The emerging role of Artificial Intelligence in proton therapy

Isaksson, Lars Johannes; Mastroleo, Federico; Vincini, Maria Giulia; Marvaso, Giulia; Zaffaroni, Mattia; Gola, Michal; Mazzola, Giovanni Carlo; Bergamaschi, Luca; Gaito, Simona; Alongi, Filippo

Published in:
Critical Reviews in Oncology/Hematology

DOI:
10.1016/j.critrevonc.2024.104485

Critical Reviews in Oncology / Hematology 204 (2024) 104485

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

The emerging role of Artificial Intelligence in proton therapy: A review

Lars Johannes Isaksson [a,b,1], Federico Mastroleo [a,b,1], Maria Giulia Vincini [a,*], Giulia Marvaso [a,b,*], Mattia Zaffaroni [a], Michał Gola [c], Giovanni Carlo Mazzola [a], Luca Bergamaschi [a], Simona Gaito [d,e], Filippo Alongi [f], Jerome Doyen [g,h], Piero Fossati [i,j], Karin Haustermans [k], Morten Høyer [l], Johannes Albertus Langendijk [m], Raùl Matute [n], Ester Orlandi [o,p], Marco Schwarz [q], Esther G.C. Troost [r,s,t,u,v], Vladimir Vondracek [w], Davide La Torre [b,x], Giuseppe Curigliano [b,y], Giuseppe Petralia [b,z], Roberto Orecchia [aa], Daniela Alterio [a], Barbara Alicja Jereczek-Fossa [a,b]

[a] Division of Radiation Oncology, IEO European Institute of Oncology IRCCS, Milan 20141, Italy
[b] Department of Oncology and Hemato-Oncology, University of Milan, Milan 20141, Italy
[c] Department of Human Histology and Embryology, Collegium Medicum, School of Medicine, University of Warmia and Mazury, Olsztyn 10-082, Poland
[d] Proton Clinical Outcomes Unit, The Christie NHS Proton Beam Therapy Centre, Manchester M20 4BX, UK
[e] Division of Clinical Cancer Science, School of Medical Sciences, The University of Manchester Manchester M13 9PL, UK
[f] Department of Advanced Radiation Oncology, IRCCS Sacro Cuore Don Calabria, 37024 Negrar-Verona, Italy & DSMC, University of Brescia, Brescia, Italy
[g] Centre Antoine-Lacassagne, University of Côte d'Azur, Nice 06189, France
[h] University Côte d'Azur, CNRS UMR 7284, INSERM U1081, Centre Antoine Lacassagne, Institute for Research on Cancer and Aging of Nice (IRCAN), 06189 Nice, France, Centre Antoine Lacassagne, Nice 06189, France
[i] EBG MedAustron GmbH, Marie-Curie-Str. 5, Wiener Neustadt 2700, Austria
[j] Department of General and Translational Oncology and Hematology, Karl Landsteiner University of Health Sciences, Krems an der Donau, 3500, Austria
[k] Department of Radiation Oncology, University Hospitals Leuven, Leuven, Belgium
[l] Aarhus University (AU), Nordre Ringgade 1, Aarhus C 8000, Denmark
[m] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[n] Centro de Protonterapia Quironsalud, Pozuelo de Alarcón, Madrid 28223, Spain
[o] Radiation Oncology Unit, Clinical Department, CNAO National Center for Oncological Hadrontherapy, Pavia, Italy
[p] Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy
[q] Radiation Oncology Department, University of Washington, Seattle, WA 98109, USA
[r] OncoRay-National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden-Rossendorf, Dresden 01309, Germany
[s] German Cancer Consortium (DKTK), Partner Site Dresden, and German Cancer Research Center (DKFZ), Heidelberg, Germany
[t] National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany: German Cancer Research Center (DKFZ), Heidelberg, Germany; Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, and Helmholtz Association/Helmholtz-Zentrum Dresden-Rossendorf (HZDR), Dresden 01307, Germany
[u] Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden 01309, Germany
[v] Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiooncology-OncoRay, Dresden 01328, Germany
[w] Proton Therapy Centre Czech, Prague, Czech Republic and Department of Health Care Disciplines and Population Protection, Faculty of Biomedical Engineering, Czech Technical University Prague, Kladno, Czech Republic
[x] SKEMA Business School, Université Côte d'Azur, Sophia Antipolis, France
[y] Division of Early Drug Development for Innovative Therapy, European Institute of Oncology, IRCCS, Milan 20141, Italy
[z] Division of Radiology, IEO European Institute of Oncology IRCCS, Milan 20141, Italy
[aa] Scientific Directorate, IEO European Institute of Oncology IRCCS, Milan 20141, Italy

A R T I C L E I N F O

Keywords:
Artificial intelligence

A B S T R A C T

Artificial intelligence (AI) has made a tremendous impact in the space of healthcare, and proton therapy is not an exception. Proton therapy has witnessed growing popularity in oncology over recent decades, and researchers

* Corresponding authors.
E-mail addresses: mariagiulia.vincini@ieo.it (M.G. Vincini), Giulia.marvaso@ieo.it (G. Marvaso).
[1] Co-first author

https://doi.org/10.1016/j.critrevonc.2024.104485
Received 23 April 2024; Accepted 25 August 2024
Available online 2 September 2024
1040-8428/

Proton therapy
Review

are increasingly looking to develop AI and machine learning tools to aid in various steps of the treatment planning and delivery processes. This review delves into the emergent role of AI in proton therapy, evaluating its development, advantages, intended clinical contexts, and areas of application. Through the analysis of 76 studies, we aim to underscore the importance of AI applications in advancing proton therapy and to highlight their prospective influence on clinical practices.

1. Introduction

Over the past decades, proton therapy (PT) has been affirming its role, reaching more than 113 operational PT centers worldwide and an additional 32 in construction as of December 2023 (PTCOG, 2023). Although the scope of indications is gradually expanding and scientific interest in PT is growing, with an annual increase of up to 13 % in new publications on the subject (Vincini et al., 2023), it is still less commonly prescribed compared to photon therapy. In fact, only about 1 % of patients undergoing radiation therapy receive proton or heavy-ion treatments (Mohan, 2022). Due to their favorable dosimetric properties, protons are often the preferred treatment option for cancers in children, or those located around sensitive organs (critical organs-at-risk, OARs) like the brain, spinal cord, heart, or eyes (Hu et al., 2018). Furthermore, PT has also been associated with a reduced risk of secondary malignancies (Lewis et al., 2022; Jain et al., 2020) and with a lower severe radiation-induced lymphopenia rate compared to intensity-modulated radiotherapy. The latter could be of great importance in patients also treated with immunotherapy, as radiation treatment-related lymphopenia is potentially correlated with inferior survival rates among these patients (Cho et al., 2019; Chen et al., 2023a).

Even though PT holds promise from various perspectives, it could come with some drawbacks. First and foremost, PT is more expensive than conventional radiotherapy (Bortfeld and Loeffler, 2017; Huang et al., 2021), not only because it requires investing in new equipment and infrastructure, but also because of the increased indirect costs of human resources, maintenance, and overhead (Chen et al., 2023b). PT can also require a longer treatment time than traditional photon-beam treatments due to the complex machinery and the need for more precise planning and setup (Jin et al., 2020). In a recent survey study answered by 19 different PT centers, the responders cited reimbursement issues (29 %) and/or technical limitations (20 %) among the major reasons for not treating patients with PT (Tambas et al., 2022). In addition, centers offering PT must deal with the standard implications that come with conventional radiation therapy, including every aspect of the treatment planning procedure. The multifaceted and complex challenges in PT position it as a field where the advent of new developments in artificial intelligence (AI) could have a substantial influence.

AI is a branch of computer science that focuses on creating systems capable of performing tasks that typically require human intelligence, including learning, reasoning, problem-solving, perception, and language understanding. It simulates human cognitive functions using algorithms, a process that incorporates a diverse range of techniques. These include machine learning (ML), which focuses on the development of systems that can learn from and make decisions based on data; neural networks, which are inspired by the human brain's structure and function; deep learning (DL), a subset of ML that uses layered neural networks for more complex data interpretation; and natural language processing, which enables machines to understand and interpret human language.

Applications of AI span a diverse array of medical contexts, encompassing tasks such as estimating the side effects of various treatment regimens, segmenting regions of interest in medical images, ameliorating treatment planning and delivery, and generating synthetic data (Li et al., 2022; Landry et al., 2023; Krishnamurthy et al., 2022; Yousefirizi et al., 2021). Beyond simply overcoming challenges like treatment time, these advancements could transform PT by boosting its therapeutic benefits, making it a more powerful and accessible option for a wider range of cancer patients. Moreover, in the modern era of big data, AI-based algorithms are expected to leverage the information in clinical, biological, technical, dosimetric, and imaging sources to its fullest extent, paving the way for better utilization of PT on a patient-by-patient basis.

In this review, we survey the landscape of AI applications in PT, focusing on how AI tools are being developed and used for PT today, what their advantages and disadvantages are, and what clinical contexts they are designed for. Given the potential of AI applications, it is imperative to explore and assess their potential impact on clinical practice in PT.

2. Methods

2.1. Data collection

The Scopus and PubMed databases were searched for the following keywords and collected all unique hits:

- Title: "proton therapy", "proton beam therapy", "proton radiotherapy", or "proton radiation therapy", and
- Title or abstract: "artificial intelligence", "machine learning", "deep learning", "artificial neural network*", "support vector machine*", "random forest*", or "radiomic*", and
- Language: English

In addition to including the catch-all terms *AI* and *machine learning*, these keywords were chosen to mimic the most common machine learning methods applied in radiation therapy (Engineering Mathematics, 2021). For each paper, publication date, abstract, URL, DOI, and BibTeX entries were collected.

2.2. Analysis

To identify trends in the field, a statistical analysis was conducted on the collected papers, examining publication year, cancer site, and keywords (including adaptive therapy, neural networks and DL, convolutional neural networks (CNNs), and radiomics). The results were then visualized through plots.

To aid in the analysis, the large language model ChatGPT (version gpt-4–0613) [https://cdn.openai.com/papers/gpt-4-system-card.pdf] was used to answer questions regarding the topic of each paper and summarize their conclusion. Specifically, we gave the model the abstract and asked it to answer the following questions: "What was AI used for in the study? Answer in one sentence.", "What is the key takeaway of the paper? Answer in one sentence.", and "What organ/body region is the paper focused on?". To condition the model into answering consistently and truthfully, we gave it the following system prompt[1]: "You will be asked to read a scientific paper abstract and then answer questions about it. The paper is about a specific AI application in PT. Please prioritize correctness in your answers. If you don't know the answer, respond with \'N/A\'.". The metadata, abstracts, and ChatGPT answers for all papers are available online in Supplementary Table 1.

[1] The system prompt is a special message used to steer the model's behavior. The model is trained to always pay special attention to it.

By using Latent Dirichlet Allocation (LDA[2]) on the collection of abstracts and the answers to the "What was AI used for in the study? Answer in one sentence." question, we delineated the thematic content of the papers into various topics. Each paper was then categorized into one of the derived topics, following a manual review and subsequent refinement of certain categories.

3. Results

3.1. Statistics

A total of 76 unique papers were included in the review, the vast majority of which (71 papers, or 93 %) were published in 2020–2023 (Fig. 1). Most papers (29) (Barajas et al., 2021; Baumann et al., 2020; Chang et al., 2022a, 2022b, 2022c, 2023a, 2023b, 2022c; Charyyev et al., 2020; Grewal et al., 2020; Gueth et al., 2013; Hu et al., 2020; Javaid et al., 2021; Jiang et al., 2023; Kazemi Kozani and Magiera, 2022; Lerendegui-Marco et al., 2022; Li et al., 2019; Ma et al., 2020; Newpower et al., 2023; Polf et al., 2022; Sato et al., 2023; Schilling et al., 2023; Smolders et al., 2023; Stasica et al., 2023; Yamazaki et al., 2023; Yao et al., 2021; York et al., 2021; Zhang et al., 2022a, 2020) did not focus on a specific body region or cancer site, but among those that did, head and neck (19 papers) (Chang et al., 2022b; Borderias-Villarroel et al., 2023; Chen et al., 2022; Deiter et al., 2020; Harms et al., 2020; Huet-Dastarac et al., 2023; Kalendralis et al., 2023; Kouwenberg et al., 2021; Lalonde et al., 2020; Liu et al., 2022, 2021; Mentzel et al., 2022; Pang et al., 2023; Pietsch et al., 2023; Thummerer et al., 2020a; Wang et al., 2021; Zhang et al., 2022b; Zimmermann et al., 2022), prostate (9 papers) (Bazargani et al., 2023; Elmahdy et al., 2018, 2019; Jiang et al., 2022a; Vazquez et al., 2023; Wang et al., 2022a; Yang et al., 2021; Zhang et al., 2023; Zimmermann et al., 2021), and brain (9 papers) (Zimmermann et al., 2022; Dominietto et al., 2019; Kazemifar et al., 2020; Maspero et al., 2020; Pirlepesov et al., 2022; Qiu et al., 2020; Thummerer et al., 2020b; Wang et al., 2022b, 2022c) were the most studied ones, followed by the lung (7 papers) (Zhang et al., 2023; O'Reilly et al., 2020; Smolders et al., 2022; Spezialetti et al., 2021; Thummerer et al., 2021, 2022; Zhang et al., 2021), liver (3 papers) (Chamseddine et al., 2023; Jampa-Ngern et al., 2021; Liu et al., 2019), colon (3 papers) (Zhang et al., 2021; Florkow et al., 2020; Uh et al., 2021), and eye (1 paper) (Antonioli et al., 2021) (Fig. 2).

The most common clinical subject area of the studies was adaptive PT (n=20), followed by pediatric cancers (n=5). Most studies (n=52) explicitly focused on various aspects of artificial neural networks and DL, with 15 studies specifically dedicated to CNNs. Other ML approaches were rarely mentioned, with the only recurring methods being random forests and gradient-boosted models (n=5). Only one study investigated radiomics.

3.2. Topics of AI applications in PT

In this section, we cover the articles in the seven resulting categories of AI applications in PT:

- AI for anatomical delineation and segmentation (3 papers)
- AI for image enhancement and quality (6 papers)
- AI for synthetic image generation (14 papers)
- AI for treatment planning, support, and delivery (10 papers)
- AI for dose prediction (24 papers)
- AI for outcome prediction (6 papers)
- Other (13 papers)

An overview of the different papers, their corresponding cancer site, and their topic is presented in Table 1.

3.2.1. AI for anatomical delineation and segmentation

Manual delineation of organs and regions of interest is a laborious and time-intensive process, prompting the exploration of alternative approaches. Within this context, AI is emerging as a promising adjunct for the identification and segmentation of anatomical structures, primarily through DL techniques. Smolders et al. (2023). utilized DL to automate the delineation of target and OAR contours in daily imaging before treatment, finding that, while the dosimetric impact of using automatic contours for OAR is minimal, the significance of automatic target contours necessitates manual verification due to their substantial impact. Further studies have focused on intensity-modulated PT (IMPT) for prostate cancer, including an automated bladder segmentation model utilizing deformable image registration and a 3D CNN, which demonstrated high accuracy and promising potential for online adaptive PT (Zhang et al., 2022b). Building on their prior work, the authors developed a robust registration pipeline for automatic bladder segmentation, achieving 80 % usability without manual corrections (Zimmermann et al., 2022). This suggests improved system robustness and potential for reduced side effects. Numerous commercially available auto-contouring algorithms have also started to emerge for use in clinical software, but these tend to diverge from the conventional academic scientific model, making them more difficult to scrutinize.

3.2.2. AI for Image Enhancement and Quality Improvement

AI models can enhance and improve the quality of medical images, potentially offering clinicians clearer insights and improving the accuracy and robustness of quantitative analyses. Yamazaki et al. (2023) focused on enhancing 3D surface imaging through the light sectioning method, integrating it with computed tomography (CT) data to prevent collisions in PT. On the other hand, Uh et al. (2021) developed a DL model to improve abdominal and pelvic Cone Beam CT (CBCT) images in children using a combined dataset and body size normalization, achieving improved accuracy, dose distribution, and proton range compared to separate models for each region.

Barajas et al. (Krishnamurthy et al., 2022) and York et al. (Stasica et al., 2023) both leverage machine learning techniques for noise reduction and image correction in Compton camera data used for PT. Barajas et al. employ machine learning ensembles like random forests, while York et al. utilize DL approaches. In a related setting, Chang et al. (2022a) developed an unsupervised framework for metal artifact reduction in patients with implants, while Charyyev et al. (2020) used a residual GAN to improve the image quality of proton portal imaging, particularly beneficial for patient position verification.

3.2.3. AI for synthetic image generation

Synthetic data refers to artificially generated datasets that mimic real-world data without involving the collection of information from actual patients. This approach can be used to enlarge existing datasets without concerns for privacy and time-consuming data collection, thereby efficiently improving AI model performance. In the area of synthetic data generating to improve PT, two standout applications are:

- generating synthetic CT images (sCTs) from CBCT images, typically to improve dose calculation and treatment planning in adaptive PT and;
- generating sCTs from magnetic resonance (MR) images, often with the vision of an MR-only PT workflow.

A series of recent studies have investigated the use of sCTs for adaptive PT. One study found that a conditional Generative Adversarial Network (cGAN) was the most effective architecture in creating sCT from CBCT for nasopharyngeal cancer treatment planning (Pang et al., 2023). Studies have also shown that cone-beam CT-based synthetic CTs (both in 3D and 4D), particularly when enhanced with a patient-specific

[2] LDA is a natural language processing technique used to model topics in corpra of text.

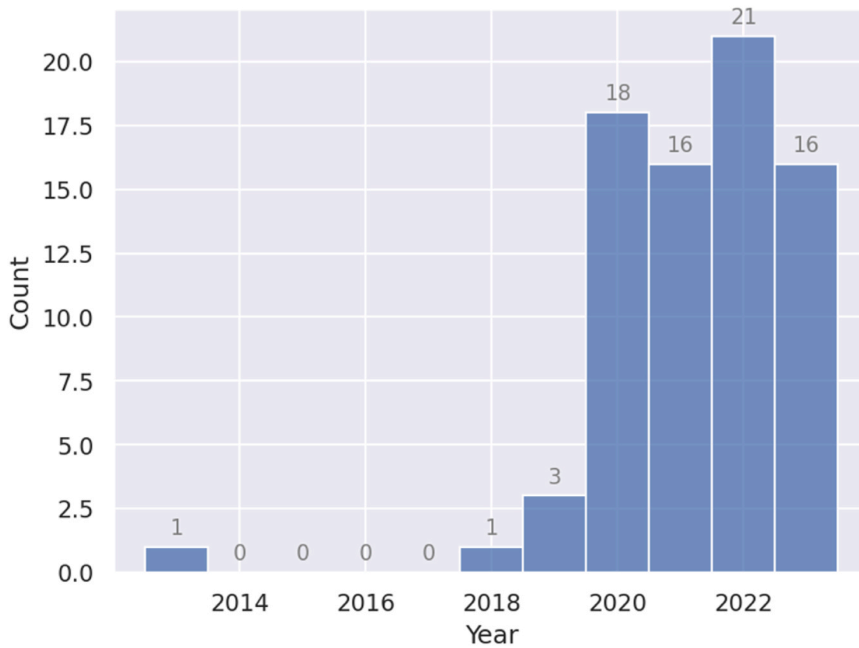

Fig. 1. Number of studies on AI applications for proton therapy published each year.

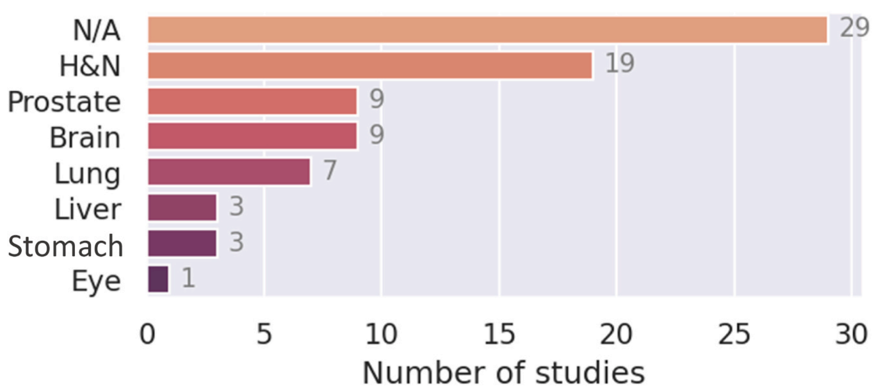

Fig. 2. Number of studies focusing on each specific body region. Most papers did not cover a particular region or cancer site (N/A). *List of abbreviations: H&N (Head and neck).*

correction method, can be effectively used for accurate proton dose calculations in lung cancer patients, despite the correction method having only limited influence on clinically relevant parameters (Thummerer et al., 2021, 2022). Additionally, Wang et al., 2022b highlighted the superiority of cycle-generative adversarial networks (cycle-GANs) with self-attention over conventional GANs in generating sCT for children with brain tumors. The effectiveness of generating sCTs from CBCT and MR images for head and neck cancer was explored by Thummerer et al., 2020a, 2020b, noting the superior image quality and dose calculation accuracy of CBCT-based sCTs created by a CNN.

Research on generating sCTs from MR images has advanced steadily in recent years. Zimmermann et al., 2022, 2021 demonstrated the potential of 3D U-Net and ResNet-based architectures and pre-trained neural networks, respectively, in creating sCTs for PT in meningioma and prostate cancer, emphasizing MR sequence independence and expanded field of view capabilities. This application has been extended to pediatric patients with abdominal tumors, affirming the practicality of an MR-only workflow in photon-radiotherapy and PT planning using AI-generated sCTs (Florkow et al., 2020). In this scenario, a conditional GANs was also used for brain tumor sCT generation, highlighting the dosimetric precision and accuracy in MR-based dose calculation for pediatric brain cancer, even with heterogeneous data sets (Kazemifar et al., 2020; Maspero et al., 2020). Liu et al., 2019 contributed to this field by showcasing the feasibility of DL methods in the nonlinear mapping of MR and CT pairs, specifically for abdominal sCT image generation, furthering the prospect of an MR-only approach in liver proton radiotherapy.

A couple of papers have made strides in enhancing MR-only treatment planning for PT by generating synthetic relative proton stopping power (sRPSP) images and synthetic dual-energy CT (sDECT) from MR sequences. Wang et al., 2022c focused on developing sRPSP images from MR sequences and a quality assurance (QA) tool for safe in tegration into clinical practice. Utilizing images of 195 pediatric brain tumor patients, the team trained seventeen consistent-cycle generative adversarial network (ccGAN) models with various MR sequence combinations, finding that sRPSP images from a single T1-weighted or T2-weighted sequence outperformed multi-sequence models in mean absolute error (MAE). Liu et al., 2021 set out to overcome the limitation of MR in providing stopping power ratio (SPR) information by generating sDECT from MR to calculate SPR maps for PT. Employing a novel label GAN-based model, they validated their approach using 57 head and neck cancer patient datasets, showing that the generated sDECT and derived SPR maps closely matched clinical DECT and corresponding SPR, with significantly improved accuracy over traditional Cycle GANs.

Table 1
Overview of included documents.

Author		Year, journal	Site	Category
Antonioli et al.	Convolutional Neural Networks Cascade for Automatic Pupil and Iris Detection in Ocular Proton Therapy.	2021, Sensors (Basel)	eye	Other
Barajas et al.	Classification of Compton Camera Based Prompt Gamma Imaging for Proton Radiotherapy by Random Forests	2021, NA	n/a	AI for Image Enhancement and Quality
Baumann et al.	Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer	2020, JAMA Oncol	n/a	AI for Outcome Prediction
Bazargani et al.	Magnetic resonance imaging radiomic features for recurrent prostate cancer following proton radiation therapy–A pilot study	2023, Urol Oncol	prostate	Other
Borderias et al.	Machine learning-based automatic proton therapy planning: Impact of post-processing and dose-mimicking in plan robustness.	2023, Med Phys	head & neck	AI for Treatment Planning, Support, and Delivery
Chamseddine et al.	Predictive Model of Liver Toxicity to Aid the Personalized Selection of Proton Versus Photon Therapy in Hepatocellular Carcinoma	2023, Int J Radiat Oncol Biol Phys	liver	AI for Outcome Prediction
Chang et al.	Multimodal imaging-based material mass density estimation for proton therapy using supervised deep learning.	2023, Br J Radiol	n/a	AI for Dose Prediction and Calculation
Chang et al.	Dual-energy CT based mass density and relative stopping power estimation for proton therapy using physics-informed deep learning.	2022, Phys Med Biol	n/a	AI for Dose Prediction and Calculation
Chang et al.	Physics-informed multi-modal imaging-based material characterization for proton therapy	2023, NA	n/a	AI for Dose Prediction and Calculation
Chang et al.	An unsupervised patient-specific metal artifact reduction framework for proton therapy	2022, NA	n/a	AI for Image Enhancement and Quality
Chang et al.	A Deep Learning Approach to Transform Two Orthogonal X-Ray Images to Volumetric Images for Image-guided Proton Therapy	2022, NA	n/a	AI for Treatment Planning, Support, and Delivery
Chang et al.	Validation of a deep learning-based material estimation model for Monte Carlo dose calculation in proton therapy.	2022, Phys Med Biol	n/a	AI for Treatment Planning, Support, and Delivery
Charyyev et al.	High quality proton portal imaging using deep learning for proton radiation therapy: A phantom study	2020, Biomed Phys Eng Express	n/a	AI for Image Enhancement and Quality
Chen et al.	Predictive performance of different NTCP techniques for radiation-induced esophagitis in NSCLC patients receiving proton radiotherapy	2022, Scientific Reports	head & neck	AI for Outcome Prediction
Deiter et al.	Evaluation of replanning in intensity-modulated proton therapy for oropharyngeal cancer: Factors influencing plan robustness.	2020, Med Dosim	head & neck	AI for Treatment Planning, Support, and Delivery
Dominietto et al.	Role of Complex Networks for Integrating Medical Images and Radiomic Features of Intracranial Ependymoma Patients in Response to Proton Radiotherapy	2020, Front Med (Lausanne)	brain	Other
Elmahdy et al.	Robust contour propagation using deep learning and image registration for online adaptive proton therapy of prostate cancer.	2019, Med Phys	prostate	AI for Anatomical Delineation and Segmentation
Elmahdy et al.	Evaluation of multi-metric registration for online adaptive proton therapy of prostate cancer	2018, NA	prostate	AI for Anatomical Delineation and Segmentation
Florkow et al.	Deep learning-enabled MRI-only photon and proton therapy treatment planning for pediatric abdominal tumors.	2020, Radiother Oncol	colon	AI for Synthetic Data Generation
Grewal et al.	Prediction of the output factor using machine and deep learning approach in uniform scanning proton therapy.	2020, J Appl Clin Med Phys	n/a	Other
Gueth et al.	Machine learning-based patient specific prompt-gamma dose	2013, Phys Med Biol	n/a	AI for Dose Prediction and Calculation

(continued on next page)

Table 1 (*continued*)

Author		Year, journal	Site	Category
	monitoring in proton therapy.			
Harms et al.	Cone-beam CT-derived relative stopping power map generation via deep learning for proton radiotherapy	2020, Med Phys	head & neck	AI for Dose Prediction and Calculation
Hu et al.	A machine learning framework with anatomical prior for online dose verification using positron emitters and PET in proton therapy.	2020, Phys Med Biol	n/a	AI for Dose Prediction and Calculation
Huet et al.	Patient selection for proton therapy using Normal Tissue Complication Probability with deep learning dose prediction for oropharyngeal cancer.	2023, Med Phys	head & neck	AI for Outcome Prediction
Jampa et al.	Prediction of liver Dmean for proton beam therapy using deep learning and contour-based data augmentation.	2021, J Radiat Res	liver	AI for Dose Prediction and Calculation
Javaid et al.	Denoising proton therapy Monte Carlo dose distributions in multiple tumor sites: A comparative neural networks architecture study.	2021, Phys Med	n/a	AI for Dose Prediction and Calculation
Jiang et al.	A feasibility study of enhanced prompt gamma imaging for range verification in proton therapy using deep learning.	2023, Phys Med Biol	n/a	Other
Jiang et al.	3D in vivo dose verification in prostate proton therapy with deep learning-based proton-acoustic imaging	2022, Phys Med Biol	prostate	AI for Treatment Planning, Support, and Delivery
Kalendralis et al.	Technical note: A knowledge graph approach to registering tumor specific data of patient-candidates for proton therapy in the Netherlands.	2022, Med Phys	head & neck	Other
Kazemi et al.	Machine learning-based event recognition in SiFi Compton camera imaging for proton therapy monitoring.	2022, Phys Med Biol	n/a	AI for Treatment Planning, Support, and Delivery
Kazemifar et al.	Dosimetric evaluation of synthetic CT generated with GANs for MRI-only proton therapy treatment planning of brain tumors.	2020, J Appl Clin Med Phys	brain	AI for Synthetic Data Generation
Kouwenberg et al.	Model based patient pre-selection for intensity-modulated proton therapy (IMPT) using automated treatment planning and machine learning.	2021, Radiother Oncol	head & neck	AI for Treatment Planning, Support, and Delivery
Lalonde et al.	Evaluation of CBCT scatter correction using deep convolutional neural networks for head and neck adaptive proton therapy.	2020, Phys Med Biol	head & neck	AI for Dose Prediction and Calculation
Lerendegui-Marco et al.	Towards machine learning aided real-time range imaging in proton therapy.	2022, Sci Rep	n/a	Other
Li et al.	Technical Note: Machine learning approaches for range and dose verification in proton therapy using proton-induced positron emitters.	2019, Med Phys	n/a	AI for Dose Prediction and Calculation
Liu et al.	Synthetic dual-energy CT for MRI-only based proton therapy treatment planning using label-GAN	2021, Phys Med Biol	head & neck	AI for Synthetic Data Generation
Liu et al.	Machine learning based oxygen and carbon concentration derivation using dual-energy CT for PET-based dose verification in proton therapy.	2022, Med Phys	head & neck	Other
Liu et al.	MRI-based treatment planning for proton radiotherapy: Dosimetric validation of a deep learning-based liver synthetic CT generation method	2019, Phys Med Biol	liver	AI for Synthetic Data Generation
Ma et al.	Feasibility study of patient-specific dose verification in proton therapy utilizing positron emission tomography (PET) and generative adversarial network (GAN).	2020, Med Phys	n/a	AI for Dose Prediction and Calculation
Maspero et al.	Deep learning-based synthetic CT generation for pediatric brain MR-only photon and proton radiotherapy	2020, Radiother Oncol	brain	AI for Synthetic Data Generation
Mentzel et al.	Small beams, fast predictions: a comparison of machine learning dose prediction models for proton minibeam therapy	2022, Med Phys	head & neck	AI for Dose Prediction and Calculation

(*continued on next page*)

Table 1 (*continued*)

Author		Year, journal	Site	Category
Newpower et al.	Spot delivery error predictions for intensity modulated proton therapy using robustness analysis with machine learning.	2023, J Appl Clin Med Phys	n/a	AI for Treatment Planning, Support, and Delivery
O'Reilly et al.	Dose to Highly Functional Ventilation Zones Improves Prediction of Radiation Pneumonitis for Proton and Photon Lung Cancer Radiation Therapy	2020, Int J Radiat Oncol Biol Phys	lung	Other
Pang et al.	Comparison and evaluation of different deep learning models of synthetic CT generation from CBCT for nasopharynx cancer adaptive proton therapy.	2023, Med Phys	head & neck	AI for Synthetic Data Generation
Pietsch et al.	Automatic detection and classification of treatment deviations in proton therapy from realistically simulated prompt gamma imaging data.	2022, Med Phys	head & neck	Other
Pirlepesov et al.	Three-dimensional dose and LETD prediction in proton therapy using artificial neural networks	2022, Med Phys	brain	AI for Dose Prediction and Calculation
Polf et al.	Applications of Machine Learning to Improve the Clinical Viability of Compton Camera Based in vivo Range Verification in Proton Radiotherapy	2022, Front Phys	n/a	Other
Qiu et al.	A Comparison Study of Machine Learning (Random Survival Forest) and Classic Statistic (Cox Proportional Hazards) for Predicting Progression in High-Grade Glioma after Proton and Carbon Ion Radiotherapy	2020, Front Oncol	brain	AI for Outcome Prediction
Sato et al.	A simulation study of in-beam visualization system for proton therapy by monitoring scattered protons.	2023, Front Med (Lausanne)	n/a	AI for Dose Prediction and Calculation
Schilling et al.	Uncertainty-aware spot rejection rate as quality metric for proton therapy using a digital tracking calorimeter.	2023, Phys Med Biol	n/a	AI for Dose Prediction and Calculation
Smolders et al.	Deformable Image Registration Uncertainty Quantification Using Deep Learning for Dose Accumulation in Adaptive Proton Therapy	2022, NA	lung	Other
Smolders et al.	Dosimetric comparison of autocontouring techniques for online adaptive proton therapy.	2023, Phys Med Biol	n/a	AI for Anatomical Delineation and Segmentation
Spezialetti et al.	Using Deep Learning for Fast Dose Refinement in Proton Therapy	2021, NA	lung	AI for Dose Prediction and Calculation
Stasica et al.	Single proton LET characterization with the Timepix detector and artificial intelligence for advanced proton therapy treatment planning.	2023, Phys Med Biol	n/a	Other
Thummerer et al.	Comparison of CBCT based synthetic CT methods suitable for proton dose calculations in adaptive proton therapy	2020, Phys Med Biol	brain, head & neck	AI for Synthetic Data Generation
Thummerer et al.	Comparison of the suitability of CBCT- And MR-based synthetic CTs for daily adaptive proton therapy in head and neck patients	2020, Phys Med Biol	head & neck	AI for Synthetic Data Generation
Thummerer et al.	Deep learning-based 4D-synthetic CTs from sparse-view CBCTs for dose calculations in adaptive proton therapy	2022, Med Phys	lung	AI for Synthetic Data Generation
Thummerer et al.	Clinical suitability of deep learning based synthetic CTs for adaptive proton therapy of lung cancer	2021, Med Phys	lung	AI for Synthetic Data Generation
Uh et al.	Training a deep neural network coping with diversities in abdominal and pelvic images of children and young adults for CBCT-based adaptive proton therapy.	2021, Radiother Oncol	colon	AI for Image Enhancement and Quality
Vazquez et al.	A deep learning-based approach for statistical robustness evaluation in proton therapy treatment planning: a feasibility study.	2023, Phys Med Biol	prostate	AI for Treatment Planning, Support, and Delivery
Wang et al.	Toward MR-only proton therapy planning for pediatric brain tumors: Synthesis of relative proton stopping power	2022, Med Phys	brain	AI for Synthetic Data Generation

(*continued on next page*)

Table 1 (*continued*)

Author		Year, journal	Site	Category
	images with multiple sequence MRI and development of an online quality assurance tool.			
Wang et al.	Facilitating MR-Guided Adaptive Proton Therapy in Children Using Deep Learning-Based Synthetic CT	2022, Int J Part Ther	brain	AI for Synthetic Data Generation
Wang et al.	Learning-based stopping power mapping on dual-energy CT for proton radiation therapy	2021, Int J Part Ther	head & neck	AI for Dose Prediction and Calculation
Wang et al.	Deep learning-based relative stopping power mapping generation with cone-beam CT in proton radiation therapy	2020, NA	head & neck	AI for Dose Prediction and Calculation
Wang et al.	Feasibility study of fast intensity-modulated proton therapy dose prediction method using deep neural networks for prostate cancer.	2022, Med Phys	prostate	AI for Dose Prediction and Calculation
Yamazaki et al.	A novel, end-to-end framework for avoiding collisions between the patient's body and gantry in proton therapy.	2023, Med Phys	n/a	AI for Image Enhancement and Quality
Yang et al.	Exploratory Investigation of Dose-Linear Energy Transfer (LET) Volume Histogram (DLVH) for Adverse Events Study in Intensity Modulated Proton Therapy (IMPT).	2021, Int J Radiat Oncol Biol Phys	prostate	AI for Outcome Prediction
Yao et al.	Further investigation of 3D dose verification in proton therapy utilizing acoustic signal, wavelet decomposition and machine learning.	2021, Biomed Phys Eng Express	n/a	AI for Dose Prediction and Calculation
York et al.	Promising Hyperparameter Configurations for Deep Fully Connected Neural Networks to Improve Image Reconstruction in Proton Radiotherapy	2021, NA	n/a	AI for Image Enhancement and Quality
Zhang et al.	SWFT-Net: a deep learning framework for efficient fine-tuning spot weights towards adaptive proton therapy	2022, Phys Med Biol	head & neck	AI for Treatment Planning, Support, and Delivery
Zhang et al.	Dose calculation in proton therapy using a discovery cross-domain generative adversarial network (DiscoGAN)	2021, Med Phys	lung, colon	AI for Dose Prediction and Calculation
Zhang et al.	Beam mask and sliding window-facilitated deep learning-based accurate and efficient dose prediction for pencil beam scanning proton therapy	2023, Med Phys	lung, prostate	AI for Treatment Planning, Support, and Delivery
Zhang et al.	A plan verification platform for online adaptive proton therapy using deep learning-based Monte-Carlo denoising	2022, Phys Med	n/a	AI for Dose Prediction and Calculation
Zhang et al.	A Windows GUI application for real-time image guidance during motion-managed proton beam therapy	2020, NA	n/a	AI for Treatment Planning, Support, and Delivery
Zimmermann et al.	An MRI sequence independent convolutional neural network for synthetic head CT generation in proton therapy	2021, Z Med Phys	brain, head & neck	AI for Synthetic Data Generation
Zimmermann et al.	An MR-only acquisition and artificial intelligence based image-processing protocol for photon and proton therapy using a low field MR	2021, Z Med Phys	prostate	AI for Synthetic Data Generation

3.2.4. AI for treatment planning, support, and delivery

Numerous studies have explored various aspects of treatment planning beyond radiation dose prediction. In this domain, the applications of AI encompass enhancing the quality and efficiency of treatment planning, improving the robustness and adaptability of treatment plans (insofar as handling uncertainties and variations that can occur during the course of treatment), facilitating real-time monitoring, accelerating the refinement of treatment processes, and enhancing the precision of range verification.

Borderais-Villarroel et al (York et al., 2021) and Kouwenberg et al (Harms et al., 2020) both emphasized the importance of AI in enhancing the quality and efficiency of IMPT planning, specifically in the oropharyngeal and head and neck regions. While Borderais-Villarroel et al. highlight the role of knowledge-based planning pipelines in producing clinically acceptable IMPT plans, Kouwenberg et al. demonstrate how machine learning can streamline patient selection for IMPT, thereby reducing unnecessary manual planning.

In the run for increased resilience and adaptability of treatment plans when faced with uncertainties, the robustness of IMPT treatment plans against spot delivery errors has been investigated by Newpower et al. (2023). Their work concluded that a workflow incorporating ML-predicted spot delivery errors can offer a realistic method for enhancing plan quality checks in IMPT. Deiter et al. (2020), on the other hand, discussed the role of AI in facilitating the clinical replan processes, particularly highlighting the challenges posed by setup variation in oropharyngeal cancer treatment.

In the realm of real-time *in vivo* monitoring and dose verification, several studies have investigated various benefits of AI and DL. For example, a cascaded CNN has been shown to improve image quality and accuracy in 3D proton-acoustic imaging of prostate cancer patients (Jiang et al., 2022b). In addition, further studies focused on the recognition of Compton events to reconstruct prompt gamma emission profiles (Kazemi Kozani and Magiera, 2022), enhancing the precision of online dose distribution monitoring, and on the development of real-time soft-tissue-based tumor tracking using DL (Zhang et al., 2020), which could significantly improve motion management in PT.

In terms of accelerating and refining treatment processes, the introduction of a DL framework called SWFT-Net showed promise in re-tuning spot weights and re-optimizing plans in adaptive PT with minimal need for human intervention (Zhang et al., 2022b). In a separate study, Chang et al. (2022a) utilized AI for generating volumetric images from orthogonal 2D X-ray images, facilitating real-time 3D tumor localization and enhancing treatment quality.

Finally, the potential of physics-informed DL for material property inference from dual-energy CT scans has been explored, aiming to improve the accuracy of proton range estimation in Monte Carlo dose calculations (Chang et al., 2022b). This highlights the potential of AI to refine the technical aspects of treatment planning in PT.

3.2.5. AI for dose prediction

Predicting and calculating the optimal radiation dose is a critical task in radiation therapy, as the accuracy of the dose calculation has a direct impact on the treatment outcome. Jampa-Ngern et al. (2021) introduced a "Simple Dose Prediction" tool, leveraging DL and contour-based data augmentation, to estimate the mean radiation dose to the liver. This tool, despite requiring accuracy enhancements for compatibility with 3D radiation treatment planning, was highlighted for its cost-effectiveness and potential application. Additionally, AI has been effectively applied in predicting percentile dose values at each voxel for prostate cancer treatment planning, illustrating that DL can significantly improve the accuracy and speed of robustness evaluations (Vazquez et al., 2023). In another notable study, Yao et al. (2021) developed a wavelet-based ML framework employing a bidirectional long-short-term memory (Bi-LSTM) recurrent neural network architecture for 3D dose verification, which achieved high accuracy in dose distribution prediction and correlated well with acoustic waveforms.

The use of AI to leverage multi-modal imaging, including magnetic resonance imaging (MRI) and dual-energy CT (DECT) images, could hold promise for accurately generating patient mass density maps, which are visual representations showing the distribution of different densities within a patient's body. In this setting, a physics-constrained deep learning-based multimodal imaging framework (Chang et al., 2023a, 2023b, 2022c) has been introduced, aimed at improving proton range uncertainty by leveraging insights from both physics and imaging data. Similarly, in one previous study (Chang et al., 2022b), a physics-informed DL framework was developed for deriving mass density and relative stopping power maps from DECT images.

Range prediction and verification is another application that has been investigated. By employing uncertainty-aware machine learning to predict Bragg peak positions, Schilling et al., 2023 proposed a quality control method focused on improved range verification accuracy through secondary charged particle detection. Likewise, Sato et al., 2023 demonstrated the potential of an in-beam visualization system by using a DL model to estimate range from measured currents in simulations. This method leveraged scattered protons detected by scintillation detectors and showed improved results when CT scan data was incorporated. In a similar way, Li et al., 2019 tested a feedforward and a recurrent neural network to verify the range and dose in PT by establishing the relationship between the dose distribution and the activity distribution of proton-induced positron emitters by the use of a CT-based patient phantom for simulations.

Multiple studies have also focused on applications to accelerate and speed up various moments in PT. One such approach uses DL to denoise dose calculation simulations conducted by Monte Carlo methods, a class of computational problem-solving strategies relying on probabilistic (random) simulations, often repeated a vast number of times. The CNN method proposed by Javaid et al., 2021 offered faster and more reliable simulations with fewer particles, successfully achieving results comparable to traditional methods while substantially reducing simulation time across multiple tumor sites. Concurrently, an implementation of the DiscoGAN (Discovery Cross-Domain Generative Adversarial Network) DL architecture achieved the same level of accuracy as Monte Carlo simulations while reducing computational time, marking a significant stride in optimizing PT planning (Zhang et al., 2021). Another approach is to use DL to circumvent the Monte Carlo step altogether by predicting the radiation dose directly. Mentzel et al., 2022 studied this approach within the context proton minibeam radiation therapy, highlighting that all tested DL models significantly outperformed traditional methods, with the regression-trained 3D U-Net achieving the highest accuracy.

A substantial body of research has explored the application of AI for (near) real-time or online dose prediction in the context of radiation therapy. This includes the development of an efficient DL-augmented framework designed to improve clinical decision-making and enhance replanning efficiency in online adaptive PT for prostate and lung cancers (Zhang et al., 2023). Wang et al., 2022d used a novel recurrent U-net architecture for fast 3D dose prediction in IMPT for prostate cancer patients, while Hu et al., 2020 developed a ML framework for predicting 3D dose distribution informed by proton-induced positron emitters. DiscoGAN was also adopted for patient-specific dose verification in PT (Ma et al., 2020), highlighting the combined potential of proton-induced positron emitters and ML as a tool for online dose verification.

Precise dose calculation has posed a significant challenge in adaptive therapy. To this end, a U-net CNN for scatter correction in CBCT images has enhanced both the accuracy and speed of treatment for head and neck cancer (Lalonde et al., 2020). Furthermore, both Harms et al. (2020) and Wang et al. (2020) predicted relative stopping power maps from daily CBCT images, enabling more adaptive treatment planning for IMPT in head-and-neck cancer patients.

In addition, a ML method has been proposed to detect discrepancies between planned and delivered doses using prompt-gamma devices, demonstrating enhanced sensitivity over traditional methods, although computational time remains a challenge (Gueth et al., 2013).

Finally, artificial neural networks were utilized in developing a three-dimensional dose-weighted linear energy transfer prediction model for cranial PT (Pirlepesov et al., 2022), marking a first in the field. The promising dose accuracy supports future investigations to enable the full potential of knowledge-based planning PT.

3.2.6. AI for outcome prediction

Like its applications in other areas of radiation oncology, AI can be employed in PT to estimate and forecast the consequences of treatment, including side effects, toxicities, and clinical and technical endpoints. In this scenario, an AI tool for predicting radiation dose distributions and estimating normal tissue complication probability (NTCP) in oropharyngeal cancer was developed by Huet-Dastarac et al. (2023), achieving notable accuracy. Similarly, Chamseddine et al. (2023) used a shallow CNN to create a predictive model for liver toxicity in hepatocellular carcinoma, focusing on the interplay of photon and proton dose data with patient characteristics.

ML-based models have also been adopted to predict radiation-induced side effects, such as rectal bleeding in prostate cancer patients (Yang et al., 2022) and esophagitis in lung cancer patients (Chen et al., 2022), with the authors suggesting that simpler models might be preferable in scenarios with limited data. Qiu et al. (2020) focused on predicting tumor progression in high-grade glioma using random survival forests, but found that the Cox proportional hazards model was more effective in terms of accuracy and interpretability. Finally, Baumann et al. (2020) used an ensemble ML approach to estimate propensity scores for modeling adverse outcomes and survival in patients with nonmetastatic, locally advanced cancer, showing that proton chemoradiotherapy could reduce acute adverse events compared to photon chemoradiotherapy, with similar survival rates.

3.2.7. Other

AI encompasses a variety of applications in PT that extend beyond the categories previously mentioned. One study tried to improve verification of PT simulations by measuring individual particle types and energies within the treated area by using a special detector and AI (Stasica et al., 2023). The measured linear energy transfer values agreed well with simulations, demonstrating a potentially simpler and more accessible method for validating simulations and improving treatment planning accuracy. Furthermore, Lerendegui-Marco et al. (2022) enhanced the signal-to-total ratio in the i-TED detector system using AI, showing its potential in real-time range imaging. The use of a UNet and ResNet framework was also explored for deriving elemental concentrations from dual-energy CT images, with a focus on PT dose verification in the head region (Liu et al., 2022).

Multiple studies have explored the implications of using AI to analyze prompt gamma imaging data in their research. Jiang et al. (2023) demonstrated the feasibility of utilizing a two-tier DL-based system to generate 3D prompt gamma images for more accurate and precise *in vivo* range verification. In another study, Polf et al. (Ma et al., 2020) explored the potential of DL by implementing a neural network for processing real-world prompt gamma data, which not only improved data fidelity but also enhanced image reconstruction and treatment delivery verification. Building upon this progress, Pietsch et al. (Lui et al., 2021) further demonstrated the effectiveness of CNNs in automatically detecting and classifying treatment deviations during head-and-neck cancer radiotherapy using simulated prompt gamma imaging data.

Kalendralis et al. (2023) developed a knowledge graph compliant with FAIR data principles, aiming to standardize the data collection of tumor group data to ensure flexibility and interoperability for data exchange between radiotherapy centers. Grewal et al. (2020) demonstrated the use of Gaussian process regression and shallow neural networks in predicting output and monitor units in uniform scanning PT based on patient quality assurance data. Their method showed superior performance over traditional empirical models. In ocular PT, a CNNs framework has been proposed for automatic pupil and iris detection, paralleling the accuracy of manual labeling (Antonioli et al., 2021).

Other clinical studies investigated the Prostate Imaging-Reporting and Data System (PI-RADS) in prostate cancer, finding a correlation with cancer recurrence post-PT (Bazargani et al., 2023), and the adoption of radiomic data in clinical practice to enhance disease monitoring and prognostic assessment of intracranial ependymoma (Dominietto et al., 2019). Lastly, AI has been adopted to predict uncertainties in deformable image registration in lung adaptive radiotherapy, estimating dosimetric uncertainty effectively (Smolders et al., 2022), and to improve predictions of radiation pneumonitis outcomes by considering radiation dose to ventilated lung regions (O'Reilly et al., 2020).

4. Conclusion

This review, encompassing 76 studies, underscores the multifaceted potential of AI to PT by minimizing inherent limitations and maximizing therapeutic efficacy. From optimizing treatment planning workflows to facilitating precise prediction of adverse events, AI demonstrates impactful utility across a spectrum of PT applications. Notably, the rapidly evolving landscape of AI research in PT indicates substantial potential for workflow optimization and clinical decision-making enhancements. While initial explorations have laid the groundwork for understanding AI's applicability in PT, further research inspired by the diverse scenarios discussed herein is warranted to fully unlock the promise of this emerging field.

CRediT authorship contribution statement

Conceptualization: LJI, FM, MGV, GM, MZ. Methodology: LJI. Software: LJI. Formal analysis: LJI. Data curation: LJI, FM, MGV, MZ. Writing – original draft: LJI, FM, MGV, MZ. Writing – review & editing: All authors. Supervision: DA, BAJF, GM

Informed Consent Statement

Not applicable.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Declaration of Competing Interest

BAJF received speaker fees from Roche, Bayer, Janssen, Ipsen, Accuray, Astellas, Elekta, IBA and Astra Zeneca (all outside the current project). EGCT is member of the scientific advisory board of IBA and received speaker fees from Elekta (all outside the current manuscript). M.G.V received a research fellowship from the Associazione Italiana per la Ricerca sul Cancro (AIRC) entitled "Radioablation ± hormonotherapy for prostate cancer oligorecurrences (RADIOSA trial): potential of imaging and biology" registered at Clinical Trials.gov NCT03940235, approved by the Ethics Committee of IEO and Centro Cardiologico Monzino (IEO-997). GC reports speakers fee and advisory board from Roche, Novartis, Lilly, Pfizer, Astra Zeneca, Daichii Sankyo, Ellipsis, Veracyte, Exact Science, Celcuity, Merck, BMS, Gilead, Sanofi, Menarini. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. The remaining authors declare no conflicts of interest.

Acknowledgments

IEO: the European Institute of Oncology, is partially supported by the Italian Ministry of Health (with "Ricerca Corrente" and "5 × 1000" funds) and by Institutional grants from Accuray Inc. and Ion Beam Applications (IBA).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2024.104485.

References

Antonioli, L., et al., 2021. Convolutional neural networks cascade for automatic pupil and iris detection in ocular proton therapy. Sensors 21, 4400.

Barajas, C.A., Kroiz, G.C., Gobbert, M.K., Polf, J.C., 2021. Classification of compton camera based prompt gamma imaging for proton radiotherapy by random forests. Int. Conf. Comput. Sci. Comput. Intell. CSCI *2021*, 308–311. https://doi.org/10.1109/CSCI54926.2021.00124.

Baumann, B.C., et al., 2020. Comparative effectiveness of proton vs photon therapy as part of concurrent chemoradiotherapy for locally advanced cancer. JAMA Oncol 6, 237–246.

Bazargani, S., et al., 2023. Magnetic resonance imaging radiomic features for recurrent prostate cancer following proton radiation therapy-A pilot study. Urol. Oncol. 41, 145.e1–145.e5.

Borderias-Villarroel, E., et al., 2023. Machine learning-based automatic proton therapy planning: Impact of post-processing and dose-mimicking in plan robustness. Med. Phys. 50, 4480–4490.

Bortfeld, T.R., Loeffler, J.S., 2017. Three ways to make proton therapy affordable. Nature 549, 451–453.

Chamseddine, I., et al., 2023. Predictive model of liver toxicity to aid the personalized selection of proton versus photon therapy in hepatocellular carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 116, 1234–1243.
Chang, C.-W., , 2022. A deep learning approach to transform two orthogonal X-ray images to volumetric images for image-guided proton therapy. 12032, 120321S (2022a)..
Chang, C.-W., et al., 2022a. An unsupervised patient-specific metal artifact reduction framework for proton therapy. Med. Imaging 2022 Image-Guid. Proced. Robot. Interv. Model. 12034, 193–199.
Chang, C.-W., et al., 2022b. Dual-energy CT based mass density and relative stopping power estimation for proton therapy using physics-informed deep learning. Phys. Med. Biol. 67.
Chang, C.-W., et al., 2023a. Multimodal imaging-based material mass density estimation for proton therapy using supervised deep learning. Br. J. Radiol. 96, 20220907.
Chang, C.-W., et al., 2023b. Physics-informed multi-modal imaging-based material characterization for proton therapy. Phys. Med. Imaging 12463, 545–550.
Chang, C.-W., et al., 2022c. Validation of a deep learning-based material estimation model for Monte Carlo dose calculation in proton therapy. Phys. Med. Biol. 67.
Charyyev, S., et al., 2020. High quality proton portal imaging using deep learning for proton radiation therapy: a phantom study. Biomed. Phys. Eng. Express 6, 035029.
Chen, Y.H., Blommestein, H.M., Klazenga, R., Uyl-de Groot, C., van Vulpen, M., 2023b. Costs of newly funded proton therapy using time-driven activity-based costing in The Netherlands. Cancers 15, 516.
Chen, Z., Dominello, M.M., Joiner, M.C., Burmeister, J.W., 2023a. Proton versus photon radiation therapy: A clinical review. Front. Oncol. 13, 1133909.
Chen, M., et al., 2022. Predictive performance of different NTCP techniques for radiation-induced esophagitis in NSCLC patients receiving proton radiotherapy. Sci. Rep. 12.
Cho, Y., et al., 2019. Impact of Treatment-Related Lymphopenia on Immunotherapy for Advanced Non-Small Cell Lung Cancer. Int. J. Radiat. Oncol. Biol. Phys. 105, 1065–1073.
Deiter, N., et al., 2020. Evaluation of replanning in intensity-modulated proton therapy for oropharyngeal cancer: Factors influencing plan robustness. Med. Dosim. Off. J. Am. Assoc. Med. Dosim. 45, 384–392.
Dominietto, M., et al., 2019. Role of Complex Networks for Integrating Medical Images and Radiomic Features of Intracranial Ependymoma Patients in Response to Proton Radiotherapy. Front. Med. 6, 333.
Elmahdy, M.S., et al., 2018. Evaluation of Multi-metric Registration for Online Adaptive Proton Therapy of Prostate Cancer. Biomed. Image Regist. 94–104. https://doi.org/10.1007/978-3-319-92258-4_9.
Elmahdy, M.S., et al., 2019. Robust contour propagation using deep learning and image registration for online adaptive proton therapy of prostate cancer. Med. Phys. 46, 3329–3343.
Engineering Mathematics and Artificial Intelligence: Foundations, Methods, and Applications. Routledge & CRC Press ⟨https://www.routledge.com/Engineering-Mathematics-and-Artificial-Intelligence-Foundations-Methods/Kunze-La-Torre-Riccoboni-Galan/p/book/9781032255675⟩. (2021).
Florkow, M.C., et al., 2020. Deep learning-enabled MRI-only photon and proton therapy treatment planning for paediatric abdominal tumours. Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol. 153, 220–227.
Grewal, H.S., Chacko, M.S., Ahmad, S., Jin, H., 2020. Prediction of the output factor using machine and deep learning approach in uniform scanning proton therapy. J. Appl. Clin. Med. Phys. 21, 128–134.
Gueth, P., et al., 2013. Machine learning-based patient specific prompt-gamma dose monitoring in proton therapy. Phys. Med. Biol. 58, 4563–4577.
Harms, J., et al., 2020. Cone-beam CT-derived relative stopping power map generation via deep learning for proton radiotherapy. Med. Phys. 47, 4416–4427.
Huang, D., et al., 2021. Cost-Effectiveness Models of Proton Therapy for Head and Neck: Evaluating Quality and Methods to Date. Int. J. Part. Ther. 8, 339–353.
Huet-Dastarac, M., et al., 2023. Patient selection for proton therapy using Normal Tissue Complication Probability with deep learning dose prediction for oropharyngeal cancer. Med. Phys. 50, 6201–6214.
Hu, M., Jiang, L., Cui, X., Zhang, J., Yu, J., 2018. Proton beam therapy for cancer in the era of precision medicine. J. Hematol. Oncol.J Hematol Oncol 11, 136.
Hu, Z., et al., 2020. A machine learning framework with anatomical prior for online dose verification using positron emitters and PET in proton therapy. Phys. Med. Biol. 65, 185003.
Jain, V., et al., 2020. Predicted Secondary Malignancies following Proton versus Photon Radiation for Oropharyngeal Cancers. Int. J. Part. Ther. 6, 1–10.
Jampa-Ngern, S., et al., 2021. Prediction of liver Dmean for proton beam therapy using deep learning and contour-based data augmentation. J. Radiat. Res. (Tokyo), rrab095. https://doi.org/10.1093/jrr/rrab095.
Javaid, U., Souris, K., Huang, S., Lee, J.A., 2021. Denoising proton therapy Monte Carlo dose distributions in multiple tumor sites: A comparative neural networks architecture study. Phys. Medica PM Int. J. Devoted Appl. Phys. Med. Biol. Off. J. Ital. Assoc. Biomed. Phys. AIFB 89, 93–103.
Jiang, Y.-X., Chen, Y., Sun, H.-H., Xu, S.-C., 2022b. Effects of Cyclooxygenase-2 Inhibitors on Gastrointestinal Malignancies: a Systematic Review and Meta-analysis. Indian J. Surg. Oncol. 13, 348–355.
Jiang, Z., Polf, J.C., Barajas, C.A., Gobbert, M.K., Ren, L., 2023. A feasibility study of enhanced prompt gamma imaging for range verification in proton therapy using deep learning. Phys. Med. Biol. 68.
Jiang, Z., et al., 2022a. 3D in vivo dose verification in prostate proton therapy with deep learning-based proton-acoustic imaging. Phys. Med. Biol. 67.
Jin, M.C., et al., 2020. Impact of proton radiotherapy on treatment timing in pediatric and adult patients with CNS tumors. Neuro-Oncol. Pract. 7, 626–635.
Kalendralis, P., et al., 2023. Technical note: A knowledge graph approach to registering tumour specific data of patient-candidates for proton therapy in the Netherlands. Med. Phys. 50, 1044–1050.
Kazemi Kozani, M., Magiera, A., 2022. Machine learning-based event recognition in SiFi Compton camera imaging for proton therapy monitoring. Phys. Med. Biol. 67.
Kazemifar, S., et al., 2020. Dosimetric evaluation of synthetic CT generated with GANs for MRI-only proton therapy treatment planning of brain tumors. J. Appl. Clin. Med. Phys. 21, 76–86.
Kouwenberg, J., et al., 2021. Model based patient pre-selection for intensity-modulated proton therapy (IMPT) using automated treatment planning and machine learning. Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol. 158, 224–229.
Krishnamurthy, R., et al., 2022. Using Artificial Intelligence for Optimization of the Processes and Resource Utilization in Radiotherapy. JCO Glob. Oncol., e2100393 https://doi.org/10.1200/GO.21.00393.
Lalonde, A., Winey, B., Verburg, J., Paganetti, H., Sharp, G.C., 2020. Evaluation of CBCT scatter correction using deep convolutional neural networks for head and neck adaptive proton therapy. Phys. Med. Biol. 65 https://doi.org/10.1088/1361-6560/ab9fcb.
Landry, G., Kurz, C., Traverso, A., 2023. The role of artificial intelligence in radiotherapy clinical practice. BJR|Open 5, 20230030.
Lerendegui-Marco, J., Balibrea-Correa, J., Babiano-Suárez, V., Ladarescu, I., Domingo-Pardo, C., 2022. Towards machine learning aided real-time range imaging in proton therapy. Sci. Rep. 12.
Lewis, L., et al., 2022. Intensity Modulated Proton Therapy Better Spares Non-Adjacent Organs and Reduces the Risk of Secondary Malignant Neoplasms in the Treatment of Sinonasal Cancers. Med. Dosim. 47, 117–122.
Liu, Y., Zhou, L., Peng, H., 2022. Machine learning based oxygen and carbon concentration derivation using dual-energy CT for PET-based dose verification in proton therapy. Med. Phys. 49, 3347–3360.
Liu, R., et al., 2021. Synthetic dual-energy CT for MRI-only based proton therapy treatment planning using label-GAN. Phys. Med. Biol. 66, 065014.
Liu, Y., et al., 2019. MRI-based treatment planning for proton radiotherapy: dosimetric validation of a deep learning-based liver synthetic CT generation method. Phys. Med. Biol. 64, 145015.
Li, G., Wu, X., Ma, X., 2022. Artificial intelligence in radiotherapy. Semin. Cancer Biol. 86, 160–171.
Li, Z., et al., 2019. Technical Note: Machine learning approaches for range and dose verification in proton therapy using proton-induced positron emitters. Med. Phys. 46, 5748–5757.
Ma, S., et al., 2020. Feasibility study of patient-specific dose verification in proton therapy utilizing positron emission tomography (PET) and generative adversarial network (GAN). Med. Phys. 47, 5194–5208.
Maspero, M., et al., 2020. Deep learning-based synthetic CT generation for paediatric brain MR-only photon and proton radiotherapy. Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol. 153, 197–204.
Mentzel, F., et al., 2022. Small beams, fast predictions: a comparison of machine learning dose prediction models for proton minibeam therapy. Med. Phys. 49, 7791–7801.
Mohan, R., 2022. A Review of Proton Therapy - Current Status and Future Directions. Precis. Radiat. Oncol. 6, 164–176.
Newpower, M.A., Chiang, B.-H., Ahmad, S., Chen, Y., 2023. Spot delivery error predictions for intensity modulated proton therapy using robustness analysis with machine learning. J. Appl. Clin. Med. Phys. 24, e13911.
O'Reilly, S., et al., 2020. Dose to Highly Functional Ventilation Zones Improves Prediction of Radiation Pneumonitis for Proton and Photon Lung Cancer Radiation Therapy. Int. J. Radiat. Oncol. Biol. Phys. 107, 79–87.
Pang, B., et al., 2023. Comparison and evaluation of different deep learning models of synthetic CT generation from CBCT for nasopharynx cancer adaptive proton therapy. Med. Phys. 50, 6920–6930.
Pietsch, J., et al., 2023. Automatic detection and classification of treatment deviations in proton therapy from realistically simulated prompt gamma imaging data. Med. Phys. 50, 506–517.
Pirlepesov, F., et al., 2022. Three-dimensional dose and LETD prediction in proton therapy using artificial neural networks. Med. Phys. 49, 7417–7427.
Polf, J.C., et al., 2022. Applications of Machine Learning to Improve the Clinical Viability of Compton Camera Based in vivo Range Verification in Proton Radiotherapy. Front. Phys. 10, 838273.
PTCOG - (2023)Facilities in Operation. ⟨https://www.ptcog.site/index.php/facilities-in-operation-public⟩.
Qiu, X., et al., 2020. A Comparison Study of Machine Learning (Random Survival Forest) and Classic Statistic (Cox Proportional Hazards) for Predicting Progression in High-Grade Glioma after Proton and Carbon Ion Radiotherapy. Front. Oncol. 10, 551420.
Sato, S., Yokokawa, H., Hosobuchi, M., Kataoka, J., 2023. A simulation study of in-beam visualization system for proton therapy by monitoring scattered protons. Front. Med. 10, 1038348.
Schilling, A., et al., 2023. Uncertainty-aware spot rejection rate as quality metric for proton therapy using a digital tracking calorimeter. Phys. Med. Biol. 68.
Smolders, A., et al., 2023. Dosimetric comparison of autocontouring techniques for online adaptive proton therapy. Phys. Med. Biol. 68.
Smolders, A., Lomax, T., Weber, D.C., Albertini, F., 2022. Deformable Image Registration Uncertainty Quantification Using Deep Learning for Dose Accumulation in Adaptive Proton Therapy. In: Hering, A., et al. (Eds.), in *Biomedical Image Registration*. Springer International Publishing, Cham, pp. 57–66. https://doi.org/10.1007/978-3-031-11203-4_7.
Spezialetti, M., et al., 2021. Using Deep Learning for Fast Dose Refinement in Proton Therapy. in *2021*. IEEE International Conference on Systems, Man, and Cybernetics (SMC) 1783–1789. https://doi.org/10.1109/SMC52423.2021.9658879.

Stasica, P., et al., 2023. Single proton LET characterization with the Timepix detector and artificial intelligence for advanced proton therapy treatment planning. Phys. Med. Biol. 68.
Tambas, M., et al., 2022. Current practice in proton therapy delivery in adult cancer patients across Europe. Radiother. Oncol. 167, 7–13.
Thummerer, A., et al., 2020a. Comparison of the suitability of CBCT- and MR-based synthetic CTs for daily adaptive proton therapy in head and neck patients. Phys. Med. Biol. 65, 235036.
Thummerer, A., et al., 2020b. Comparison of CBCT based synthetic CT methods suitable for proton dose calculations in adaptive proton therapy. Phys. Med. Biol. 65, 095002.
Thummerer, A., et al., 2021. Clinical suitability of deep learning based synthetic CTs for adaptive proton therapy of lung cancer. Med. Phys. 48, 7673–7684.
Thummerer, A., et al., 2022. Deep learning-based 4D-synthetic CTs from sparse-view CBCTs for dose calculations in adaptive proton therapy. Med. Phys. 49, 6824–6839.
Uh, J., Wang, C., Acharya, S., Krasin, M.J., Hua, C.-H., 2021. Training a deep neural network coping with diversities in abdominal and pelvic images of children and young adults for CBCT-based adaptive proton therapy. Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol. 160, 250–258.
Vazquez, I., et al., 2023. A deep learning-based approach for statistical robustness evaluation in proton therapy treatment planning: a feasibility study. Phys. Med. Biol. 68.
Vincini, M.G., et al., 2023. More than five decades of proton therapy: a bibliometric overview of the scientific literature. Cancers 15, 5545.
Wang, T., et al., 2021. Learning-based stopping power mapping on dual-energy CT for proton radiation therapy. Int. J. Part. Ther. 7, 46–60.
Wang, W., et al., 2022a. Feasibility study of fast intensity-modulated proton therapy dose prediction method using deep neural networks for prostate cancer. Med. Phys. 49, 5451–5463.
Wang, C., Uh, J., Merchant, T.E., Hua, C.-H., Acharya, S., 2022b. Facilitating MR-guided adaptive proton therapy in children using deep learning-based synthetic CT. Int. J. Part. Ther. 8, 11–20.
Wang, C., et al., 2022c. Toward MR-only proton therapy planning for pediatric brain tumors: Synthesis of relative proton stopping power images with multiple sequence MRI and development of an online quality assurance tool. Med. Phys. 49, 1559–1570.
Wang, W., et al., 2022d. Feasibility study of fast intensity-modulated proton therapy dose prediction method using deep neural networks for prostate cancer. Med. Phys. 49, 5451–5463.
Wang, T., et al., 2020. Deep learning-based relative stopping power mapping generation with cone-beam CT in proton radiation therapy. In: in *Medical Imaging 2020: Physics of Medical Imaging*, vol. 11312. SPIE, pp. 1124–1129.
Yamazaki, Y., Terunuma, T., Kato, T., Komori, S., Sakae, T., 2023. A novel, end-to-end framework for avoiding collisions between the patient's body and gantry in proton therapy. Med. Phys. 50, 6684–6692.
Yang, Y., et al., 2021. Exploratory investigation of dose-linear energy transfer (LET) Volume Histogram (DLVH) for adverse events study in intensity modulated proton therapy (IMPT). Int. J. Radiat. Oncol. Biol. Phys. 110, 1189–1199.
Yang, Z., et al., 2022. Exploring new catechin derivatives as SARS-CoV-2 Mpro inhibitors from tea by molecular networking, surface plasma resonance, enzyme inhibition, induced fit docking, and metadynamics simulations. Comput. Biol. Med. 151.
Yao, S., Hu, Z., Xie, Q., Yang, Y., Peng, H., 2021. Further investigation of 3D dose verification in proton therapy utilizing acoustic signal, wavelet decomposition and machine learning. Biomed. Phys. Eng. Express 8.
York, S.A., et al., 2021. Promising hyperparameter configurations for deep fully connected neural networks to improve image reconstruction in proton radiotherapy. IEEE International Conference on Big Data (Big Data) 5648–5657. https://doi.org/10.1109/BigData52589.2021.9671404.
Yousefirizi, F., Jha, A.K., Brosch-Lenz, J., Saboury, B., Rahmim, A., 2021. Toward high-throughput artificial intelligence-based segmentation in oncological PET imaging. PET Clin 16, 577–596.
Zhang, G., Chen, X., Dai, J., Men, K., 2022a. A plan verification platform for online adaptive proton therapy using deep learning-based Monte–Carlo denoising. Phys. Med. 103, 18–25.
Zhang, Z., et al., 2020. A Windows GUI application for real-time image guidance during motion-managed proton beam therapy 11315, 113152F.
Zhang, G., Zhou, L., Han, Z., Zhao, W., Peng, H., 2022b. SWFT-Net: a deep learning framework for efficient fine-tuning spot weights towards adaptive proton therapy. Phys. Med. Biol. 67.
Zhang, L., et al., 2023. Beam mask and sliding window-facilitated deep learning-based accurate and efficient dose prediction for pencil beam scanning proton therapy. Med. Phys. https://doi.org/10.1002/mp.16758.
Zhang, X., et al., 2021. Dose calculation in proton therapy using a discovery cross-domain generative adversarial network (DiscoGAN). Med. Phys. 48, 2646–2660.
Zimmermann, L., et al., 2022. An MRI sequence independent convolutional neural network for synthetic head CT generation in proton therapy. Z. Für Med. Phys. 32, 218–227.
Zimmermann, L., et al., 2021. An MR-only acquisition and artificial intelligence based image-processing protocol for photon and proton therapy using a low field MR. Z. Med. Phys. 31, 78–88.