

Introduction

Contents

1	Context	1
2	Problematic	2
3	State of the Art	3
3.1	Research	3
	Automated rule implementation and reasoning	3
	Knowledge-based radiotherapy planning	3
	Conventional techniques	3
	MCO	3
	Wish list	3
	Pareto surface narrowing	3
	Pareto surface exploration	4
3.2	Commercial	4
	Pinnacle AutoPlanning	4
	Eclipse Rapidplan	4
	RayStation auto-planning	4
	mCycle	4
4	Unsolved problems	4
5	Thesis overview	4
5.1	Fluence Map Optimization	5
5.2	Semi-automation	5
5.3	Full-automation	5
5.4	Hybrid-automation	5

Abstract

This chapter provides a comprehensive overview of the current landscape in radiotherapy planning. We begin by re-contextualizing the field and outlining the critical challenges and limitations traditional methods face. The state of the art is then explored, detailing advancements in automated rule implementation, knowledge-based radiotherapy planning, and Multi-Criteria Optimization (MCO). We address the pivotal role of automated and knowledge-based techniques in improving treatment efficiency. The commercial solutions, such as Pinnacle AutoPlanning, Eclipse RapidPlan, and RayStation are discussed. We identify unresolved problems within the field, setting the stage for the subsequent sections of the thesis.

1 Context

Cancer remains one of the leading causes of mortality worldwide, with its incidence projected to rise in the coming decades [QMR⁺16, SPSM16]. As our understanding of cancer biology evolves and diagnostic techniques improve, the demand for effective and personalized treatment strategies continues to grow [HHD17]. Radiotherapy has emerged as a cornerstone in cancer management, either as a standalone treatment or in combination with other modalities such as surgery, chemotherapy, and immunotherapy [RMA⁺15, RDR15]. Radiotherapy leverages ionizing radiation to damage cancer cells' DNA, impeding

their ability to proliferate and ultimately leading to cell death [YCA⁺15]. The efficacy of radiotherapy lies in its ability to deliver precise doses of radiation to tumor volumes while minimizing exposure to surrounding healthy tissues [Mal12]. This delicate balance between tumor control and normal tissue toxicity underscores the importance of treatment planning in radiotherapy [Das09].

The advent of advanced imaging technologies [LZ24], coupled with sophisticated delivery systems like Multi-Leaf Collimator Linear Accelerators (MLC-LINACs), Tomotherapy units, and CyberKnife systems, has revolutionized the field of radiation oncology [KMHL08, XV01]. These technological advancements have paved the way for highly conformal treatment techniques. Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) techniques offer unprecedented levels of dose sculpting, allowing for escalated doses to tumors while better sparing organs at risk [NWA⁺18, EDFWF11, DBB⁺11]. However, the increased complexity of modern radiotherapy techniques has led to a corresponding increase in the complexity of treatment planning [Fra12, Rob08]. The process of creating an optimal treatment plan involves multiple steps, including Beam Orientation Optimization (BOO) [PBX00, PLB⁺01], Fluence Map Optimization (FMO) [LCM08, RDL04, LFC06], Leaf Sequencing (LS) [CHLW03, CHL⁺05, XHV02], and (sometimes) Direct Aperture Optimization (DAO) [SEL⁺02, ESN⁺03, ACT⁺07]. Each step requires careful consideration of numerous variables and constraints, making the planning process time-consuming and labor-intensive [WZHZ19].

In this context, this thesis aims to explore and advance the radiotherapy treatment planning automation field, focusing on developing novel algorithms and methodologies to enhance treatment plans' efficiency, quality, and consistency. By building upon the foundational knowledge of radiotherapy physics, biology, and clinical workflow, we seek to contribute to the ongoing evolution of radiation oncology and, ultimately, to improve outcomes for cancer patients.

2 Problematic

Traditional manual radiotherapy planning procedures are inherently subjective and time-consuming. The reliance on individual planner expertise often leads to variability in treatment plan quality [CLP⁺08, BGA⁺05, DCC⁺08, WBFM07]. This treatment plan diversity can induce inconsistencies in patient care. While efforts have been made to enhance consistency [BM11], significant variability among planners and institutions persists. There is a pressing need for more standardized planning approaches. The automation of treatment planning processes presents a promising solution to these challenges.

Moreover, the time-intensive nature of manual optimization [ZPS⁺20] and the growing demand for radiotherapy services have created a pressing need to develop automated approaches to streamline the radiotherapy planning process. Automation enables the treatment of more patients and facilitates exploring a broader range of treatment options.

By applying computational algorithms and artificial intelligence, automated planning systems offer the potential to enhance radiotherapy treatment delivery significantly. These systems can improve patient throughput and resource allocation by reducing planning time and increasing the efficiency of radiotherapy departments. Automated planning can improve plan quality and consistency, reducing variability and ensuring optimal treatment outcomes. Furthermore, the ability to enable rapid re-planning facilitates adaptive radiotherapy, allowing for adjustments to treatment plans in response to changes in tumor volume or patient anatomy. Finally, automated systems can explore a more expansive solution space, potentially discovering novel and innovative planning strategies that may improve treatment outcomes.

However, the development and implementation of automated planning systems pose challenges. These challenges include the creation of robust optimization algorithms, integrating with existing Treatment Planning Systems, and validating against current clinical standards.

3 State of the Art

3.1 Research

Automated rule implementation and reasoning An automated computer program with predefined rules and so called "if-then" ¹ structures is a solution for implementing simple clinical guidelines. In this context, the treatment planning system directly interprets patient anatomy and dosimetric requirements, simulating the decision-making process traditionally employed in manual treatment planning [RLB05]. By adhering to a structured, logical framework derived from human-defined protocols, automated reasoning in radiotherapy (ARIR) can significantly reduce the need for manual intervention, particularly for repetitive tasks.

Some modern TPS vendors have incorporated ARIR solutions, offering scripting capabilities that enable users to customize the planning process. For instance, the Varian Eclipse [Var24] system includes an application programming interface (API) that facilitates user-defined scripting functions.

Knowledge-based radiotherapy planning Knowledge-based radiotherapy planning (KBRP) represents an objective methodology for incorporating patient-specific data and historical experience into the treatment planning process [NSSW14]. By automating the optimization of KBRP, it is anticipated that a viable alternative to the current human-centric treatment planning paradigm can be established. A prevalent KBRP approach involves leveraging a database of historical benchmark plans to learn patient-specific dosimetric parameters and generate new treatment plans. Automated KBRP tools effectively set optimization parameters based on the desired dose-volume histogram. Previous studies have reported notable dosimetric improvements in treatment plans generated by KBRP approaches compared to benchmark data, particularly regarding sparing organs at risk [FBC⁺14, TDD⁺15].

Conventional techniques Memorial Sloan Kettering Cancer Center developed advanced optimization tools, including hierarchical constrained optimization, convex approximations, and Lagrangian methods. These tools addressed the complexity and enhanced the speed, quality, and accessibility of standardized yet personalized care [ZHZ⁺22].

Multi Criteria Optimization In DVH-based inverse optimization used by most commercial TPS, a cost function must be defined to solve the minimization problem. This function combines data from all volumes of interest as a weighted sum of penalties from each DVH constraint. The weighting coefficients reflect tradeoffs between the target(s) and different OARs. However, this approach requires online re-optimization if dosimetric preferences change during plan evaluation, making it time-consuming to find the optimal balance. Multi-criteria optimization (MCO) was introduced to address this, enabling the simultaneous generation of multiple "anchor" plans. Each anchor plan optimizes one OAR's DVH criterion for maximal sparing without compromising tumor target dosimetry [LSB03, TKM⁺07]. These plans form a hypersurface in the N -dimension space, where N is the number of independent OAR dosimetric constraints. Referred to as the Pareto surface, this hypersurface contains the optimal plans following different dosimetric criteria.

Wish list MCO can also be applied in an a priori approach, where dosimetric preferences are defined before inverse optimization. In this method, a fully automated process generates a single optimal plan without the need for human interaction [BSK⁺07]. Breedveld et al. introduced this approach in their work on IMRT Cycle (iCycle) [BSVH12], where the optimal plan is guided by a predefined "wish list" of dosimetric criteria, each assigned a specific priority.

Pareto surface narrowing In theory, MCO requires generating numerous plans to construct the Pareto surface, which can be time-intensive, even with automation. However, Craft and Bortfeld analyzed head and neck IMRT plans and demonstrated that only a few plans are needed to form a Pareto database [CB08]. Using objective correlation matrices and principal component analysis (PCA) of beamlet solutions, Craft and Bortfeld showed that if N independent dosimetric criteria are defined, $N + 1$ plans

¹Also known as "expert" systems.

are sufficient to construct a feasible Pareto surface. This insight facilitated the practical clinical use of MCO, first implemented in the RayStation TPS [Ray24].

Pareto surface exploration Previous research has explored Pareto optimal tradeoffs in various domains. Gebru et al., for instance, investigated methods for evaluating Pareto optimality [GLW⁺23]. Similarly, Cilla et al. conducted a comprehensive analysis of Pareto fronts [CID⁺18]. These studies provide valuable insights into the principles and techniques associated with Pareto optimization. Craft et al. proposed a method for generating multiple Pareto optimal dose distributions, allowing clinicians to make informed decisions based on their specific preferences and clinical contexts [CHSB07]

3.2 Commercial

Pinnacle AutoPlanning AutoPlanning in the Pinnacle TPS is an automated radiotherapy planning tool that optimizes treatment plans based on user-defined prescriptions and organ-at-risk constraints. AutoPlanning was initially used for prostate cancer and expanded to more complex treatments. Determining best practices for the optimal use of AP remains a challenge [REB⁺19]. Most patients are treated using VMAT techniques, with most treatment plans being generated solely by AP without requiring additional manual adjustments [MBK⁺21]. However, the dose calculation engine is recognized as an area with potential for improvement.

Eclipse Rapidplan RapidPlan (Varian) is a knowledge-based planning (KBP) tool that predicts dose-volume histograms (DVHs) based on patient anatomy and treatment parameters, using principal component analysis to model correlations between dosimetric and geometric features. RapidPlan has been used at Institut du Cancer Avignon-Provence, with 83% of plans meeting clinical criteria in a single optimization [MBK⁺21]. However, fine-tuning objectives for optimal trade-offs can be time-consuming, and the model's performance is limited by the variability of the training database.

RayStation auto-planning RayStation TPS Auto-Panning demonstrated similar or better target coverage, conformity, and organ-at-risk sparing than manual planning, with a significant reduction in manual operation time but increased computer processing time [YSZ⁺20]. The planning process depends on the use of IronPython-based automated scripts. However, the qualifications required to develop and manage these scripts and the responsibility in case of failure still need to be clarified.

mCycle The autoplanning solution mCycle, developed by Elekta, utilizes an a priori multi-criteria optimization algorithm. Leon Berard Cancer Center (Lyon, France) tested the solution and found all plans were considered clinically acceptable, with an optimization time between 30 and 60 minutes [MBK⁺21]. However, obtaining a robust wish list is complex and center-dependent. There needs to be an extensive discussion with the clinical team to assign the plan constraints and priority for each OAR objective.

4 Unsolved problems

Numerous approaches have been investigated to automate the radiotherapy treatment planning process. Despite these efforts, a consensus on the optimal method has yet to be established, and few automated solutions have been adopted in clinics. The challenges associated with automating radiotherapy treatment planning remain a significant area of inquiry within the field. This thesis addresses this critical issue by proposing advancements in key areas that may contribute to developing a fully automated treatment planning system.

5 Thesis overview

This section provides a comprehensive summary of the forthcoming chapters of this thesis.

5.1 Fluence Map Optimization

Chapter 3 is dedicated to developing computational methods for FMO. The chapter begins by assessing the discretization strategies. Naive approaches for optimization are explored, stepping up to a formalization of the classical FMO problem. A significant focus is placed on incorporating medical constraints and the corresponding importance factors associated with each constraint, which are critical in ensuring clinically viable treatment plans. The performance of various optimization algorithms is evaluated and compared, providing insights into their relative efficiencies in solving the FMO problem. This primary work was published in the form of an ArXiv article.

5.2 Semi-automation

Using graph-based analysis

Chapter 4 explores the interrelationships between radiotherapy treatment plans by defining a distance metric. This distance is then used to cluster plans into meaningful groups. The clustering forms a basis for developing a semi-automated framework for treatment plan optimization. Leveraging graph-based methodologies, this approach reduces the need for manual intervention in the planning process while ensuring the generation of high-quality plans. The potential of this semi-automated framework to streamline clinical workflows was presented at the 2024 European Society for Radiotherapy and Oncology (ESTRO) conference.

5.3 Full-automation

With reinforcement learning and conventional treatment optimization techniques

Chapter 5 addresses the limitations of classical optimization techniques in fully automating the treatment planning process. This chapter introduces a framework that integrates reinforcement learning with conventional optimization. The reinforcement learning agent is driven by clinical expertise and can be specialized to center-specific guidelines. The techniques found have been published through a peer-reviewed journal article, a presentation at the Artificial Intelligence in Medicine (AIME) 2024 conference, and a poster presentation at the American Society for Radiation Oncology (ASTRO) 2024 meeting.

5.4 Hybrid-automation

Via target DVHs deep dose and dose mimicking technique

The final research chapter, Chapter 6, presents a hybrid approach to automating treatment planning. This approach combines deep learning for dose prediction with target DVHs and plan-mimicking strategies. This methodology bridges the gap between fully automated AI-driven techniques and traditional planning methods, offering a more adaptable and clinically feasible solution. The hybrid model provides a mechanism for mimicking high-quality plans from experienced planners. This research has been presented at the French Society of Medical Physics (SFPM) and the French Society for Radiation Oncology (SFRO) 2024 meetings.

References

- [ACT⁺07] Ergun E. Ahunbay, Guang-Pei Chen, Steven Thatcher, Paul A. Jursinic, Julia White, Katherine Albano, and X. Allen Li. Direct aperture optimization-based intensity-modulated radiotherapy for whole breast irradiation. *International Journal of Radiation Oncology*Biophysics*, 67(4):1248–1258, 2007.
- [BGA⁺05] Jörg Bohsung, Sofie Gillis, Rafael Arrans, Annemarie Bakai, Carlos De Wagter, Tommy Knöös, Ben J. Mijnheer, Marta Paiusco, Bruce A. Perrin, Hans Welleweerd, and Peter Williams. Imrt treatment planning—a comparative inter-system and inter-centre planning exercise of the estro quasimodo group. *Radiotherapy and Oncology*, 76(3):354–361, Sep 2005.

- [BM11] Jamie Bahm and Lynn Montgomery. Treatment planning protocols: A method to improve consistency in imrt planning. *Medical Dosimetry*, 36(2):117–118, Jun 2011.
- [BSK⁺07] Sebastiaan Breedveld, Pascal RM Storchi, Marleen Keijzer, Arnold W Heemink, and Ben JM Heijmen. A novel approach to multi-criteria inverse planning for imrt. *Physics in Medicine & Biology*, 52(20):6339, 2007.
- [BSVH12] Sebastiaan Breedveld, Pascal R. M. Storchi, Peter W. J. Voet, and Ben J. M. Heijmen. icycle: Integrated, multicriterial beam angle, and profile optimization for generation of coplanar and noncoplanar imrt plans. *Medical Physics*, 39(2):951–963, 2012.
- [CB08] David Craft and Thomas Bortfeld. How many plans are needed in an imrt multi-objective plan database? *Physics in Medicine & Biology*, 53(11):2785, 2008.
- [CHL⁺05] Danny Z. Chen, Xiaobo S. Hu, Shuang Luan, Shahid A. Naqvi, Chao Wang, and Cedric X. Yu. Generalized geometric approaches for leaf sequencing problems in radiation therapy. In Rudolf Fleischer and Gerhard Trippen, editors, *Algorithms and Computation*, pages 271–281, Berlin, Heidelberg, 2005. Springer Berlin Heidelberg.
- [CHLW03] Danny Z. Chen, Xiaobo S. Hu, Shuang Luan, and Chao Wang. Geometric algorithms for static leaf sequencing problems in radiation therapy. In *Proceedings of the Nineteenth Annual Symposium on Computational Geometry*, SCG '03, page 88–97, New York, NY, USA, 2003. Association for Computing Machinery.
- [CHSB07] David Craft, Tarek Halabi, Helen A. Shih, and Thomas Bortfeld. An approach for practical multiobjective imrt treatment planning. *International Journal of Radiation Oncology*Biophysics*, 69(5):1600–1607, 2007.
- [CID⁺18] Savino Cilla, Anna Ianaro, Francesco Deodato, Gabriella Macchia, Cinzia Digesù, Vincenzo Valentini, and Alessio G. Morganti. Optimal beam margins in linac-based vmat stereotactic ablative body radiotherapy: a pareto front analysis for liver metastases. *Medical Dosimetry*, 43(3):291–301, 2018.
- [CLP⁺08] Hans T. Chung, Brian Lee, Eileen Park, Jiade J. Lu, and Ping Xia. Can all centers plan intensity-modulated radiotherapy (imrt) effectively? an external audit of dosimetric comparisons between three-dimensional conformal radiotherapy and imrt for adjuvant chemoradiation for gastric cancer. *International Journal of Radiation Oncology, Biology, Physics*, 71(4):1167–1174, Jul 2008.
- [Das09] Shiva K. Das. A method to dynamically balance intensity modulated radiotherapy dose between organs-at-risk. *Medical Physics*, 36(5):1744–1752, 2009.
- [DBB⁺11] Melanie T.M. Davidson, Samuel J. Blake, Deidre L. Batchelar, Patrick Cheung, and Katherine Mah. Assessing the role of volumetric modulated arc therapy (vmat) relative to imrt and helical tomotherapy in the management of localized, locally advanced, and post-operative prostate cancer. *International Journal of Radiation Oncology*Biophysics*, 80(5):1550–1558, 2011.
- [DCC⁺08] Indra J. Das, Chee-Wai Cheng, Kashmiri L. Chopra, Raj K. Mitra, Shiv P. Srivastava, and Eli Glatstein. Intensity-Modulated Radiation Therapy Dose Prescription, Recording, and Delivery: Patterns of Variability Among Institutions and Treatment Planning Systems. *JNCI: Journal of the National Cancer Institute*, 100(5):300–307, 03 2008.
- [EDFWF11] Craig Elith, Shane E. Dempsey, Naomi Findlay, and Helen M. Warren-Forward. An introduction to the intensity-modulated radiation therapy (imrt) techniques, tomotherapy, and vmat. *Journal of Medical Imaging and Radiation Sciences*, 42(1):37–43, 2011.
- [ESN⁺03] M A Earl, D M Shepard, S Naqvi, X A Li, and C X Yu. Inverse planning for intensity-modulated arc therapy using direct aperture optimization. *Physics in Medicine & Biology*, 48(8):1075, apr 2003.
- [FBC⁺14] Antonella Fogliata, Francesca Belosi, Alessandro Clivio, Piera Navarria, Giorgia Nicolini, Marta Scorsetti, Eugenio Vanetti, and Luca Cozzi. On the pre-clinical validation of a com-

mercial model-based optimisation engine: Application to volumetric modulated arc therapy for patients with lung or prostate cancer. *Radiotherapy and Oncology*, 113(3):385–391, Dec 2014.

- [Fra12] B.A. Fraass. Impact of complexity and computer control on errors in radiation therapy. *Annals of the ICRP*, 41(3-4):188–196, 2012. PMID: 23089018.
- [GLW⁺23] Tsegawbizu Gebru, Kirk Luca, Jonathan Wolf, Oluwatosin Kayode, Xiaofeng Yang, Justin Roper, and Jiahao Zhang. Evaluating pareto optimal tradeoffs for hippocampal avoidance whole brain radiotherapy with knowledge-based multicriteria optimization. *Medical Dosimetry*, 48(4):273–278, 2023.
- [HHD17] David H Howard, Jason Hockenberry, and Guy David. Personalized medicine when physicians induce demand. Working Paper 24054, National Bureau of Economic Research, November 2017.
- [KMHL08] Eric E Klein, Maria Mamalui-Hunter, and Daniel A Low. Delivery of modulated electron beams with conventional photon multi-leaf collimators. *Physics in Medicine & Biology*, 54(2):327, dec 2008.
- [LCM08] Gino J. Lim, Jaewon Choi, and Radhe Mohan. Iterative solution methods for beam angle and fluence map optimization in intensity modulated radiation therapy planning. *OR Spectrum*, 30(2):289–309, Apr 2008.
- [LFC06] Eva K. Lee, Tim Fox, and Ian Crocker. Simultaneous beam geometry and intensity map optimization in intensity-modulated radiation therapy. *International Journal of Radiation Oncology*Biophysics*, 64(1):301–320, 2006.
- [LSB03] Michael Lahanas, Eduard Schreibmann, and Dimos Baltas. Multiobjective inverse planning for intensity modulated radiotherapy with constraint-free gradient-based optimization algorithms. *Physics in Medicine & Biology*, 48(17):2843, 2003.
- [LZ24] Wang Li and Ming Zhang. Advances in medical imaging technologies and their impact on clinical practices. *Medicine Insights*, 1(2):1–8, Feb. 2024.
- [Mal12] Julian Malicki. The importance of accurate treatment planning, delivery, and dose verification. *Rep Pract Oncol Radiother*, 17(2):63–65, mar 2012.
- [MBK⁺21] P. Meyer, M.-C. Biston, C. Khamphan, T. Marghani, J. Mazurier, V. Bodez, L. Fezzani, P.A. Rigaud, G. Sidorski, L. Simon, and C. Robert. Automation in radiotherapy treatment planning: Examples of use in clinical practice and future trends for a complete automated workflow. *Cancer/Radiothérapie*, 25(6):617–622, 2021. 32e Congrès national de la Société française de radiothérapie oncologique.
- [NSSW14] Obioma Nwankwo, Dwi Seno K Sihono, Frank Schneider, and Frederik Wenz. A global quality assurance system for personalized radiation therapy treatment planning for the prostate (or other sites). *Physics in Medicine & Biology*, 59(18):5575, aug 2014.
- [NWA⁺18] Lydia W. Ng, Kenneth K. Wong, Chia-Ling Ally Wu, Richard Sposto, and Arthur J. Olch. Dose sculpting intensity modulated radiation therapy for vertebral body sparing in children with neuroblastoma. *International Journal of Radiation Oncology*Biophysics*, 101(3):550–557, 2018.
- [PBX00] A. B. Pugachev, A. L. Boyer, and L. Xing. Beam orientation optimization in intensity-modulated radiation treatment planning. *Medical Physics*, 27(6):1238–1245, 2000.
- [PLB⁺01] Andrei Pugachev, Jonathan G. Li, Arthur L. Boyer, Steven L. Hancock, Quynh-Thu Le, Sarah S. Donaldson, and Lei Xing. Role of beam orientation optimization in intensity-modulated radiation therapy. *International Journal of Radiation Oncology*Biophysics*, 50(2):551–560, 2001.
- [QMR⁺16] Anne S. Quante, Chang Ming, Miriam Rottmann, Jutta Engel, Stefan Boeck, Volker Heine-mann, Christoph Benedikt Westphalen, and Konstantin Strauch. Projections of cancer

- incidence and cancer-related deaths in germany by 2020 and 2030. *Cancer Medicine*, 5(9):2649–2656, 2016.
- [Ray24] RayStation. Raystation tps, 2024.
- [RDL04] H Edwin Romeijn, James F Dempsey, and Jonathan G Li. A unifying framework for multi-criteria fluence map optimization models. *Physics in Medicine & Biology*, 49(10):1991, may 2004.
- [RDR15] Kobe Reynders and Dirk De Ruyscher. Radiotherapy and immunotherapy: Improving cancer treatment through synergy. In *Immuno-Oncology*. S.Karger AG, 09 2015.
- [REB⁺19] Anne Richter, Florian Exner, Klaus Bratengeier, Bülent Polat, Michael Flentje, and Stefan Weick. Impact of beam configuration on vmat plan quality for pinnacle3auto-planning for head and neck cases. *Radiation Oncology*, 14(1):12, Jan 2019.
- [RLB05] Delphine Rossille, Jean-François Laurent, and Anita Burgun. Modelling a decision-support system for oncology using rule-based and case-based reasoning methodologies. *International Journal of Medical Informatics*, 74(2):299–306, 2005. MIE 2003.
- [RMA⁺15] Romain Rivoirard, Coralie Moncharmont, Avi Assouline, Pierre Auberdiac, Benoit Mery, Alexander Tuan Falk, Pierre Annède, Jane-Chloé Trone, Jean-Baptiste Guy, Nicolas Vial, Pierre Fournel, Yacine Merrouche, Cyrus Chargari, and Nicolas Magné. Radiotherapy for head and neck cancer in nonagenarian patients: a possible cornerstone? *European Archives of Oto-Rhino-Laryngology*, 272(3):719–725, Mar 2015.
- [Rob08] M. H. Robinson. Radiotherapy: technical aspects. *Medicine*, 36(1):9–14, Jan 2008.
- [SEL⁺02] D. M. Shepard, M. A. Earl, X. A. Li, S. Naqvi, and C. Yu. Direct aperture optimization: A turnkey solution for step-and-shoot imrt. *Medical Physics*, 29(6):1007–1018, 2002.
- [SPSM16] C. R. Smittenaar, K. A. Petersen, K. Stewart, and N. Moitt. Cancer incidence and mortality projections in the uk until 2035. *British Journal of Cancer*, 115(9):1147–1155, Oct 2016.
- [TDD⁺15] Jim P. Tol, Alexander R. Delaney, Max Dahele, Ben J. Slotman, and Wilko F.A.R. Verbakel. Evaluation of a knowledge-based planning solution for head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics*, 91(3):612–620, Mar 2015.
- [TKM⁺07] Christian Thieke, Karl-Heinz Küfer, Michael Monz, Alexander Scherrer, Fernando Alonso, Uwe Oelfke, Peter E Huber, Jürgen Debus, and Thomas Bortfeld. A new concept for interactive radiotherapy planning with multicriteria optimization: first clinical evaluation. *Radiotherapy and Oncology*, 85(2):292–298, 2007.
- [Var24] Varian. Eclipse™ 2024.
- [WBFM07] MJ Williams, MJ Bailey, D Forstner, and PE Metcalfe. Multicentre quality assurance of intensity-modulated radiation therapy plans: A precursor to clinical trials. *Australasian Radiology*, 51(5):472–479, 2007.
- [WZHZ19] Chunhao Wang, Xiaofeng Zhu, Julian C. Hong, and Dandan Zheng. Artificial intelligence in radiotherapy treatment planning: Present and future. *Technology in Cancer Research & Treatment*, 18:1533033819873922, 2019. PMID: 31495281.
- [XHV02] Ping Xia, Andrew B. Hwang, and Lynn J. Verhey. A leaf sequencing algorithm to enlarge treatment field length in imrt. *Medical Physics*, 29(6):991–998, 2002.
- [XV01] Ping Xia and Lynn J. Verhey. Delivery systems of intensity-modulated radiotherapy using conventional multileaf collimators. *Medical Dosimetry*, 26(2):169–177, Jun 2001.
- [YCA⁺15] Brian Yard, Eui Kyu Chie, Drew J. Adams, Craig Peacock, and Mohamed E. Abazeed. Radiotherapy in the era of precision medicine. *Seminars in Radiation Oncology*, 25(4):227–236, 2015. Predictors of Radiation Response.
- [YSZ⁺20] Yiwei Yang, Kainan Shao, Jie Zhang, Ming Chen, Yuanyuan Chen, and Guoping Shan. Automatic planning for nasopharyngeal carcinoma based on progressive optimization

in raystation treatment planning system. *Technology in Cancer Research & Treatment*, 19:1533033820915710, 2020. PMID: 32552600.

- [ZHZ⁺22] Masoud Zarepisheh, Linda Hong, Ying Zhou, Qijie Huang, Jie Yang, Gourav Jhanwar, Hai D. Pham, Pinar Dursun, Pengpeng Zhang, Margie A. Hunt, Gig S. Mageras, Jonathan T. Yang, Yoshiya (Josh) Yamada, and Joseph O. Deasy. Automated and clinically optimal treatment planning for cancer radiotherapy. *INFORMS Journal on Applied Analytics*, 52(1):69–89, 2022.
- [ZPS⁺20] Quanbin Zhang, Yingying Peng, Xianlu Song, Hui Yu, Linjing Wang, and Shuxu Zhang. Dosimetric evaluation of automatic and manual plans for early nasopharyngeal carcinoma to radiotherapy. *Medical Dosimetry*, 45(1):e13–e20, 2020.