraint exceedance may be clinically justifiable.

Integration of automated methods to quantify and navigate these trade-offs along a Pareto front is feasible using MCO frameworks, allowing clinicians to interactively select the most appropriate plan where conventional constraint-based planning is insufficient, as demonstrated in brachytherapy applications.[1,2] For the development of a similar approach in proton therapy, it is important that the plans are robustly optimized, as in clinical practice.

Although an a posteriori MCO approach could, in principle, also be applied to non-complex cases, its use as a standard is not advised. Generating a set of Pareto optimal plans is more resource intensive, and subsequent manual navigation and evaluation of trade-offs introduces additional workload and time demands. Thus, in situations where compromising both target coverage and serial OAR constraints is unnecessary, as is the case for most patients presented in this thesis, an automated IMPT planning approach based on a single, predefined treatment site specific wish-list remains the most efficient and appropriate solution.

IMPLICATIONS FOR CLINICAL IMPLEMENTATION OF AUTOMATED IMPT PLANNING

For clinical adoption of automated IMPT planning systems, regulatory considerations are essential. In the European Union, clinical implementation of medical software is governed by the Medical Device Regulation (MDR), which aims to ensure the safety and performance of medical devices, including software-based tools such as automated treatment planning systems. These regulations apply to both commercially developed products and in-house software used within healthcare institutions. The MDR allows healthcare institutions to use self-developed software without a CE certification, providing that specific conditions are met. These include adherence to the general safety and performance requirements, maintaining appropriate internal technical documentation and justifying the absence of equivalent commercial alternatives.[3]

The clinical validation presented in this thesis demonstrates the feasibility of automated IMPT planning in a clinical setting. While not yet available for external deployment, this thesis provides essential evidence for future regulatory approval, by generating clinical evidence and identifying cases where clinical performance requirements are met. Future collaboration with commercial vendors could facilitate broader deployment and interoperability with existing treatment planning systems.

Once automated planning tools are clinically implemented, it remains important to regularly perform quality control checks, and see whether improvements in plan quality are possible, i.e. by investigating new strategies or techniques. Continuous improvement, such as updating the wish-list according to new insights and clinical protocols or integrating novel optimization methods, will ensure that automated planning evolves alongside clinical protocols and technological advances.

The introduction of automated IMPT planning will also reshape the role of treatment planners, shifting their responsibilities from primarily manual plan generation to evaluating automatically generated plans and participating in clinical decision making at the treatment machine, including performing plan adaptations when required. Maintaining the skills, motivation, confidence, and clinical insight of clinical treatment planners and radiation oncologists remains essential, as their expertise is crucial for the continued development and refinement of automated tools. In particular, their experience will be invaluable in the innovation of new treatment strategies and the exploration of emerging techniques using automated planning, thereby supporting the delivery of the best possible treatment for patients.

FUTURE DIRECTIONS: DEEP LEARNING AND ADVANCED TREATMENT TECHNIQUES

To further streamline the clinical workflow, automation must extend beyond plan generation. One major component that remains time-consuming and prone to inter- and intra observer variability is contouring, where targets and OARs are manually delineated. Automated segmentation solutions for OARs in HNC based on deep learning models are already available, with several commercially implemented in clinical practice.[4,5] In contrast, although automated lymph node delineation has recently become commercially available, no clinically implemented automated tumor delineation solutions currently exist for HNC. Nevertheless, several investigations into deep learning-based auto-segmentation using MRI, PET/CT [6,7] or multimodality imaging [8] are ongoing. Automating these steps is essential to support rapid adaptive replanning and to fully exploit the potential of automated IMPT planning.

Erasmus-iCycle enables automated IMPT optimization over several hours without user intervention, making it well-suited for offline adaptation to address gradual anatomical changes. Whereas manual replanning may take several days, automated overnight optimization enables treatment the next day after radiation oncologist approval, substantially reducing manual planner workload. However, for online

adaptation strategies, fast replanning must be performed during the treatment fraction while the patient remains in the same position on the treatment couch.

For photon therapy, rapid re-planning workflows are already clinical applicable via commercially available systems, enabling adaptation to day-to-day variations, and thereby facilitating personalized patient care.[9–11] Currently, such strategies are not clinically feasible in proton therapy due to the absence of fast, high-quality on-board imaging, as well as sufficiently rapid replanning algorithms and quality assurance tools which needs to be automated too. To address this, Oud et al.[12] proposed a fast re-optimization method integrated in Erasmus-iCycle, in which spot addition and re-optimization were completed in an average of 3.4 minutes. This approach prevented target coverage deterioration while allowing the use of small setup robustness settings, thereby reducing NTCPs compared to standard offline replanning. Furthermore, fast Monte Carlo dose calculation algorithms have been developed, but still needs to be integrated into Erasmus-iCycle.[13]

An additional motivation for daily online adaptive strategies, compared to trigger-based offline replanning, is the potential to reduce treatment margins, offering further reductions in patient toxicity. Moreover, patient toxicity could be reduced by changing the optimization strategy toward NTCP-based objectives rather than OAR dose objectives, as OAR dose reductions does not always yield clinically relevant benefits when the dose reduction occurs in the shallow region of the NTCP curve. To this end, Erasmus-iCycle could be extended to incorporate NTCP-gain-based optimization, thereby potentially further improving and individualizing patient care. Continued development of TCP and NTCP models remains essential, using updated patient outcome data obtained with the most recent treatment techniques.

Deep learning approaches

In recent years, knowledge-based and deep learning approaches for automated proton therapy planning have also been investigated and validated for HNC. Delaney et al.[14,15] evaluated a commercially available knowledge-based planning (KBP) method and reported comparable target coverage with reduced OAR doses compared to clinical IMPT plans. Plan generation with this method required less than 10 minutes. Van Bruggen et al.[16,17] assessed a commercially available deep learning-based method, where the generated plans required subsequent fine-tuning to meet clinical requirements, resulting in an average total planning time of 2.5 hours. Such approaches are therefore highly valuable for generating plans

automatically, with substantial reductions in time and workload. In addition, their commercial availability facilitates broad clinical accessibility.

However, general limitations of such deep-learning or KBP approaches include the requirement for large amounts of training data, typically hundreds of cases, and the quality of the resulting plans is inherently dependent on the historical plans used for training, which may limit further plan improvements. In addition, such models are often perceived as black boxes, raisings concerns regarding transparency, interpretability, and the ability to control or easily adjust the underlying model parameters. Nonetheless, deep learning approaches offer important advantages, including very fast execution times and the potential to develop a single model applicable across multiple treatment sites, thereby substantially increasing versatility and clinical efficiency.

Building on existing studies of deep learning and knowledge-based planning, combining deep learning prediction with Erasmus-iCycle MCO presents a realistic strategy to achieve rapid, but individualized automated IMPT planning. A deep learning model could be trained using high-quality MCO plans as input, ensuring that the generated plans are of clinically acceptable quality, even if not always optimal for an individual patient. When clinical protocols are updated, new high-quality Erasmus-iCycle plans could be batch-generated to retrain the model, thereby addressing data availability challenges and ensuring continued plan quality improvement. The validated Erasmus-iCycle wish-lists developed in this thesis, would remain essential as a reference framework, guiding the model toward improved planning performance based on evolving clinical insights.

Furthermore, deep learning models could assist in the quality assurance, by predicting the reliability of delineations or automatically generated plans, and by comparing their quality to clinical reference plans. Such tools could also support the development and refinement of wish-lists, for which time investment remains substantial. In the future, wish-lists themselves might be generated or optimized through deep learning approaches, enabling the model to learn how input wish-list parameters influence plan quality. While all resulting plans must continue to be reviewed and approved by physicians, predictions of plan reliability or uncertainty could help clinicians focus on cases or regions where plan quality may be suboptimal.

Advanced treatment techniques

Our automated planning approach is also highly suitable for investigating new treatment strategies or techniques. Using a single wish-list, Erasmus-iCycle enables

fully automated treatment planning with consistent plan quality, facilitating unbiased comparisons between techniques by applying the same optimization functions and dose computation algorithms. For example, as in **Chapter 5**, the dosimetric added value of incorporating transmission beams (TBs) to IMPT was evaluated. TBs have smaller lateral penumbras compared to conventional IMPT beams, thereby potentially reducing dose to adjacent healthy tissues. It was hypothesized that in complex cases, where targets are located in close proximity to serial OARs, TBs could improve target coverage while further sparing critical structures. Our results demonstrated reduced serial OAR doses, however, these reductions were generally of limited clinical relevance, and target coverage was not improved beyond what was already achieved with automated IMPT planning. Such unbiased investigations of alternative strategies or techniques are generally not feasible with manual planning due to inter- and intraplanner variability and the high workload involved, underscoring the practical and methodological advantages of automated planning, especially in the context of personnel shortages.

Another technique that particularly will benefit from automated planning is proton arc therapy, in which dose is delivered from a large number of gantry angles, thereby increasing the degrees of freedom during plan optimization. Determining the optimal distribution of energy layers and spots across these gantry angles while adhering to clinical goals makes optimization of a proton arc plans challenging and time consuming, underscoring the necessity of automation. Recent planning studies on proton arc in HNC showed reduction of predicted toxicities as compared to IMPT [18–20], a finding that was also recently confirmed using Erasmus-iCycle. [21]

Proton arc can be delivered in either a dynamic or static arc. In dynamic arc proton therapy, protons are delivered during continuous gantry rotation around the patient. Currently, no clinical treatment machine is capable of dynamic arc proton therapy delivery with a rotating gantry, although several development efforts are ongoing. The main advantage of dynamic arc delivery is the potential to substantially reduce treatment times, thereby increasing patient throughput. This becomes particularly relevant given the increasing number of patients requiring RT and the need for efficient use of treatment resources.

In static arc proton therapy, a step-and-shoot delivery technique is applied over a large number of gantry angles, with multiple energy layers per direction. A major advantage of this method is that it can be delivered on all treatment machines capable of conventional IMPT. However, delivery times may be prolonged due to the switching times between energy layers. Recent clinical experience in four HNC

patients demonstrated that static arc proton therapy can achieve comparable or reduced treatment times relative to conventional multi-field IMPT through careful selection of planning parameters, such as employing 20 static beam directions.[20] Dosimetric analyses by Kong et al.[22] further indicate that a 36-field proton arc provides comparable target coverage and OAR sparing to a 10-beam IMPT plan, suggesting that reduced-field static arc configurations may be a practical compromise when delivery time is a limiting factor.

While proton arc therapy can improve dose conformality and thereby potentially reduce treatment-related toxicity, there are indications that proton arc has a higher sensitivity to inter-fraction anatomical changes compared to conventional IMPT. This increased sensitivity is due to interlaced spot maps coming from a multiple of directions, in contrast to the set of stacked energy layers from a limited number of directions in IMPT.[19,23] Consequently, the benefits of reaching such high levels dose conformality could come at the cost of an increased need for plan adaptations during the treatment course. This emphasizes the importance of streamlining, and ideally automating, the adaptive proton therapy workflow. While automation is already beneficial for conventional multi-field IMPT, it becomes even more critical for proton arc therapy, where the higher conformality may necessitate more frequent replanning.

FUTURE OUTLOOK

The future clinical landscape of proton therapy will be shaped by the further expansion of automated planning to new treatment strategies, such as proton arc therapy, and by the integration of automation across all stages of the workflow, from segmentation and planning to (online) adaptation and quality assurance. Over the next 5–10 years, we see the field evolve towards daily online adaptive planning, real-time dose recalculation, and deep learning-assisted decision support are seamlessly embedded into routine clinical practice. This transformation will increase efficiency and consistency, enable smaller treatment margins, improve target coverage, and reduce normal tissue toxicity, ultimately enhancing patient outcomes.

While photon-based radiotherapy is already advancing in online adaptive workflows, the potential benefits of proton therapy, i.e. higher conformality and reduced normal tissue dose, remain relevant, particularly for anatomically complex cases. Nevertheless, as adaptive photon techniques continue to evolve, the relative clinical benefit of protons must be reassessed in the context of new photon standards, including margin-free online adaptive delivery.

Deep learning-based approaches offer further opportunities to accelerate planning while maintaining high-quality plans. Erasmus-iCycle generated plans can serve as high-quality training data, enabling a two-step workflow in which deep learning predicts initial optimization objectives for targets and OARs, followed by multi-criteria optimization to achieve individualized trade-offs. Such an approach combines the speed of deep learning with the individualized trade-offs achievable through MCO, maintaining clinical quality while dramatically reducing planning time. Clinically applied plans could then be incorporated into a continuous feedback loop, ensuring that the deep learning model remains updated with the most recent and highest-quality plans. In addition, deep learning-based decision support tools may complement automated planning by assisting in plan evaluation, plan adaptation, and predictive modeling of patient-specific toxicity (i.e., by NTCP), thereby extending the impact of automation beyond plan generation alone.

The studies presented in this thesis demonstrate that automated proton therapy planning has been clinically validated across various treatment sites, each with different levels of planning complexity, providing a solid foundation for future integration of automation throughout the workflow. Successful implementation drastically reduces planning time and workload, thereby enabling higher patient throughput and shorter waiting times. The time and workload reductions achieved through automation can be reinvested in the evaluation and clinical translation of new techniques, ultimately contributing to consistent, high-quality treatment plans and efficient, evidence-based use of clinical resources.

In the coming years, integration of automation with advanced modalities, such as dynamic proton arc therapy, daily online adaptive planning with reduced margins, or NTCP-gain-based optimization, will further reduce toxicity, shorten treatment times, and enhance both efficiency and consistency in proton therapy. At the same time, future work should focus on developing real-time quality assurance tools and validating automated planning and new techniques across institutions. While clinical expertise remains essential, automation will not only enhance consistency and efficiency, but also enable innovations and adaptive strategies that would be unfeasible through manual planning alone.

REFERENCES

1. Maree SC, Luong NH, Kooreman ES, van Wieringen N, Bel A, Hinnen KA, et al. Evaluation of bi-objective treatment planning for high-dose-rate prostate brachytherapy—A retrospective observer study. Brachytherapy 2019;18:396–403. https://doi.org/10.1016/J.BRACHY.2018.12.010.
2. Barten D, Bouter A, van Wieringen N, Pieters B, Hinnen K, Westerveld G, et al. PD-0821 Artificial Intelligence based planning of HDR prostate brachytherapy: first clinical experience. Radiother Oncol 2021;161:S653–5. https://doi.org/10.1016/S0167-8140(21)07100-0.
3. Beckers R, Kwade Z, Zanca F. The EU medical device regulation: Implications for artificial intelligence-based medical device software in medical physics. Phys Medica 2021;83:1–8. https://doi.org/10.1016/J.EJMP.2021.02.011.
4. van der Veen J, Willems S, Deschuymer S, Robben D, Crijns W, Maes F, et al. Benefits of deep learning for delineation of organs at risk in head and neck cancer. Radiother Oncol 2019;138:68–74. https://doi.org/10.1016/j.radonc.2019.05.010.
5. White Papers | RaySearch Laboratories. 2020.
6. Berthon B, Evans M, Marshall C, Palaniappan N, Cole N, Jayaprakasam V, et al. Head and neck target delineation using a novel PET automatic segmentation algorithm. Radiother Oncol 2017;122:242–7. https://doi.org/10.1016/j.radonc.2016.12.008.
7. Ji K, Wu Z, Han J, Jia J, Zhai G, Liu J. Application of 3D nnU-Net with Residual Encoder in the 2024 MICCAI Head and Neck Tumor Segmentation Challenge. Head Neck Tumor Segmentation MR-Guided Appl First MICCAI Challenge, HNTS-MRG 2024, Held Conjunction with MICCAI 2024, Marrakesh, Morocco, Oct 17, 2024, Proc 2025;15273:250–8. https://doi.org/10.1007/978-3-031-83274-1_20.
8. Wei Z, Ren J, Eriksen JG, Jensen K, Mortensen HR, Korreman SS, et al. An interactive deep-learning workflow for head and neck gross tumour volume segmentation. Phys Imaging Radiat Oncol 2025;35:100820. https://doi.org/10.1016/J.PHRO.2025.100820.
9. Raaymakers BW, Jürgenliemk-Schulz IM, Bol GH, Glitzner M, Kotte ANTJ, Van Asselen B, et al. First patients treated with a 1.5 T MRI-Linac: Clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. Phys Med Biol 2017;62:L41–50. https://doi.org/10.1088/1361-6560/AA9517.
10. Winkel D, Bol GH, Kroon PS, van Asselen B, Hackett SS, Werensteijn-Honingh AM, et al. Adaptive radiotherapy: The Elekta Unity MR-linac concept. Clin Transl Radiat Oncol 2019;18:54–9. https://doi.org/10.1016/J.CTRO.2019.04.001.
11. Nasser N, Yang GQ, Koo J, Bowers M, Greco K, Feygelman V, et al. A head and neck treatment planning strategy for a CBCT guided ring gantry online adaptive radiotherapy system. J Appl Clin Med Phys 2023;24:e14134. https://doi.org/10.1002/ACM2.14134.
12. Oud M, Breedveld S, Rojo-Santiago J, Giżyńska MK, Kroesen M, Habraken S, et al. A fast and robust constraint-based online re-optimization approach for automated online adaptive intensity modulated proton therapy in head and neck cancer. Phys Med Biol 2024;69:075007. https://doi.org/10.1088/1361-6560/AD2A98.

13. Pastor-Serrano O, Perkó Z. Millisecond speed deep learning based proton dose calculation with Monte Carlo accuracy. Phys Med Biol 2022;67:105006. https://doi.org/10.1088/1361-6560/AC692E.

14. Delaney AR, Verbakel WF, Lindberg J, Koponen TK, Slotman BJ, Dahele M. Evaluation of an Automated Proton Planning Solution. Cureus 2018;10. https://doi.org/10.7759/CUREUS.3696.

15. Delaney AR, Dong L, Mascia A, Zou W, Zhang Y, Yin L, et al. Automated Knowledge-Based Intensity-Modulated Proton Planning: An International Multicenter Benchmarking Study. Cancers (Basel) 2018;10. https://doi.org/10.3390/CANCERS10110420.

16. van Bruggen IG, Huiskes M, de Vette SPM, Holmström M, Langendijk JA, Both S, et al. Automated Robust Planning for IMPT in Oropharyngeal Cancer Patients Using Machine Learning. Int J Radiat Oncol 2023;115:1283–90. https://doi.org/10.1016/J.IJROBP.2022.12.004.

17. van Bruggen IG, van Dijk M, Brinkman-Akker MJ, Löfman F, Langendijk JA, Both S, et al. Clinical implementation of deep learning robust IMPT planning in oropharyngeal cancer patients: A blinded clinical study. Radiother Oncol 2024;200:110522. https://doi.org/10.1016/J.RADONC.2024.110522.

18. de Jong BA, Battinelli C, Free J, Wagenaar D, Engwall E, Janssens G, et al. Spot scanning proton arc therapy reduces toxicity in oropharyngeal cancer patients. Med Phys 2023;50:1305–17. https://doi.org/10.1002/MP.16098.

19. De Jong BA, Zhao L, Liu P, Wase V, Marthin O, Sundström J, et al. Early generation dynamic and static proton arc treatment planning algorithms assessment in oropharyngeal cancer patients. Med Phys 2025;52:e17916. https://doi.org/10.1002/MP.17916.

20. Fracchiolla F, Engwall E, Mikhalev V, Cianchetti M, Giacomelli I, Siniscalchi B, et al. Static proton arc therapy: Comprehensive plan quality evaluation and first clinical treatments in patients with complex head and neck targets. Med Phys 2025;52:3191–203. https://doi.org/10.1002/MP.17669.

21. Kong W, Huiskes M, Habraken SJM, Astreinidou E, Rasch CRN, Heijmen BJM, et al. Is there added value to discrete proton arc therapy? Radiother. Oncol., vol. 206, Elsevier; 2025, p. S3475–7. https://doi.org/10.1016/S0167-8140(25)00683-8.

22. Kong W, Huiskes M, Habraken SJM, Astreinidou E, Rasch CRN, Heijmen BJM, et al. Automated planning for bias-free validation of discrete proton arc therapy for oropharyngeal cancer. Int J Part Ther 2025:101209. https://doi.org/10.1016/J.IJPT.2025.101209.

23. Engwall E, Marthin O, Wase V, Sundström J, Mikhalev V, de Jong BA, et al. Partitioning of discrete proton arcs into interlaced subplans can bring proton arc advances to existing proton facilities. Med Phys 2023;50:5723–33. https://doi.org/10.1002/MP.16617.