Digital Twins: Proof of concept for vision loss prediction by digital twins in radiotherapy

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Abstract

Cancer remains a major global health challenge, requiring continuous advancements in therapeutic strategies such as radiotherapy. In the era of precision medicine where treatment selection is done in a highly personalized fashion, there is a critical need to simulate the effects of the various therapeutic options that are possible for a given patient without exposing him/her to the toxicities of treatments. This study investigates the potential of digital twins to predict doses received by organs at risk during radiotherapy, comparing three beam modalities: photons, protons, and carbon ions and simulate their effects. The objective is to select the most efficient / less toxic radiotherapy modality, i.e. to minimize toxicity while ensuring optimal tumor coverage. Dose distributions and normal tissue complication probabilities are evaluated using matRad, an open-source treatment planning tool. Using a schematic proof-of-concept digital twin, the results indicate that carbon ions provide the highest precision, significantly reducing both maximum and average doses to organs at risk while maintaining effective tumor coverage. These findings represent a promising preliminary step toward increasingly realistic multi-variable digital twins to enable more personalized and less toxic treatments.

Keywords: cancer treatment, precision radiotherapy, personalized treatment, digital twins, carbon ions

1 Introduction

Cancer remains one of the world's leading causes of death, requiring advanced therapeutic strategies such as radiotherapy (Baskar et al., 2012). Radiotherapy is among the most crucial cancer treatment which is incorporated into at least two-thirds of cancer treatment plans in Western countries (Chen and Kuo, 2017; Valentini et al., 2020). The aim of radiotherapy is to optimize the balance between tumor eradication and minimizing side effects on healthy tissues (Baumann and Petersen, 2005). However, personalizing treatments remains a major challenge. According to Deasy (2024), integrating predictive models combining genomics, radiomics, and dosiomics could significantly improve dose planning and anticipation of tumor response to treatment. In conventional treatments, photons are the most commonly used beams. Although effective in targeting tumors, they have significant off-target diffusion, unnecessarily exposing surrounding tissues to high doses. To overcome these limitations, proton and carbon ion therapy have been developed, offering greater precision and reduced side effects due to their unique physical properties, particularly the Bragg peak (Kiseleva et al., 2022). This allows for a dose distribution more focused on the tumor while minimizing exposure to organs at risk (OARs). Additionally, the higher relative biological effectiveness (RBE) of carbon ions enhances their therapeutic potential (Chang et al., 2024; Abdollahi et al., 2024). Despite these advances, treatment planning remains complex and requires sophisticated modeling and optimization tools. In this context, digital twins, a virtual replica of the patient including clinical and imaging data, are emerging as a promising solution to refine dose distribution, anticipate side effects, and improve treatment personalization (Chaudhuri et al., 2023).

One of the main challenges in radiotherapy is achieving the optimal trade-off between complete tumor coverage, represented by the Clinical Target Volume (CTV), and minimizing radiation exposure to OARs. This challenge is particularly critical when tumors are located near highly sensitive structures such as the optic nerve, eyeballs, or lenses, where excessive exposure can lead to severe complications, including vision loss (Deasy, 2024). Digital twins could play a key role in addressing this challenge by enabling precise beam adjustments and more accurate predictions of treat-

ment outcomes, ultimately improving patient safety This study aims to demonstrate the feasibility of using digital twins to predict the doses received by optical OARs in radiotherapy and to identify optimal beam configurations that minimize optical toxicity while ensuring effective CTV coverage. To achieve this, three beam modalities (photons, protons, and carbon ions) were compared in terms of maximum and average doses delivered to critical structures within the treatment area.

2 Materials and methods

The data used in this study come from five anonymized clinical cases of patients who have already been treated, in accordance with ethical guarantees and the non-opposition of patients, in compliance with current legislation. The data set consists of DICOM files (Digital Imaging and Communications in Medicine), including planning CT images that model patient anatomy and tumor location, the RTStruct file defines the contours of structures, and the RTDose file contains dose distribution maps from pre-existing treatment plans. The studied cases involve tumors located near critical structures such as the optic nerves, brain, and eyes. These complex locations require precise dose optimization to minimize toxicity while ensuring effective tumor coverage.

The first step in creating a digital twin is to simulate dose distribution in critical structures using MatRad, an open-source radiotherapy planning software (Wieser et al., 2017) . This choice was driven by the lack of free access to commercial treatment planning systems (TPS) for people not involved in patient care and the flexibility MatRad offers for testing various scenarios. The workflow begins with data import, where CT images are loaded and critical structures are segmented. This is followed by beam configuration, where beam types (photons, protons, carbon ions), bixel width, and incidence angles are defined (at the exclusion of multiple other parameters for sake of simplicity at this proof-of-concept step). The next step is dose simulation, which computes the dose distribution using built-in optimization algorithms, including influence matrix calculation and dose optimization. Finally, results are analyzed through the generation of dose-volume histograms (DVH) and extraction of the doses for each critical structure.

Three distinct types of beams are compared in this study: photons (the most commonly used beam, but with significant off-target dose diffusion), protons (enhanced by the Bragg peak phenomenon), and carbon ions (which offer a low dose spread with enhanced biological effects).
The main objective of the simulations is to minimize the maximum doses received by OARs, particularly the optic nerves, while ensuring optimal tumor coverage and performing sensitivity analysis on parameters such as beam angles.

Simulations are evaluated using the following metrics: the maximum and mean doses calculated for the OARs and CTV. Plus, the DVH histograms, which represent the proportion of volume exposed to different doses, and Normal Tissue Complication Probability (NTCP) are considered.

NTCP is a crucial concept in radiotherapy, as it helps oncologists predict the risks associated with cancer treatment, to inform the patients or minimize the risks by re-optimizing the treatment plan before delivering it. This mathematical model predicts the probability of adverse side effects occurring in healthy tissues following radiation exposure. It is particularly important in treatment planning, as it enables a balance between maximizing efficacy against the tumor and minimizing risks to surrounding healthy tissue. This model uses the cumulative normal distribution to assess the risk of complications in normal tissues after radiotherapy. The formula for calculating NTCP is provided by Chaikh et al. (2020) as follows:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{t^2}{2}\right) dt \quad (1)$$

where

$$t = \frac{gEUD - TD_{50}}{m \times TD_{50}} \quad (2)$$

TD_{50} is the dose at which 50% of patients experience a specific complication in an organ, while m represents the slope at the TD_{50} point. The generalized equivalent uniform dose ($gEUD$) is calculated based on the doses received by different organ sub-volumes. The $gEUD$ formula is:

$$gEUD = \left(\sum_{M} v_M \cdot (D[M])^{\alpha}\right)^{1/\alpha} \quad (3)$$

Where v_M represents the partial volume receiving a certain dose $D[M]$ at the points M of the organ.

To study different cases and beam configurations, as well as to compute NTCP, a custom script in MATLAB, the same programming language used by matRad, was developed, making use of matRad's open-source accessibility to incorporate customized configurations. By following the documentation, the existing workflow was replicated and extended with additional features. The first enhancement involved automating the simulation process, enabling the execution of multiple simulations in sequence, thereby improving reproducibility and reducing manual intervention. The second key improvement was the integration of NTCP computation, a feature not natively available in matRad. This was achieved by implementing a custom function that retrieves dose values and applies the NTCP formula directly within the workflow. These modifications accelerated data retrieval, optimized the overall analysis process, and helped improve the accuracy and efficiency of the results.

3 Results

This study compares the impact of photon, proton, and carbon ion beams on the doses received by OARs and CTV.

Organs	Doses (Gy)					
	Photon		Proton		Carbon ions	
	max	mean	max	mean	max	mean
Left eye	96.67	22.09	49.99	7.76	28.35	5.12
Right eye	82.20	6.25	27.57	1.95	16.50	1.54
Brain	88.66	9.08	98.10	2.43	147.59	2.83
Left lens	21.33	7.33	7.86	1.73	6.48	1.81
Right lens	3.94	2.06	1.42	0.20	1.53	0.32
Chiasma	60.52	58.87	65.15	60.55	63.37	60.39
Left retina	96.67	24.99	49.99	8.92	28.35	5.61
Right retina	82.20	7.18	27.58	2.27	16.50	1.69
Left Optic Nerve	72.04	58.97	66.22	39.71	64.48	35.65
Right Optic Nerve	75.90	42.75	62.98	28.18	65.33	27.73
CTV	70.97	59.85	75.64	59.04	118.22	59.27

Table 1: Maximum and average doses received by OAR according to beam type (photons, protons, carbon ions).

Table 1 summarizes the performance of each beam type in terms of maximum and mean doses for critical structures. Additionally, dose distribution graphs are provided to illustrate the differences between the three radiation modalities. The results highlight significant dose variations depending on the beam type. Photons exhibit the highest maximum doses for OARs, reaching up to 82.20 Gy for the right eye. Their wider dose distribution leads to increased irradiation of surrounding tissues. In contrast, protons improve dose localization, resulting in lower average doses for certain structures, such as the crystalline lenses. Finally, carbon ions demonstrate the highest precision, delivering the lowest maximum doses (28.35 Gy for the left eye) while effectively maintaining tumor coverage.

Table 2 presents the NTCP values, highlighting the superior sparing of healthy tissue achieved with protons and carbon ions compared to photons. The NTCP for photons is particularly high for radiosensitive organs, with a value of 1.0 for the right lens and 0.29 for the right retina, indicating a substantial risk of complications. In contrast, protons reduce these risks, lowering the NTCP to 0.94 for the right lens and 0.014 for the right retina. Carbon ions achieve the lowest values, with an NTCP of 0.045 for the right lens and 2.1×10^{-4} for the right retina, confirming their superior precision and potential for minimizing radiation-induced toxicity.

Organ	NTCP (%)		
	Photons	Protons	Carbon
Brain	8.63×10^{-5}	1.36×10^{-7}	1.15×10^{-6}
Brainstem	0.00025	8.6×10^{-9}	4.9×10^{-8}
Right Lens	1.0	0.94	0.045
Left Lens	0.39	0.0011	0.00046
Right Optic Nerve	0.20	0.0092	0.0087
Left Optic Nerve	0.024	0.00045	0.0012
Optic Chiasm	0.042	0.00018	0.00061
Hypothalamus	0.028	4.8×10^{-9}	1.7×10^{-9}
Right Retina	0.29	0.014	0.00021
Left Retina	0.10	0.0019	7.5×10^{-5}
Right Parotid	1.4×10^{-8}	1.4×10^{-8}	1.4×10^{-8}
Left Parotid	1.4×10^{-8}	1.4×10^{-8}	1.4×10^{-8}
Spinal Cord	5.5×10^{-9}	5.5×10^{-9}	5.5×10^{-9}
External Brainstem	0.00023	8.4×10^{-9}	4.9×10^{-8}
Pituitary Gland	2.8×10^{-7}	9.3×10^{-8}	1.4×10^{-7}
Internal Brainstem	0.00015	9.6×10^{-9}	4.4×10^{-8}

Table 2: Comparison of NTCP for different organs and radiation types.

Figure 1 illustrates the dose distribution for the three types of radiation. Photon beams exhibit the widest dose distribution, with significant spread into surrounding tissues. Proton beams offer better dose localization but still show some diffusion beyond the target. In contrast, carbon ions deliver the most concentrated dose, characterized by a sharp dose fall-off outside the tumor, thereby minimizing unwanted damage to healthy tissues.

Figure 2 illustrates the differences in dose distribution for the three beam types. The photon DVHs shows that a large volume is exposed to lower doses, with a slower decline as the dose increases, indicating significant irradiation of surrounding tissues. In contrast, proton DVHs demonstrate improved dose localization with steeper declines, reducing exposure to healthy tissue. Finally, carbon ions exhibit the sharpest drop in irradiated volume at high doses, allowing precise tumors targeting while minimizing damage.

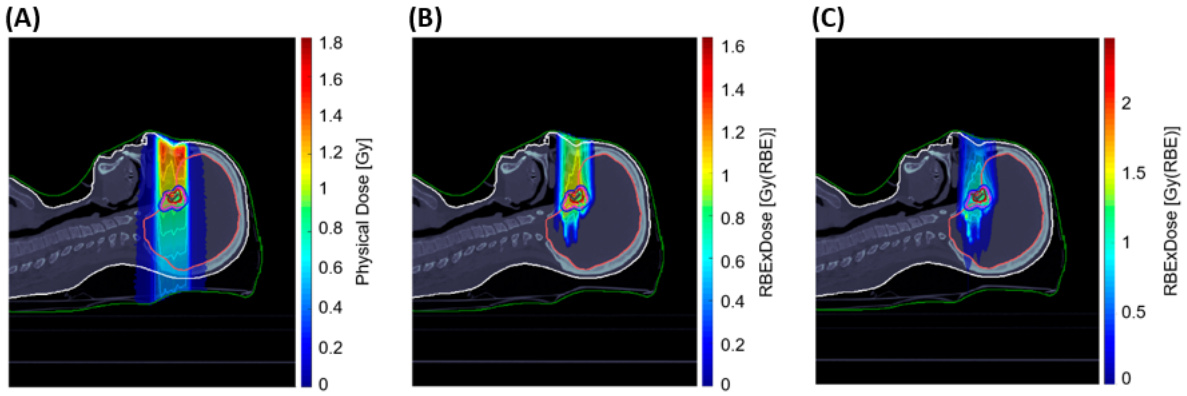

Figure 1: Dose distributions for photons (A), protons (B), and carbon ions (C).

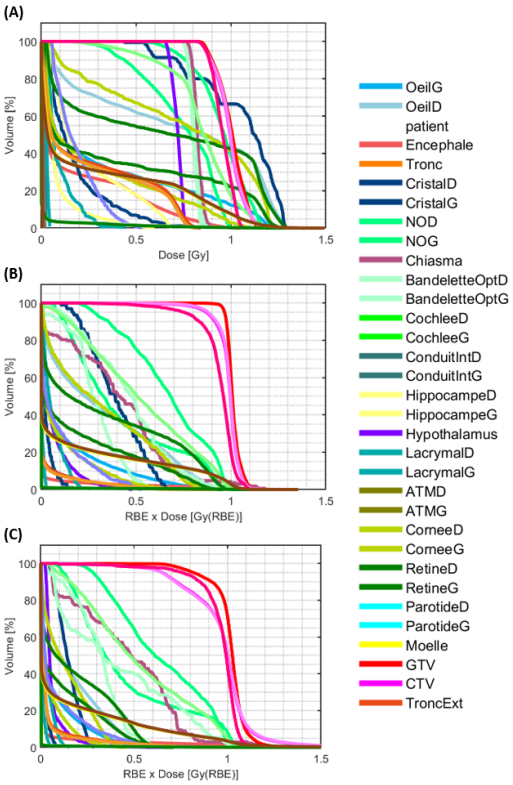

Figure 2: DVH illustrating dose exposure for photons (A), protons (B), and carbon ions (C).

4 Discussion

The results highlighted significant differences between photon, proton, and carbon ion therapy in terms of dose distribution and optical toxicity in para-optic tumor treatment. While photons remain widely used in conventional radiotherapy, their higher dose diffusion leads to increased exposure of surrounding healthy tissues (Chen et al., 2023). In contrast, proton therapy demonstrates improved dose localization due to the Bragg peak, resulting in lower mean doses to critical structures (Chen et al., 2023; Lane et al., 2023). However, protons can still exhibit a certain degree of diffusion, particularly for structures adjacent to the tumor. This suggests that while protons offer a significant advantage over photons, their capacity to fully spare OARs remains limited in highly complex cases. Carbon ion therapy exhibits the steepest dose fall-off outside the tumor target, minimizing exposure to healthy tissues. The DVH illustrates a sharp decrease in irradiated volume at high doses, reinforcing the potential of carbon ions for treating radio-resistant tumors while limiting toxicity. These findings confirm their suitability for tumors located near critical structures, where precise dose control is essential to reducing side effects.

The integration of digital twins in radiotherapy planning represents a promising approach to optimizing treatment personalization (Sumini et al., 2024). By providing a virtual replica of the patient, digital twins enable individualized dose simulations, allowing for better selection of beam parameters to minimize OAR toxicity while maintaining optimal tumor coverage. Our results showed that in cases where tumors are located near highly sensitive structures such as the optic nerves, carbon ion therapy appears to be the most suitable option under the simplistic assumptions made for the ballistics. The reduced off-target exposure observed in this study suggests a lower risk of complications such as radiation-induced vision loss. However, proton therapy remains a viable alternative when access to carbon ion treatment is limited, as it still provides significant dose reduction compared to photons. Furthermore, the NTCP analysis supports these findings by quantifying the probability of

radiation-induced complications. Photons exhibited the highest NTCP values for radio-sensitive structures, particularly for the lens and retina, confirming their higher risk of adverse effects. Proton therapy showed a substantial reduction in NTCP, though still presenting some risk due to residual dose diffusion into surrounding tissues. Carbon ions demonstrated the lowest NTCP values, reinforcing their ability to spare critical structures while maintaining effective tumor coverage. These results highlight the importance of selecting the most appropriate modality based on patient-specific constraints and tumor location. These results emphasize the need for treatment planning strategies that extend beyond conventional photon therapy, particularly in cases requiring maximum OAR preservation. Integrating digital twins into clinical practice could help refine these strategies by predicting individual patient responses and guiding radiation oncologists toward the most effective modality.

Despite these promising findings, certain limitations must be considered. The small sample size (five patients) restricts the generalizability of the conclusions. Additionally, while matRad provides a robust open-source platform for radiotherapy simulations, it does not include all the advanced functionalities of commercial TPS, which may cause slight variations in dose calculation accuracy. Moreover, this study does not take into account patient-specific biological factors, such as genetic predisposition or comorbidities (e.g., diabetes), which could influence the response of healthy tissue to radiotherapy. Integrating such parameters into digital twin models could further enhance predictive accuracy.

To further improve treatment personalization, future research should explore the integration of additional physiological and biological parameters into digital twin models. This could enhance the ability to predict not only physical dose distributions but also patient-specific toxicity risks. Additionally, the potential of carbon ion therapy deserves further exploration. Despite its demonstrated advantages in precision and reduced toxicity, its clinical implementation remains limited due to high costs and infrastructure constraints. Future studies should assess the cost-effectiveness of carbon ion therapy and explore ways to make this technology more accessible. Finally, the integration of artificial intelligence (AI) into digital twins could open up new perspectives for treatment optimization. AI-driven models could analyze large quantities of clinical data to refine predictive models, enabling even more accurate dose planning and side-effect anticipation. The combination of digital twins and AI could thus lead to a new era of personalized and safer radiotherapy.

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