Physica Medica 61 (2019) 52–57

Contents lists available at ScienceDirect

Physica Medica

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

Original paper

The impact of dose algorithms on tumor control probability in intensity-modulated proton therapy for breast cancer

Xiaoying Liang[a,*], Julie A. Bradley[a], Dandan Zheng[b], Michael Rutenberg[a], Raymond Mailhot Vega[a], Nancy Mendenhall[a], Zuofeng Li[a]

[a] Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, USA
[b] Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, NE, USA

ARTICLE INFO

Keywords:
IMPT
Dose calculation algorithms
TCP
Breast cancer

ABSTRACT

Purpose: To evaluate the radiobiological impact of PB algorithm versus MC algorithm in intensity-modulated proton therapy (IMPT) plans for breast cancer treatment.

Methods: 20 breast cancer patients who received IMPT to the breast/chest wall and regional lymphatics were included in this study. For each patient, 2 IMPT plans were generated: a PB-optimized plan and a MC-optimized plan. The radiobiological and dosimetric impact to the CTV of the dose algorithms was assessed. The Poisson Linear-Quadratic model was used to estimate the tumor control probability (TCP). The influence of the model parameter uncertainties on the TCP was tested against different sets of published model parameters.

Results: The PB-optimized plans significantly under-dosed the target as compared to the MC-optimized plans. The median (range) differences in CTV $D_{95\%}$ and CTV Dmean were 1.9 (1.2–3.1) Gy and 1.2 (0.5–1.9) Gy, corresponding to 3.8% (2.4 – 6.2%) and 2.4% (1.0 – 3.8%) of the prescription dose. The TCP was lower in the PB-optimized plans than the MC-optimized plans. The median (range) of the TCP differences (ΔTCP) were 4% (2 – 6%), 3% (2 – 5%), and 2% (1 – 3%), respectively, when calculated using 3 different model parameter sets. The ΔTCP correlated with the CTV dose difference, and moderately correlated with the CTV volume.

Conclusion: Due to the inaccurate dose modeling, PB-optimized plans under-dose the target and therefore yield a lower TCP compared to MC-optimized plans in breast IMPT. The magnitude of the resulting difference in TCP reached 6% in our study.

1. Introduction

Current proton therapy clinical practices primarily use the pencil-beam (PB) algorithm for dose calculations, as it has been the mainstay of commercially-available proton dose calculation algorithms and offers efficient treatment planning workflow. On the other hand, PB algorithms are known to be inaccurate in heterogeneous tissue environment or when a range shifter is used. To this end, Monte Carlo (MC) algorithm have recently been introduced into proton treatment planning systems that provide much more accurate dose modeling. Several phantom studies have demonstrated that the Monte Carlo (MC) algorithm provides more accurate treatment planning than the PB algorithm [1–5]. Clinical lung patient studies by Maes et al. [6] and breast patient studies by Liang et al. [7] recommend the use of the MC algorithm for clinical treatment planning. However, such studies are still lacking in providing insights to clinicians on the actual clinical impact. So far, assessing the radiobiological impact of proton dose algorithms on clinical cases has not been well reported.

Models for estimating the tumor control probability (TCP) and normal tissue complication probability in radiation therapy were first proposed in the late 1980s [8–13]. In the area of proton therapy, a few published clinical studies have analyzed dose errors with the PB algorithm [6,7,14,15]. The study by Schuemann et al. [15] also assessed the TCP for double-scattered proton therapy. To the best of our knowledge, there is no report assessing clinical outcomes or TCP impact for intensity-modulated proton therapy (IMPT). In the current study, we evaluated the radiobiological and dosimetric impact of PB versus MC dose algorithms in IMPT plans for breast cancer patients.

* Corresponding author at: Department of Radiation Oncology, University of Florida & University of Florida Health Proton Therapy Institute, 2015 North Jefferson St., Jacksonville, FL 32206, USA.
E-mail address: xliang@floridaproton.org (X. Liang).

https://doi.org/10.1016/j.ejmp.2019.04.011
Received 21 December 2018; Received in revised form 12 April 2019; Accepted 13 April 2019
Available online 03 May 2019

2. Materials and methods

2.1. Patient selection and treatment planning

This study was approved by our academic center's institutional review board (IRB# 201702651). Twenty breast cancer patients (stage T1-T2, post-mastectomy or post-lumpectomy) who received adjuvant proton IMPT radiotherapy to the breast/chest wall and regional lymphatics at our institution between 2017 and 2018 were included in the analysis. All patients were simulated in the supine position with arms above the head using a wing board and a Vac-Lok immobilization bag (CIVCO Radiotherapy, Coralville, IA, USA). IMPT treatment plans were created in RayStation, version 6, treatment planning system (RaySearch Laboratories, Stockholm, Sweden). The total dose prescribed was 50 Gy (RBE) over 25 fractions of 2 Gy (RBE). A constant relative biological effectiveness (RBE) value of 1.1 was applied. For each plan, 2 en-face angles between 0° and 30° were used. A 7.4-cm water equivalent Lucite range shifter was used for each beam. The selective robust optimization strategy [16] using both robust objectives on the clinical target volume (CTV) with a 5-mm setup uncertainty and 3.5% range uncertainty and normal objectives on the planning target volume (PTV) was used to achieve a robust plan against uncertainties with the desired dose distribution. All optimizations were carried out on a 2-mm calculation grid for 200 iterations. For each patient, two plans were generated:

1) *PB-optimized plan*: The PB algorithm was used for optimization and the final dose was initially computed using the PB algorithm. Thereafter, the plan was normalized so that 95% of the PTV was covered by 95% of the prescription dose. As the PB algorithm could not provide accurate dosimetry for the breast IMPT plans [7], for the purpose of this study, we recomputed the final dose using the MC algorithm to reflect the true delivered dose of the PB-optimized plan.
2) *MC-optimized plan*: While maintaining the identical objective function, including the robust optimization settings used in the PB-optimized plan, but resetting the monitor units, and spot geometry and weighting, the plan was then optimized using the MC algorithm with a sampling history of 50,000 ions/spot. The final dose was computed using the MC algorithm with 0.5% statistical uncertainty. Thereafter, the plan was normalized so that 95% of the PTV was covered by 95% of the prescription dose.

2.2. Tumor control probability calculation

The Poisson Linear-Quadratic (PLQ) model was used to estimate the TCP. The PLQ model [8] is derived from the linear-quadratic cell survival model using the Poisson distribution:

$$TCP = [\exp(-\exp[e\gamma - \frac{EQD_2}{D_{50}}(e\gamma - \ln(\ln(2)))])]$$

where γ is the normalized dose-response gradient, D_{50} represents the dose yielding 50% TCP, and EQD_2 is the equivalent dose given in 2-Gy fractions.

TCP model parameter values were originally obtained by fitting models to clinical data and are therefore dependent on various factors such as patient cohort, treatment techniques, and dose algorithm etc. [17]. To determine the parameters to be used for the current study and to study the influence of the model parameter uncertainties, we reviewed the literature and identified three parameter sets as listed in Table 1: (A) the parameter sets from Plataniotis et al.'s study [18], in which the dose-response relationship was investigated with the existing clinical data from randomized controlled trials of adjuvant radiotherapy vs no adjuvant radiotherapy. For the current study, we converted their reported biological effective dose (BED) based on a α/β of 4 Gy to 2-Gy fractionation dose equivalent. (B) and (C) the two most relevant parameter sets from Okunieff et al.'s [19] comprehensive review of the dose-response data from over 60 studies.

2.3. Dosimetry and TCP evaluation

For all plans, target coverage was evaluated on CTV on nominal scenario as well as perturbed scenarios for setup and range errors. Although the PTV is not used in plan evaluation, we found that normalizing the dose to the PTV provides an efficient workflow achieving satisfactory CTV coverage for both nominal and perturbed scenarios. The impact of the dose algorithms was evaluated by comparing the target coverage (CTV $D_{95\%}$ and CTV Dmean), the hotspot (CTV $D_{2\%}$), and the TCP from the PB-optimized plans and the MC-optimized plans. Pairwise differences in planned dose and estimated TCP were evaluated using a non-parametric Wilcoxon signed rank test with $p < 0.05$ taken as significant. The Pearson correlation analysis was performed to investigate the factors correlated with the magnitude of TCP difference between the PB-optimized plans and the MC-optimized plans.

3. Results

Fig. 1 illustrates the isodose distribution and dose volume histogram (DVH) comparison for a representative patient planned with the PB-optimized plan and the MC-optimized plan. For illustration purposes, the plan that was optimized and computed by the PB algorithm is also shown. The 95% isodose line covered the CTV in both the MC-optimized plan and the plan that was optimized and computed by the PB algorithm, but not in the PB-optimized plan. The PB algorithm overestimated the target dose, which led to substantial under-dosing of the CTV in the PB-optimized plan after recomputing the final dose with the MC algorithm. Table 2 lists the median (range and interquartile range (IQR)) of the CTV $D_{95\%}$, CTV $V_{95\%}$ and CTV Dmean comparing the PB-optimized plans and the MC-optimized plans. The median (range) differences in CTV $D_{95\%}$ and CTV Dmean were 1.9 (1.2–3.1) Gy and 1.2 (0.5–1.9) Gy, corresponding to 3.8% (2.4 − 6.2%) and 2.4% (1.0 − 3.8%) of the prescription dose, respectively. The median (range) difference in CTV $V_{95\%}$ was 20.8% (0.9%, 41.8%). The comparison on the hotspot represented by CTV $D_{2\%}$ is also shown in Table 2. Differently from the CTV coverage, the hotspot was comparable between these two types of plans, indicating the inaccuracy of the PB dose modeling is not uniform within the target. Table 2 also lists the dose to the heart (Dmean) and the ipsilateral lung (V_{20Gy}). The doses to heart and ipsilateral lung were comparable between the PB-optimized plans and the MC-optimized plans.

To study the TCP and the influence of different model parameters, we applied three sets of TCP model parameters, as shown in Table 1. The estimated TCP values for the 20 patients are shown in Fig. 2. The TCP values were lower in the PB-optimized plans than the MC-optimized plans for all three sets of parameters. Table 3 shows the median (range and IQR) of the TCP values calculated by the three sets of model parameters. The median (range) differences between the PB-optimized plans and the MC-optimized plans (ΔTCP) were 4% (2 − 6%), 3% (2 − 5%), and 2% (1 − 3%) for model parameter sets A, B and C, respectively. The TCP values for the MC-optimized plans were significantly greater than those of the PB-optimized plans.

The lower TCP values from the PB-optimized plans tend to associate with lower target dose coverage. When measuring the Pearson correlation coefficient for the ΔTCP (MC-optimized plans – PB-optimized plans), and the target coverage difference, the r (p) values between ΔTCP and CTV $\Delta D_{95\%}$ were 0.69 (0.0007), 0.71 (0.0005), and 0.51 (0.02) for models A, B, and C, respectively; the r (p) values between ΔTCP and CTV ΔD mean were 0.71 (0.0005), 0.81($< 10^{-4}$), and 0.52 (0.02) for models A, B, and C, respectively. Fig. 3 plots the ΔTCP (model A) versus the CTV $\Delta D_{95\%}$ and CTV ΔDmean. As the dose difference between these two types of plans is not uniformly distributed across the whole target volume, the patient with the largest CTV $D_{95\%}$ difference or CTV Dmean difference between the PB-optimized plan and the MC-

Table 1
Tumor control probability (TCP) model parameters used in the current study.

Model	D_{50} (Gy)	γ	Note
A	41.30	1.60	According to an analysis of multi-institutional randomized controlled trial data, tumor control improved with adjuvant radiotherapy versus no adjuvant radiotherapy [18]
B	39.30	1.70	Tumor control model derived from multi-institution data of adjuvant radiation therapy [19]
C	35.38	1.78	Tumor control model derived from a single-institution data of adjuvant therapy data for T1 and T2 breast cancer with regional node involvement [19]

Abbreviations: D_{50}, radiation dose required to achieve a 50% tumor control probability.

Fig. 1. An isodose distribution comparison of a representative patient planned with the pencil-beam algorithm (PB)-optimized plan (b) and the Monte Carlo algorithm (MC)-optimized plan (c). For illustration purpose, the plan that optimized and computed by the PB algorithm (a) also shown. The pink color-washed structure is the CTV. To ensure legibility, only the 95% (red) and 90% (yellow) isodose curves are shown. The dose statistics for the CTV are also shown (bottom right). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

optimized plan is not necessary to be the one with the largest TCP difference. For example, patient # 16 had the largest CTV $D_{95\%}$ difference (3.1 Gy), and the corresponding TCP difference was 4%, 4%, and 2% for model A, B, and C respectively, about the median value of the cohort distribution. The TCP difference reached 6% in our study.

A moderate negative correlation was observed between ΔTCP and the CTV volume, with r (p) values of −0.56 (0.01), −0.54 (0.01), and −0.61 (0.004) for models A, B, and C, respectively. Fig. 4 shows the ΔTCP (model A) versus the CTV volume. The smaller the CTV volume, the greater likelihood of a larger TCP difference between the PB-optimized plan and the MC-optimized plan.

Robustness evaluation was performed following range (3% under-range) and isocentric setup (x ± 3 mm, y ± 3 mm, z ± 3 mm) perturbation. The results of the +3 mm and −3 mm setup error were comparable and the resulting TCP robustness was similar among all three models. Table 4 shows the delta values representing the change in target coverage (CTV $D_{95\%}$, CTV $V_{95\%}$, and CTV Dmean), and TCP (model A) following range (3% under-range) and isocentric setup (x + 3 mm, y + 3 mm, z + 3 mm) perturbation for the PB-optimized plans and the MC-optimized plans. All changes were calculated relative to the nominal plans. The changes in CTV $D_{95\%}$, CTV Dmean, and TCP were very small and they were comparable between the PB-optimized plans and the MC-optimized plans. The median values of the change in CTV $V_{95\%}$ were 1.6% and 4.1% for the MC-optimized plans and the PB-optimized plans, respectively, suggesting the robustness of the MC-optimized plans might be marginally superior to the PB-optimized plans in the CTV $V_{95\%}$.

Table 2
The median (range; IQR) of doses to CTV and OARs in the PB-optimized plans and MC-optimized plans.

	PB-optimized plans	MC-optimized plans	P values
CTV D95% (Gy)	46.2 (range: 45.2, 46.9; IQR: 45.9, 46.9)	48.1 (range: 47.5, 48.5; IQR: 47.9, 48.3)	8.70E−05
CTV V95% (%)	76.4 (range: 54.9, 97.5; IQR: 71.9, 87.2)	98.0 (range: 94.9, 99.7; IQR: 97.1, 98.4)	8.85E−05
CTV Dmean (Gy)	48.3 (range: 47.7, 49.5; IQR: 48.2, 48.7)	49.5 (range: 48.9, 50.9; IQR: 49.4, 49.9)	8.60E−05
CTV D2% (Gy)	51.2 (range: 50.0, 55.8; IQR: 50.7, 52.0)	51.0 (range: 50.0, 57.5; IQR: 50.8, 51.5)	0.49
Heart Dmean (Gy)	0.9 (range: 0.2, 2.1; IQR: 0.4, 1.3)	0.9 (range: 0.2, 2.2; IQR: 0.4, 1.2)	0.40
Ipsilateral Lung V20Gy (%)	16.7 (range: 6.3, 31.6; IQR: 12.6, 21.9)	16.3 (range: 6.2, 30.3; IQR: 12.2, 21.0)	0.06

Abbreviations: IQR, interquartile range; CTV, clinical target volume; OAR, organ at risk; PB, pencil-beam algorithm; MC, Monte Carlo algorithm.

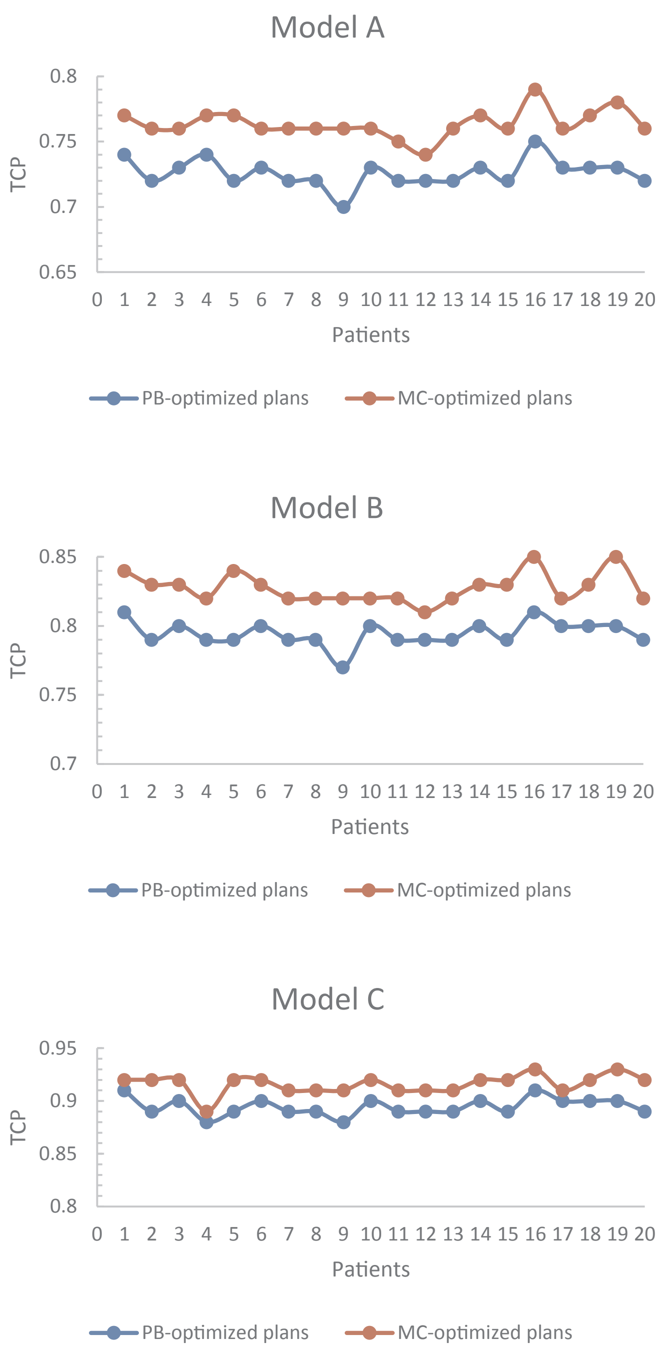

Fig. 2. A tumor control probability (TCP) comparison between the pencil-beam algorithm (PB)-optimized plans and Monte Carlo algorithm (MC)-optimized plans on 20 patients using 3 sets of model parameters.

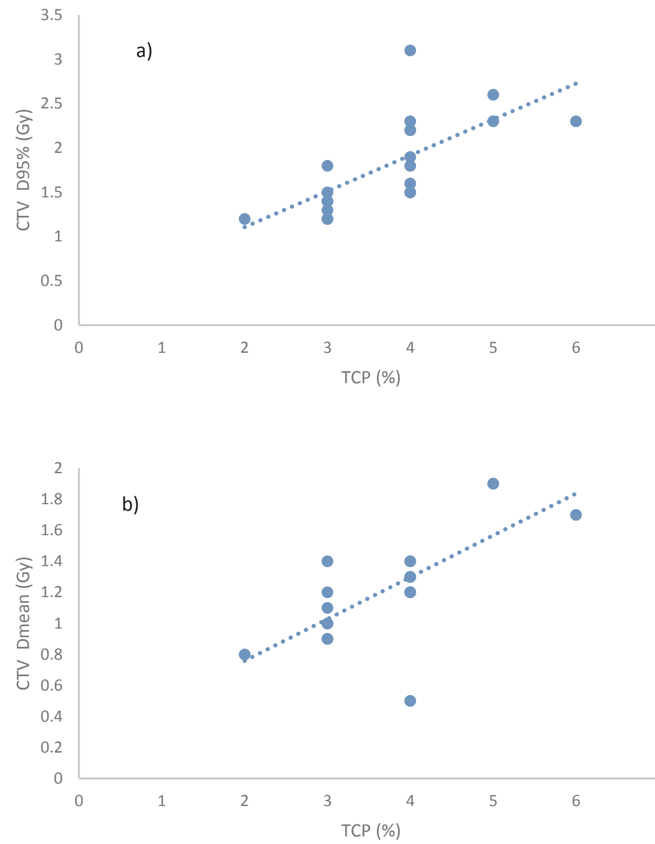

Fig. 3. The change in tumor control probability (ΔTCP) versus a) the clinical target volume (CTV) $\Delta D_{95\%}$ and b) CTV ΔD_{mean} between the pencil-beam algorithm (PB)-optimized plans and the Monte Carlo algorithm (MC)-optimized plans.

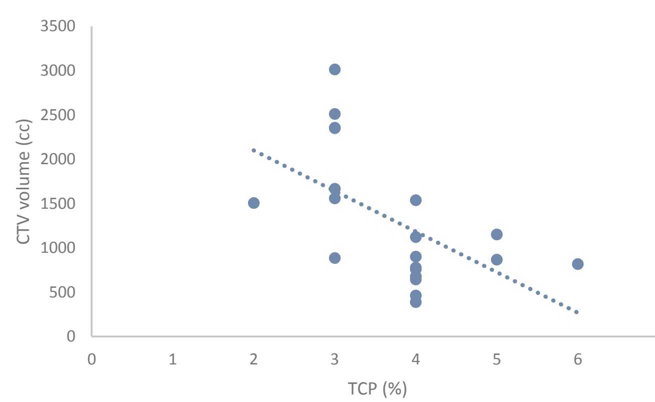

Fig. 4. The change in tumor control probability (ΔTCP) versus the clinical target volume (CTV).

Table 3
Median (range; IQR) of the estimated TCP from the PB-optimized plans and MC-optimized plans.

	TCP Model A	TCP Model B	TCP Model C
PB-optimized plans	0.72 (range: 0.70, 0.75; IQR: 0.72, 0.73)	0.79 (range: 0.77, 0.81; IQR: 0.79, 0.80)	0.89 (range: 0.88, 0.91; IQR: 0.89, 0.90)
MC-optimized plans	0.76 (range: 0.74, 0.79; IQR: 0.76, 0.77)	0.82 (range: 0.81, 0.85; IQR: 0.82, 0.83)	0.92 (range: 0.91, 0.93; IQR: 0.91, 0.92)
P values	6.8E-05	6.3E-05	6.0E-05

Abbreviations: IQR, interquartile range; TCP, tumor control probability; PB, pencil-beam algorithm; MC, Monte Carlo algorithm.

Table 4
Changes in CTV D95%, CTV V95%, CTV Dmean, and TCP (model A) under range (3%) and isocenter setup (x + 3 mm, y + 3 mm, z + 3 mm) perturbation relative to the nominal plan.

Change in dose and TCP D (3%,3 mm)	PB-optimized plans	MC-optimized plans	P value
CTV D95% (Gy)	−0.3 (range: −0.4, −0.1; IQR: −0.3, −0.2)	−0.4 (range: −0.6, 0; IQR: −0.4, −0.2)	0.06
CTV V95% (%)	−4.1 (range: −5.5, −0.1; IQR: −4.3, −2.2)	−1.6 (range: −3.9, −0.1; IQR: −1.9, −1.0)	1.88E−04
CTV Dmean (Gy)	−0.2 (range: −0.4, 0.2; IQR: −0.3, −0.1)	−0.2 (range: −0.6, 0.1; IQR: −0.3, −0.1)	0.39
TCP model A	−0.01 (range: −0.01, 0.02; IQR: −0.01, 0)	−0.01 (range: −0.02, 0.02; IQR: −0.01, 0)	1

Abbreviations: IQR, interquartile range; TCP, tumor control probability; PB, pencil-beam algorithm; MC, Monte Carlo algorithm.

4. Discussion

In the current study, we evaluated the TCP and dosimetric impact of PB versus MC dose algorithms in IMPT plans for breast cancer patients. Here it should be stated that there are uncertainties in the biological models and its associated parameters. Uncertainties can arise from numerous factors that are not taken into account when fitting the models, such as the heterogeneity of the patient cohort and variations in treatment techniques. Therefore, we carefully selected the three most relevant sets of model parameters and applied them to our data. The TCP of PB versus MC dose algorithms in IMPT plans for breast cancer patients was evaluated. The possible correlations between ΔTCP and the CTV coverage differences as well as those between ΔTCP and the CTV volume were also studied.

Notably, the innate physical and biological uncertainties of proton therapy, including uncertainties on the exact range of protons in tissue and their biological effect at the end of the range [20–22], could also impact the accuracy of TCP estimations. For the current study, a constant relative biological effectiveness (RBE) of 1.1 was applied to the entire dose distribution, as it is standardly used for clinical proton treatment planning. We did not account for the spatially variant linear energy transfer (LET) and the RBE in these proton treatment plans. Furthermore, due to the distinctly different physical properties of photons and protons, there may be differences in the biological effect of proton therapy and photon therapy. Applying the TCP parameters obtained from clinical outcome studies of photon therapy to proton therapy may also introduce unknown uncertainties. Therefore, it seems appropriate to interpret the findings of the current study as a relative comparison rather than providing absolute expected values.

PB algorithm has been the standard practice in proton therapy treatment planning, owing to its speed and efficiency as well as the relative scarcity of dosimetric and radiobiological studies on actual patients demonstrating the inadequacy of such algorithm. It has become increasingly important to study and report the clinical benefits of more accurate dose algorithms such as MC, especially now that these tools are available in commercial treatment planning systems. In the current study, we showed that PB-optimized plans significantly under-dose the CTV in breast IMPT, in agreement with the previous study by Schuemann et al. [15] where a 4% $D_{95\%}$ error was found among 10 breast cancer patients treated with double-scattered proton therapy. In the current study, we also briefly reported the doses to OARs, namely mean heart dose and ipsilateral lung V_{20Gy}. The doses to the heart and lung were comparable between the PB-optimized plans and the MC-optimized plans. For the breast cancer treatment, because the target extends to the surface, a range shifter is required for treatment planning, and the air gap is typically larger than other treatment sites to avoid a collision since the large target volume requires the use of the largest snout (30 cm × 40 cm). The combination of the use of a range shifter with the presence of a relatively large air gap led to PB dose distribution calculation errors, as the PB algorithm failed to accurately model the scatter in the range shifter and the air gap. Previous study has shown that the inaccurate modeling of the scatter in the range shifter and the air gap causes dose error at shallow depths [3]. As en-face beams were used for breast IMPT plans, the heart and lung were downstream to the CTV. Therefore, a substantial CTV coverage difference was observed, but the doses to the heart and lung were comparable, between the PB-optimized plans and the MC-optimized plans.

In addition to the study of the dosimetric impact, it is also important to translate the improved accuracy with the MC dose computation into possible clinical impact. For photon therapy, in a recently published study [23] of patients who received stereotactic body radiation therapy for early-stage non-small cell lung cancer, Ohri et al. observed a strong association between the treatment planning algorithm and local control rate. They concluded that the PB algorithm is associated with more than a 2-fold increase in the risk of local tumor progression compared with treatments planned with the MC algorithm. Another similar study by Latifi et al. [24] reviewed 200 lung cancer patients, some treated with PB algorithms and some with a more advanced convolution superposition algorithm, and found that the patients treated with the PB algorithms experienced significantly inferior local control than the patients treated with the advanced algorithms. For proton therapy, there are a few studies [6,7,14,15] analyzing dose errors with the PB algorithm. The study by Schuemann et al. [15] also estimated the TCP for five treatment sites (head-and neck, lung, breast, prostate, and liver), and reported less than 2.5% TCP difference for breast cancer treated with double-scattered proton therapy. This result, however, may not translate directly to IMPT for breast cancer because of differences in proton beam delivery techniques. In the current study, we evaluated the TCP of PB versus MC dose algorithms in IMPT plans for breast cancer patients. Treatment outcomes can be affected by several factors, including tumor histology and biology, treatment planning, and delivery techniques etc. Under-dosing the tumor due to inaccurate dose calculation in treatment planning is one potential cause for local failures. The inaccuracy of the PB algorithm relative to the MC algorithm, could lead to a lower than intended dose delivered to the tumor. In the current study, we found a statistically significant lower TCP for the PB-optimized plans compared to the MC-optimized plans for all three models. The median values of ΔTCP were 4%, 3%, and 2% for models A, B and C, respectively. The maximum ΔTCP reached 6%. A positive trend between ΔTCP and the CTV coverage difference was observed for all three models. However, on an individual level, the patient with the largest ΔTCP did not have the largest CTV $\Delta D_{95\%}$ or ΔDmean. Therefore, for maximizing the tumor control for an individual treatment, examining a few DVH points will not be able to give us the full picture of the plans. Instead, an evaluation of the TCP together with the DVH points would offer more information.

The TCP differences between the PB-optimized plans and the MC-optimized plans were moderately correlated with the CTV volume. The smaller the CTV volume, the greater the likelihood of a large TCP difference. This could be due to the inaccurate modeling of the scatter in the range shifter and the air gap causes dose error at shallow depths [3]. The smaller the CTV volume, the greater the portion of the CTV volume at a shallow depths, which leads to a greater dose difference between the PB-optimized plan and the MC-optimized plan. The greater dose difference generally tends to translate into a greater TCP difference.

In the current study, the influence of the TCP model parameter uncertainties was tested with three sets of model parameters. The same trend was observed for all three models, with some degree of magnitude difference. Models A and B yielded similar ΔTCP as well as a similar correlation coefficient between the ΔTCP and the CTV coverage difference, and between the ΔTCP and CTV volume. While models A and B were derived from data published in 2000s and 1900s, model C was derived from data published in 1976. Considering the evolution in radiotherapy technologies, we think the results from model A and B might be more relevant to our data as compared to model C.

Another point we would like to discuss is the balance between accurate dose calculation and computation efficiency, as both of them are critical for optimal clinical treatment planning workflow. The MC algorithm models the beam more accurately than the PB algorithm. However, the extended optimization time, especially when robust optimization is applied, is a major concern for planning efficiency. We have found that, typically, the MC-optimized plan takes 4 times longer to optimize than the PB-optimized plan. Nevertheless, as shown in the current study, the PB-optimized plan significantly under-dosed the CTV. This drop in CTV coverage tends to translate into a lower TCP. In addition, the TCP was estimated using population-derived parameters; the slope of the dose-response curve might be steeper for some individuals. Therefore, for some patients, the resulted TCP difference might be even higher, which might lead to a clinical meaningful difference. Consequently, despite the planning efficiency tradeoff, MC optimization is recommended for breast IMPT planning.

5. Conclusion

When planning breast IMPT with the usage of a range shifter, PB-optimized plans result in a lower TCP compared to MC-optimized plans. A positive trend between the ΔTCP and the CTV coverage difference was observed. The magnitude of the ΔTCP reached 6% in our study. Further investigation is warranted.

Conflict of interests

JB – travel grant from Ion beam application.

The other authors declare that they have no competing interests.

Acknowledgment

We would like to thank Jessica Kirwan for preparing and editing the manuscript for publication.

References

[1] Bueno M, Paganetti H, Duch MA, Schuemann J. An algorithm to assess the need for clinical Monte Carlo dose calculation for small proton therapy fields based on quantification of tissue heterogeneity. Med Phys 2013;40(8):081704. PubMed PMID: 2392730. Epub 2013/08/10. eng.

[2] Grassberger C, Daartz J, Dowdell S, Ruggieri T, Sharp G, Paganetti H. Quantification of proton dose calculation accuracy in the lung. Int J Radiat Oncol Biol Phys 2014;89(2):424–30. PubMed PMID: 24726289. Pubmed Central PMCID: 4028367. Epub 2014/04/15. eng.

[3] Saini J, Maes D, Egan A, Bowen SR, St James S, Janson M, et al. Dosimetric evaluation of a commercial proton spot scanning Monte-Carlo dose algorithm: comparisons against measurements and simulations. Phys Med Biol 2017;62(19):7659–81. PubMed PMID: 2874937Epub 2017/07/28. eng.

[4] Tourovsky A, Lomax AJ, Schneider U, Pedroni E. Monte Carlo dose calculations for spot scanned proton therapy. Phys Med Biol 2005;50(5):971–81. PubMed PMID: 15798269. Epub 2005/03/31. eng.

[5] Taylor PA, Kry SF, Followill DS. Pencil beam algorithms are unsuitable for proton dose calculations in lung. Int J Radiat Oncol Biol Phys 2017;99(3):750–6. PubMed PMID: 28843371. Pubmed Central PMCID: 5729062. Epub 2017/08/28. eng.

[6] Maes D, Saini J, Zeng J, Rengan R, Wong T, Bowen SR. Advanced proton beam dosimetry part II: Monte Carlo vs. pencil beam-based planning for lung cancer. Transl Lung. Cancer Res. 2018;7(2):114–21. PubMed PMID: 29876310. Pubmed Central PMCID: 5960654. Epub 2018/06/08. eng.

[7] Liang X, Li Z, Zheng D, Bradley JA, Rutenberg M, Mendenhall N. A comprehensive dosimetric study of Monte Carlo and pencil-beam algorithms on intensity-modulated proton therapy for breast cancer. J Appl Clin Med Phys 2018. PubMed PMID: 30488548. Epub 2018/11/30. eng.

[8] Kallman P, Agren A, Brahme A. Tumour and normal tissue responses to fractionated non-uniform dose delivery. Int J Radiat Biol 1992;62(2):249–62. PubMed PMID: 1355519. Epub 1992/08/01. eng.

[9] Lyman JT. Complication probability as assessed from dose-volume histograms. Radiat Res Suppl 1985:8. S13-PubMed PMID: 386707Epub 1985/01/01. eng.

[10] Lyman JT, Wolbarst AB. Optimization of radiation therapy, III: a method of assessing complication probabilities from dose-volume histograms. Int J Radiat Oncol Biol Phys 1987;13(1):103–9. PubMed PMID: 3804804. Epub 1987/01/01. eng.

[11] Kutcher GJ, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. Int J Radiat Oncol Biol Phys 1989;16(6):1623–30. PubMed PMID: 2722599. Epub 1989/06/01. eng.

[12] Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 1991;21(1):123–35. PubMed PMID: 2032883. Epub 1991/05/15. eng.

[13] Schultheiss TE, Orton CG. Models in radiotherapy: definition of decision criteria. Med Phys 1985;12(2):183–7. PubMed PMID: 4000074. Epub 1985/03/01. eng.

[14] Yepes P, Adair A, Grosshans D, Mirkovic D, Poenisch F, Titt U, et al. Comparison of Monte Carlo and analytical dose computations for intensity modulated proton therapy. Phys Med Biol 2018;63(4). PubMed PMID: 29339570. Pubmed Central PMCID: 5906701. Epub 2018/01/18. eng.

[15] Schuemann J, Giantsoudi D, Grassberger C, Moteabbed M, Min CH, Paganetti H. Assessing the clinical impact of approximations in analytical dose calculations for proton therapy. Int J Radiat Oncol Biol Phys 2015;92(5):1157–64. PubMed PMID: 26025779. Pubmed Central PMCID: 4509834. Epub 2015/05/31. eng.

[16] Li Y, Niemela P, Liao L, Jiang S, Li H, Poenisch F, et al. Selective robust optimization: a new intensity-modulated proton therapy optimization strategy. Med Phys 2015;42(8):4840–7. PubMed PMID: 26233211. Epub 2015/08/04. eng.

[17] Petillion S, Swinnen A, Defraene G, Verhoeven K, Weltens C, Van den Heuvel F. The photon dose calculation algorithm used in breast radiotherapy has significant impact on the parameters of radiobiological models. J Appl Clin Med Phys 2014;15(4):259–69. PubMed PMID: 25207416. Pubmed Central PMCID: 5875495. Epub 2014/09/11. eng.

[18] Plataniotis GA, Dale RG. Biologically effective dose-response relationship for breast cancer treated by conservative surgery and postoperative radiotherapy. Int J Radiat Oncol Biol Phys 2009;75(2):512–7. PubMed PMID: 19625139. Epub 2009/07/25. eng.

[19] Okunieff P, Morgan D, Niemierko A, Suit HD. Radiation dose-response of human tumors. Int J Radiat Oncol Biol Phys 1995;32(4):1227–37. PubMed PMID: 7607946. Epub 1995/07/15. eng.

[20] Wouters BG, Lam GK, Oelfke U, Gardey K, Durand RE, Skarsgard LD. Measurements of relative biological effectiveness of the 70 MeV proton beam at TRIUMF using Chinese hamster V79 cells and the high-precision cell sorter assay. Radiat Res 1996;146(2):159–70. PubMed PMID: 8693066. Epub 1996/08/01. eng.

[21] Paganetti H, Olko P, Kobus H, Becker R, Schmitz T, Waligorski MP, et al. Calculation of relative biological effectiveness for proton beams using biological weighting functions. Int J Radiat Oncol Biol Phys 1997;37(3):719–29. PubMed PMID: 9112472. Epub 1997/02/01. eng.

[22] Paganetti H. Calculation of the spatial variation of relative biological effectiveness in a therapeutic proton field for eye treatment. Phys Med Biol 1998;43(8):2147–57. PubMed PMID: 9725595. Epub 1998/09/02. eng.

[23] Ohri N, Tome W, Kalnicki S, Garg M. Stereotactic body radiation therapy for stage I non-small cell lung cancer: the importance of treatment planning algorithm and evaluation of a tumor control probability model. Pract Radiat Oncol 2018;8(2):e33–9. PubMed PMID: 292335Epub 2017/12/14. eng.

[24] Latifi K, Oliver J, Baker R, Dilling TJ, Stevens CW, Kim J, et al. Study of 201 non-small cell lung cancer patients given stereotactic ablative radiation therapy shows local control dependence on dose calculation algorithm. Int J Radiat Oncol Biol Phys 2014;88(5):1108–13. PubMed PMID: 24529716. Epub 2014/02/18. eng.