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

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Chapter 1

General Introduction

1.1 PROTON THERAPY FOR HEAD AND NECK CANCER AND SKULL BASE TUMORS

Radiation therapy is a treatment modality in which ionizing radiation is delivered to the tumor to induce DNA damage. The underlying principle relies on the differential repair capacity of normal and cancerous cells; whereas normal cells possess efficient DNA repair mechanisms, cancer cells have impaired repair capabilities, making them more susceptible to radiation-induced damage.[1] The goal of radiotherapy is to deliver sufficiently high dose to the tumor to achieve a high tumor control probability (TCP), while minimizing exposure to surrounding healthy tissue to reduce the risk of complications, referred to as the normal tissue complication probability (NTCP).[2]

Conventional radiotherapy is photon-based, where photons deposit energy along their entire path when traversing tissues. Since several years, proton therapy has become available as a treatment modality in the Netherlands. Protons are heavy particles that, depending on their energy, traverse a certain distance in tissue and deposit most of their energy at a specific depth, known as the Bragg peak. Beyond this peak, there is a steep distal dose fall-off, resulting in practically no exit dose. Due to this property, a high radiation dose can be delivered very precisely to the target volume, while surrounding healthy tissues receive only a minimal dose. To adequately cover the entire tumor volume, multiple proton beam energies, so-called pencil beams, are combined to create a spread-out Bragg peak (SOBP), see Figure 1. Furthermore, the intensity of these pencil beams can be modulated, a technique known as intensity-modulated proton therapy (IMPT). In IMPT, treatment plans are typically constructed using a limited number of fixed beam angles. Proton doses are delivered using pencil beam scanning, in which multiple narrow proton beams scan over the target surface, while energy layers are switched to irradiate the target in depth.[3]

IMPT plays a key role in the curative treatment of selected patients with head and neck cancer (HNC), as well as in the adjuvant setting for chordomas. HNC comprises a heterogeneous group of cancers, typically arising from squamous cell lining of the mucosal surfaces of the head and neck but may also originate from the salivary glands or paranasal sinuses. The annual incidence of HNC in the Netherlands is approximately 3000 cases, with tumor sites in decreasing order of incidence including the oral cavity, oropharynx, larynx, hypopharynx, salivary glands, paranasal sinuses, and nasopharynx (Figure 2).[5]

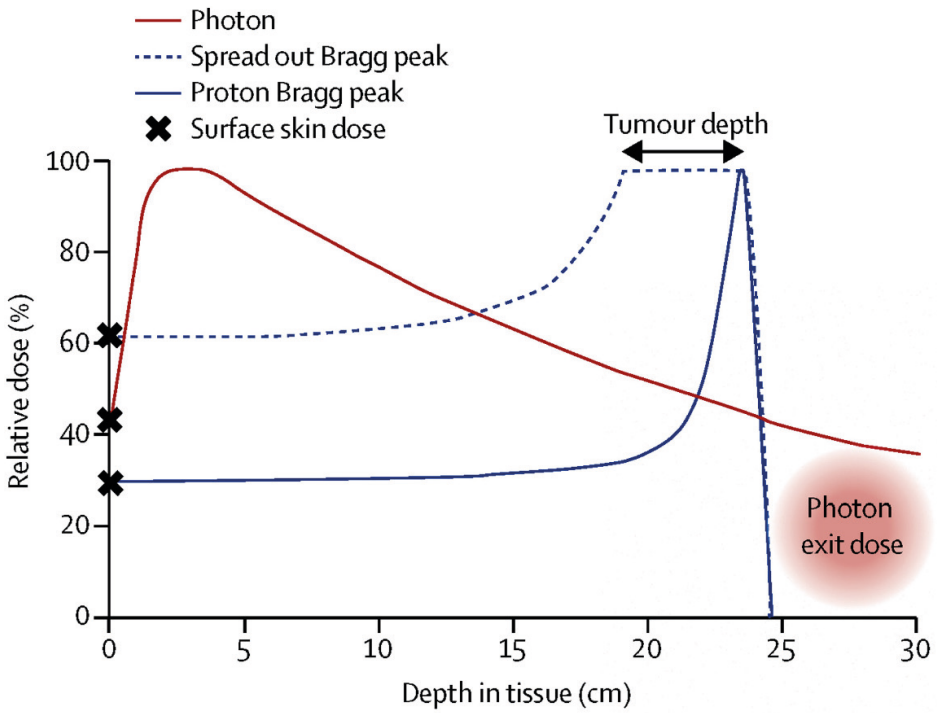

Figure 1 Depth-dose curves for photon and proton beams [4]

In the Netherlands, proton therapy for HNC patients is a model-based indication [6], meaning that only patients expected to achieve a clinically relevant reduction in toxicity compared with conventional photon therapy are eligible, qualified as reductions in NTCP for xerostomia and dysphagia above a predefined threshold.

Chordomas, in contrast, are rare, slow growing, but locally aggressive primary bone tumors originating from embryonic remnants of the notochord, with an incidence of approximately 18 cases per year in the Netherlands.[8] The most common location is the sacrum (50%), followed by the skull base (35%), and the mobile spine (15%).[9] In the context of this thesis, the term chordoma refers specifically to skull base chordoma. Skull base chordomas are considered a standard indication for proton therapy, and patients with this diagnosis are referred directly.[10]

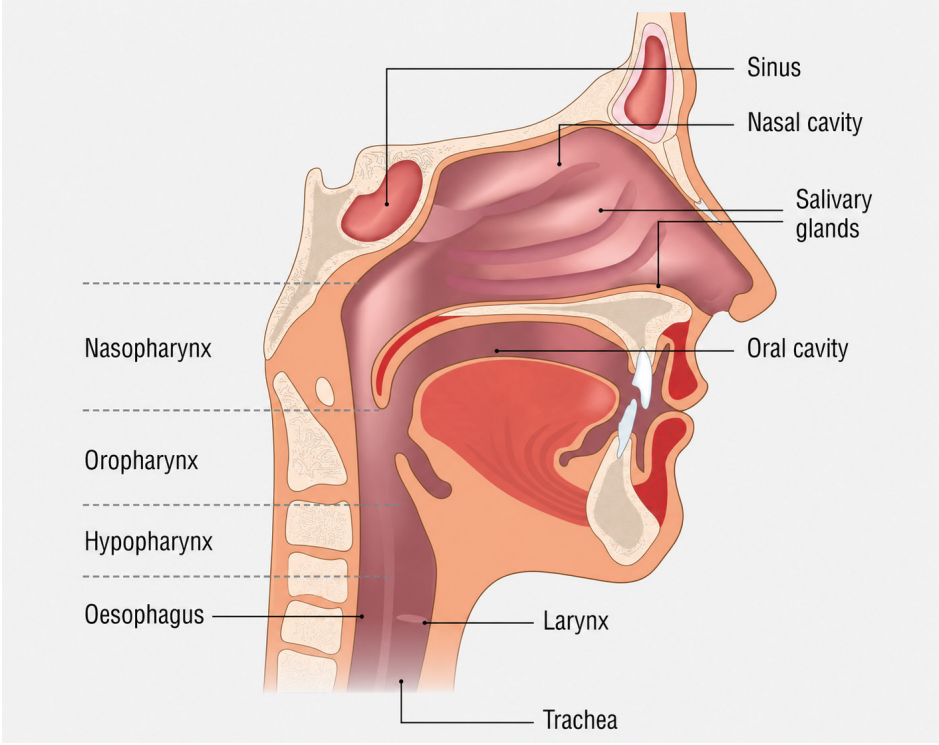

Figure 2 Anatomical structures in the head and neck [7]

For HNC, a total dose of 70 Gy is typically prescribed, while for chordomas, a total dose of 74 Gy is required due to their relative radioresistance. These doses are usually delivered in 35 and 37 daily fractions of 2 Gy, respectively.

1.2 PROTON THERAPY TREATMENT PLANNING

Prior to radiation therapy, a treatment plan with a dose distribution is created based on a planning computed tomography (CT). The CT provides electron density information required for dose calculations. Radiation oncologists delineate the visible extent of the tumor, which is expanded with a margin to account for potential subclinical microscopic disease, this defines the clinical target volume (CTV). For photon-therapy, an additional margin is added to account for setup uncertainties, such as variations in patient positioning and beam geometry during the delivery, resulting in the planning target volume (PTV). Conceptually, the PTV is covered with the prescribed radiation dose so that there is adequate assurance (e.g. 95% probability) of covering the CTV with the intended radiation dose for each fraction over the course of treatment.[11]

For proton therapy, the PTV concept is not directly applicable, as it assumes that the dose distribution shifts rigidly similar to a static cloud. However, proton dose deposition is highly sensitive to changes in tissue density along the beam path, which affect the proton range due to variations in stopping power, resulting from patient setup errors or anatomical changes. Moreover, the PTV concept does not account for range uncertainty errors, i.e. in the calculation of stopping powers of tissues. To address this, robust optimization of the CTV is employed. This technique simulates multiple dose distributions under different setup- and range uncertainty scenarios to ensure adequate CTV coverage across a defined set of possible scenarios.[12,13]

During radiotherapy, it is inevitable that surrounding healthy tissues also receive a substantial radiation dose. Damage to certain organs, referred to as organs at risk (OARs), can lead to side effects, and specific dose limits are established for them. Serial OARs, such as the brainstem, can lose functionality if even a small volume receives a dose above the tolerance limit. In contrast, parallel organs, such as the parotid glands, have compensatory capacity, and the mean dose to the entire organ is a better predictor of functional loss.[14]

1.2.1 Challenges in manual proton treatment planning

Radiotherapy treatment planning involves several trade-offs between competing clinical objectives. The treatment planning process typically requires multiple rounds of optimization, including manual adjustments to objective weights and the addition of supplementary planning goals. This process is particularly complex in HNC, where multiple target volumes are near to numerous OARs. These challenges are even more pronounced in patients with nasopharyngeal cancer or chordoma, where target volumes are in close proximity to critical neural and vascular structures. In such cases, achieving optimal target coverage may not be feasible without exceeding dose constraints, necessitating concessions in target coverage to protect critical organs, or allow exceedance of serial OAR constraints to improve target coverage. These trade-offs introduce additional planning complexity and often require numerous iterative adjustments to find a clinical acceptable dose distribution.

As a result, manual treatment planning requires a high degree of planner expertise and intervention, making the process both time consuming and labor intensive. This is particularly relevant given the expected increase in the number of cancer patients requiring radiotherapy [15], which will further increase the workload in the coming years. At the same time, many radiotherapy departments are already facing

a shortage of staff.[16,17] Streamlining the radiotherapy workflow is therefore essential to ensure the capacity to deliver treatment to all patients. Currently, manually constructing a clinical IMPT treatment plan for HNC takes around six hours, while for complex cases such as nasopharynx and chordoma, it takes several working days.

1.3 ADVANCED PROTON THERAPY TECHNIQUES

Emerging advanced proton therapy techniques include adaptive proton therapy, automated proton therapy planning, transmission beams, FLASH and proton arc therapy. In proton arc therapy, the dose is delivered from a large number of gantry angles, increasing the degrees of freedom during plan optimization. Recently, the first clinical HNC treatment worldwide using static proton arc was successfully performed.[18] Another promising development is proton-FLASH irradiation, which uses ultra-high dose rates. In vivo animal studies have shown the potential to reduce normal tissue toxicity while maintaining tumor control [19], and a first clinical trial with proton FLASH for bone metastases demonstrated feasibility.[20] In addition, transmission beams (TB) are an emerging technique, that uses single, high-energy beams that shoot through the patient. In this approach, the Bragg peak is located beyond the patient, and the tissue is irradiated with the part proximal to the Bragg peak. TBs theoretically have smaller lateral penumbras as compared to IMPT, where multiple energies are used, thereby potentially enabling sharper lateral dose fall-off.

1.3.1 Adaptive proton therapy

Since the treatment plan relies on anatomical images acquired at a single time point prior to the treatment, proton therapy is sensitive to anatomical changes during treatment, such as weight loss, tumor shrinkage, or organ motion.[21] These changes may lead to tumor underdosage or unintended exceedance of OAR dose constraints. To address such variations, adaptive proton therapy (APT) can be applied, aiming to improve the target coverage and/or reduce OAR doses. A typical radiotherapy adaptation workflow involves acquiring a new CT scan, re-delineating the targets and OARs and constructing a new treatment plan based on the updated anatomy. This process typically requires several hours to days, reflecting the associated workload. However, for proton therapy it is not yet known what the impact of plan adaptation will be on target coverage and OARs, and when and how often this needs to be applied.

APT can be categorized in offline and online approaches. In offline adaptation, the treatment plan is adjusted between fractions, and the updated plan is used for

subsequent fractions. Offline APT is suitable for gradual inter-fraction changes, such as weight loss. In online adaptation, the plan is modified while the patient is on the treatment couch, allowing delivery of the adapted plan within the same fraction in which the anatomical change is observed. Online APT can be particularly useful for day-to-day variations, such as air cavity filling.

For photon therapy, commercial systems to facilitate online adaptive treatment have recently become available.[22,23] However, comparable solutions for proton therapy are not yet clinically established. Due to the manual workload for adaptive proton therapy, automation of the key APT workflow steps, such as segmentation and plan optimization, are required when future APT is necessary.

1.3.2 Automated IMPT planning

Given the duration and workload associated with manual proton therapy planning, there is increasing need for automation in radiotherapy planning, aiming to improve plan quality while reducing the time and expertise as required for manual planning.[24,25] Over the past few years, several automated treatment planning approaches have been developed, including for proton therapy.

In template or protocol-based planning, standardized objectives for a treatment site are applied independent of the individual patient. Scripted based planning can automate parts of manual iterative tasks, such as adjusting objective weights or adding supplementary goals. The main advantages of these methods are time savings and a reduction in repetitive manual actions, but they remain semi-automatic.

Knowledge-based and deep learning planning approaches predict new treatment plans based on prior data, either from libraries of previously treated patients or from models trained on large datasets of dose distributions. A limitation of these approaches is that plan quality for new patients strongly depends on the quality of the prior data used for the library or training.

In multi-criterial optimization (MCO), trade-offs between target coverage and sparing OARs are made. The resulting plan is Pareto-optimal, meaning that improving one objective would compromise another. In a posteriori MCO, as commercially implemented in systems such as RayStation, a set of Pareto-optimal plans is automatically generated, from which the final clinically favorable plan is selected by a planner. This still requires manual intervention and subjective decision making.

In contrast, Erasmus-iCycle [26] performs a priori MCO guided by a treatment site-specific wish-list containing hard planning constraints, which can never be violated, and prioritized objectives. During optimization, objectives are sequentially minimized in order of priority while maintaining all higher-priority outcomes as constraints. If lower-priority objectives cannot be fully achieved the optimizer automatically relaxes them, to give room for optimizing other objective goals, and ensuring that each generated plan is tailored to the individual patient. Importantly, this mechanism enables fully automated, Pareto-optimal robust IMPT plan generation, without the need for manual plan selection or adjustments.

Before automated IMPT planning solutions can be implemented in clinical practice, their performance must be validated to ensure compliance with clinical requirements and alignment with existing medical device regulations. This thesis focuses on the development and clinical validation of fully automated IMPT planning using Erasmus-iCycle for HNC and chordoma.

1.4 AIM AND OUTLINE OF THIS THESIS

The goal of this work was to clinically validate fully automated multi-criteria IMPT planning for head-and-neck cancer and skull base chordoma, aiming to generate automated IMPT plans with plan quality at least equivalent to clinical IMPT plans, without hands-on planning time. 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)**.

A potential application of automated IMPT planning is adaptive IMPT. However, it remains unclear when and how often APT is necessary in HNC, and how this impacts target coverage and OAR doses. Therefore, in **Chapter 2**, a literature review was conducted to explore existing knowledge about the dosimetric impact of APT and the timing to perform a plan adaptation in IMPT for HNC. An overview of the applied techniques, timing and frequency of adaptations and the dosimetric impact on target coverage and OAR doses was summarized.

Chapter 3 presents a site-specific wish-list for HNC to enable fully automated IMPT planning using Erasmus-iCycle. The wish-list was applied to 30 hypo- and oropharyngeal cancer patients previously treated with manually created clinical

IMPT plans. Automated plans were compared to their corresponding clinical plans using dosimetric parameters (target coverage and OAR doses) and NTCP for xerostomia and dysphagia.

Subsequently, in **Chapter 4**, a clinical qualitative validation of automated planning for IMPT was performed. To this purpose, experienced HNC radiation oncologists blindly evaluated the 30 clinical- and automatically generated IMPT plans from Chapter 3. In this study, it was investigated whether the clinical and automated plans were clinically acceptable and whether the radiation oncologists had a preference for either.

For nasopharyngeal cancer, tumors are located close to critical serial OARs, requiring a dedicated planning approach. In **Chapter 5**, a wish-list specific for nasopharynx tumors was developed. Fully automated planning using a combination of IMPT with and without transmission beams (TBs) was investigated to determine whether this approach could enhance plan quality compared to IMPT planning alone. Automated plans were compared to clinical IMPT plans using dosimetric parameters and NTCP.

In **Chapter 6,** a treatment site-specific wish-list for skull base chordomas was developed to generate fully automated IMPT plans for this highly complex treatment site. Chordomas are challenging cases for IMPT planning due to the high required dose levels in close proximity to critical vascular and neural structures, as well as interference with postoperative stabilization materials. Clinically, trade-offs in target coverage underdosing and exceeding dose constraints to serial OARs are made, requiring multiple iterations and discussions with the treating physician. Automated planning may alleviate this burden, and automatically generated IMPT plans were compared to their corresponding clinical plans using dosimetric parameters for target coverage and OAR doses.

REFERENCES

1. Alfred L., Leaver D. Treatment Delivery Equipment. Princ. Pract. Radiat. Ther., ELSEVIER; 2016, p. 132–55.
2. Baumann M, Petersen C. TCP and NTCP: a basic introduction. Rays 30(2)99-104, Rev 2005.
3. Levin WP, DeLaney TF. Charged Particle Radiotherapy. Clin Radiat Oncol 2015:358-372. e2. https://doi.org/10.1016/B978-0-323-24098-7.00019-8.
4. Leeman JE, Romesser PB, Zhou Y, McBride S, Riaz N, Sherman E, et al. Proton therapy for head and neck cancer: expanding the therapeutic window. Lancet Oncol 2017;18:e254–65. https://doi.org/10.1016/S1470-2045(17)30179-1.
5. NKR Cijfers | Incidentie n.d. https://nkr-cijfers.iknl.nl/viewer/incidentie-per-jaar?language=nl_NL&viewerId=a38ed742-bdba-4e85-bf23-164bd2e26d93 (accessed September 24, 2025).
6. Langendijk JA, Hoogeman MS, Monshouwer R, Verheij M. Landelijk Indicatie Protocol Protonentherapie (versie 2.2) (LIPPv2.2) HOOFD-HALSTUMOREN 2019. https://nvro.nl/publicaties/rapporten (accessed September 24, 2025).
7. Mesia R, Taberna M. Chapter 2. Diagnosis and staging of squamous cell tumours. Head Neck Cancers Essentials Clin., 2017.
8. Chordoom | Kanker.nl n.d. https://www.kanker.nl/kankersoorten/botkanker-botsarcoom/soorten-botkanker/chordoom (accessed September 24, 2025).
9. Tenny S, Varacallo MA. Chordoma. StatPearls Publishing; 2023.
10. Standpunt Protonentherapie: Indicaties voor protonentherapie (deel 1) - Intra-oculaire tumoren, Chordomen/chondrosarcomen en Pediatrische tumoren | Zorginstituut Nederland 2010. https://www.zorginstituutnederland.nl/documenten/2010/03/23/protonentherapie-indicaties-voor-protonentherapie-deel-1---intra-oculaire-tumoren-chordomen-chondrosarcomen-en-pediatrische-tumoren (accessed September 24, 2025).
11. Gardner SJ, Kim J, Chetty IJ. Modern Radiation Therapy Planning and Delivery. Hematol Oncol Clin North Am 2019;33:947–62. https://doi.org/10.1016/J.HOC.2019.08.005.
12. Unkelbach J, Alber M, Bangert M, Bokrantz R, Chan TCY, Deasy JO, et al. Robust radiotherapy planning. Phys Med Biol 2018;63:22TR02. https://doi.org/10.1088/1361-6560/AAE659.
13. Korevaar EW, Habraken SJM, Scandurra D, Kierkels RGJ, Unipan M, Eenink MGC, et al. Practical robustness evaluation in radiotherapy – A photon and proton-proof alternative to PTV-based plan evaluation. Radiother Oncol 2019;141:267–74. https://doi.org/10.1016/j.radonc.2019.08.005.
14. Maingon P, Mammar V, Peignaux K, Truc G, Barillot I. Les contraintes aux organes à risque en radiothérapie par modulation d'intensité des cancers ORL. Cancer/Radiothérapie 2004;8:234–47. https://doi.org/10.1016/J.CANRAD.2004.06.002.
15. Cancer estimates in EU/EFTA countries up to 2040 - European Cancer Information System 2024. https://ecis.jrc.ec.europa.eu/cancer-factsheets-eu-27-countries-2022 (accessed September 24, 2025).

16. Crisp N, Chen L. Global Supply of Health Professionals. N Engl J Med 2014;370:950–7. https://doi.org/10.1056/NEJMRA1111610.

17. Lindberg J, Holmström P, Hallberg S, Björk-Eriksson T, Olsson CE. A national perspective about the current work situation at modern radiotherapy departments. Clin Transl Radiat Oncol 2020;24:127–34. https://doi.org/10.1016/j.ctro.2020.08.001.

18. 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.

19. Singers Sørensen B, Krzysztof Sitarz M, Ankjærgaard C, Johansen J, Andersen CE, Kanouta E, et al. In vivo validation and tissue sparing factor for acute damage of pencil beam scanning proton FLASH. Radiother Oncol 2022;167:109–15. https://doi.org/10.1016/j.radonc.2021.12.022.

20. Mascia AE, Daugherty EC, Zhang Y, Lee E, Xiao Z, Sertorio M, et al. Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases: The FAST-01 Nonrandomized Trial. JAMA Oncol 2023;9:62–9. https://doi.org/10.1001/JAMAONCOL.2022.5843.

21. Barker JL, Garden AS, Ang KK, O'Daniel JC, Wang H, Court LE, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. Int J Radiat Oncol 2004;59:960–70. https://doi.org/10.1016/J.IJROBP.2003.12.024.

22. 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.

23. Archambault Y, Boylan C, Bullock D, Morgas T, Peltola J, Ruokokoski E, et al. Making on-line adaptive radiotherapy possible using artificial intelligence and machine learning for efficient daily re-planning. Cdn0ScrvtComY Archambault, C Boylan, D Bullock, T Morgas, J Peltola, E Ruokokoski, A Genghi, B HaasMed Phys Int J, 2020•cdn0ScrvtCom 2020;8.

24. Berry SL, Boczkowski A, Ma R, Mechalakos J, Hunt M. Interobserver variability in radiation therapy plan output: Results of a single-institution study. Pract Radiat Oncol 2016;6:442–9. https://doi.org/10.1016/J.PRRO.2016.04.005.

25. Nelms BE, Robinson G, Markham J, Velasco K, Boyd S, Narayan S, et al. Variation in external beam treatment plan quality: An inter-institutional study of planners and planning systems. Pract Radiat Oncol 2012;2:296–305. https://doi.org/10.1016/J.PRRO.2011.11.012.

26. Breedveld S, Storchi PRM, Voet PWJ, Heijmen BJM. ICycle: Integrated, multicriterial beam angle, and profile optimization for generation of coplanar and noncoplanar IMRT plans. Med Phys 2012;39:951–63. https://doi.org/10.1118/1.3676689.