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Biological Dose Comparison between a Fixed RBE and a Variable RBE in SFO and MFO IMPT with Various Multi-Beams for Brain Cancer

Ryosuke Kohno[1,2,3], Wenhua Cao[2], Pablo Yepes[2], Xuemin Bai[2], Falk Poenisch[2], David R. Grosshans[2], Tetsuo Akimoto[3], Radhe Mohan[2]

[1]Medical Physics Section, National Institute of Radiological Sciences, Chiba, Japan
[2]Department of Radiation Physics, University of Texas MD Anderson Cancer Center, Houston, USA
[3]Division of Radiation Oncology and Particle Therapy, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center Hospital East, Chiba, Japan
Email: kohno.ryosuke@qst.go.jp

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Abstract

IMPT plans with various multi-angle beams were planned by the Varian Eclipse treatment planning system for one case of brain cancer. Dose distributions for each plan, along with the associated linear energy transfer distributions, were recomputed using an in-house fast Monte Carlo dose calculator with a FRBE of 1.1 or with a previously published VRBE model. We then compared dosimetric parameters obtained by the VRBE with those obtained by the FRBE. Biological doses obtained by the VRBE for the clinical target volume in all plans were 1% - 2% larger than those obtained by the FRBE. The minimum dose obtained by the VRBE for the right optic nerve in the MFO IMPT with 4 fields was 70% larger than that obtained by the FRBE, but the difference was only 18.1 cGy (RBE). The difference in maximum dose for the right optic nerve in the MFO IMPT with 5 fields was less than 10.4%, but the difference was 131.8 cGy (RBE). The mean difference in maximum dose was less than 2% for all other organs at risk. We found that biological dose with the FRBE had any dose errors in IMPT with various multi-angle beams.

Keywords

IMPT, Monte Carlo, Biological Dose, Variable RBE

1. Introduction

Proton beam therapy can enhance tumor control while minimizing irradiation to surrounding normal tissues in cancer care owing to the Bragg peak, with a sharp distal fall-off [1] [2]. Recently, the number of clinical proton therapy facil-

ities has increased because of this substantial potential for clinical advantages over conventional photon therapy [3] [4]. In the latest proton beam therapy, beam scanning technique [5] [6] [7] has been widely used. Especially, intensity-modulated proton therapy (IMPT), in which scanning beam lets of protons, used to "paint" radiation dose on the target, can be exploited to safely bend beams around complex critical structures, allowing improved sparing of these structures without compromising target coverage [8]. Two types of IMPT optimization exist, namely, single-field optimization (SFO) and multi-field optimization (MFO). The SFO optimizes individually each field to create a uniform dose distribution from each beam, and the MFO optimizes simultaneously spots from all the fields to get highly conformal dose distributions.

Currently, a fixed relative biological effectiveness (FRBE) relative to photons of 1.1 is used conventionally in proton beam therapy. However, the RBE of protons generally depends on the linear energy transfer (LET), the dose per fraction, and the tissue type [9]. In recent years, the potential clinical impacts of a variable RBE (VRBE) in proton beam therapy have been discussed [10] [11] [12] [13]. Frese *et al.* have investigated whether using a VRBE in IMPT will change dose distributions [14]. They indicate that the application of the VRBE is clinically more useful for accurate assessment of the feasibility of the plans from a biological point of view.

However, in that study, Wilkens and Oelfke use a pencil beam algorithm (PBA) to simulate dose and LET distributions [15]. It is common knowledge that the accuracy of the PBA [16] for protons is inadequate, especially in the presence of complex heterogeneities [17] [18]. In the SFO and MFO IMPT plans with various multi-angle beams for a brain cancer patient, physical dose differences between the PBA and Monte Carlo method have been already evaluated, and Kohno *et al.* also advocate use of a Monte Carlo method in proton treatment planning to deliver the most precise proton dose in IMPT [19].

In this study, dose distributions, along with the associated linear energy transfer (LET) distributions, were recomputed using a fast Monte Carlo dose calculator (FDC). We focused on biological dose differences between FRBE and VRBE for the same SFO and MFO IMPT plans with various multi-angle beams in the previous paper [19]. From these studies, we expect that it is useful for proton users to clarify dose differences of not only physical dose calculation algorithms but also biological dose calculation models.

2. Materials and Methods

We selected a patient with grade 3 anaplastic astrocytoma analyzed by Kohno *et al.* [19]. This patient was treated by passively scattered proton therapy at The University of Texas MD Anderson Cancer Center. **Figure 1** shows the target volumes and organs at risk (OARs) in the brain cancer treatment plan on a computed tomography slice. The target volumes are surrounded in a complicated manner by nerve, brain, brainstem, bone, and sinus cavity. As shown in

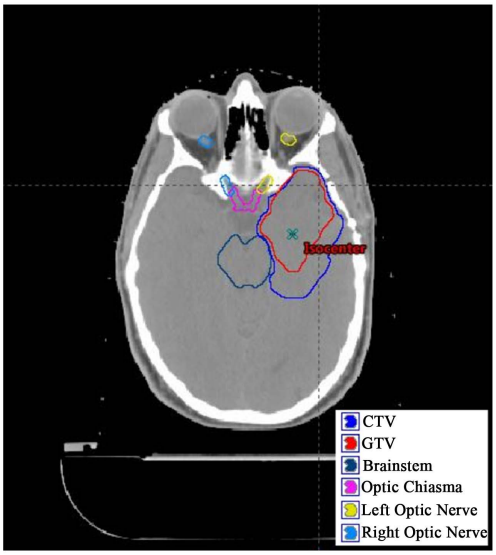

Figure 1. Contours of the GTV, CTV, and OARs drawn on the computed tomography image for the actual brain cancer IMPT plan analyzed by Kohno *et al.* [19].

Table 1, we used the SFO and MFO IMPT plans with three, four, five, six, or nine treatment fields analyzed by Kohno *et al.* [19].

SFO and MFO IMPT plans were designed by the Eclipse treatment planning system (Version 13.5; Varian Medical Systems, Inc., Palo Alto, CA). The prescribed doses were 5700 cGy (RBE) to the gross tumor volume (GTV) and 5000 cGy (RBE) to the clinical target volume (CTV) in 30 fractions. All plans were designed to cover 100% of the GTV and the CTV and to minimize the maximum dose for each OAR with the same optimization conditions as in the treatment planning system. The maximum dose constraint for the brainstem, the chiasm, left optic nerve, and right optic nerve was 5400 cGy (RBE).

The FDC [20] [21] recomputes physical dose distributions for each plan, along with the associated LET distributions. Then, to calculate a biological dose distribution, RBE was obtained by the FRBE of 1.1 and the phenomenological RBE model [22]. This phenomenological model can calculate simply the RBE as a function of the dose, the LET, and tissue-specific parameters. Using a reference radiation with parameters α_x and β_x, the RBE at proton dose (D_p) on the dose averaged LET (LET_d) is given by

$$RBE\left(D_p, LET_d, \alpha_0, \lambda, \alpha_x, \beta_x\right) = \frac{\sqrt{\alpha_x^2 + 4\beta_x D_p\left(\alpha_0 + \lambda LET_d + \beta_x D_p\right)} - \alpha_x}{2\beta_x D_p} \quad (1)$$

where α_0 and λ are the linear and the initial parameter, respectively, in terms of biologic response (α) to protons. Biological parameters given by Frese *et al.* [14] were used in this study.

To compare the FRBE and VRBE models, we performed a comparative analysis of dose distributions for each plan in each region of interest. The comparative analysis used the dosimetric parameters of minimum, maximum, and mean dose. For the CTV, we also evaluated dose to 95% of the CTV (D95), dose to

Table 1. Treatment fields and beam angles (degrees) for each plan.

Plan		Number of treatment fields	Beam angle (degrees)								
SFO	MFO										
A	**G**	3	40	100	160	NA	NA	NA	NA	NA	NA
B	**H**	4	40	80	120	160	NA	NA	NA	NA	NA
C	**I**	5	40	70	100	130	160	NA	NA	NA	NA
D	**J**	6	40	70	100	130	160	220	NA	NA	NA
E	**K**	9	40	70	100	130	160	190	220	250	280
F	**L**	9	20	60	100	140	180	220	260	300	340

5% of the CTV (D5), heterogeneity index (HI), and conformity index (CI). As defined by the Radiation Therapy Oncology Group [23], HI is the maximum dose to the CTV divided by the prescription dose, and CI is the prescription isodose volume divided by the CTV volume.

3. Results

The SFO IMPT plans obtained by the FRBE and by the VRBE models differed by a mean (±standard deviation) of 1.5% ± 0.3% in maximum dose and 1.3% ± 0.0% in mean dose (**Figure 2**). In order to observe easily dependence of dose on number of fields, all data was fitted with linear function. The difference between the models in minimum dose was somewhat larger, at 2.2% ± 0.4%. These results did not depend on number of fields or on plans. The FRBE and the VRBE models differed by a mean (±standard deviation) of 1.4% ± 0.1% in D95 and 1.3% ± 0.1% in D5. Overall, doses obtained by the VRBE were about 2% larger than those obtained by the FRBE. The FRBE and VRBE models differed by 1.6% ± 0.3% in HI and 3.9% ± 0.4% in CI, and both indexes in the VRBE deteriorated compared with those in the FRBE.

Minimum, maximum, and mean dose obtained by the FRBE and the VRBE models in the SFO IMPT plans for the OARs are shown in **Figure 3**. For each site, the differences in minimum dose were larger than the differences in maximum and mean dose. The difference in minimum dose in the right optic nerve in plan B was the largest among the plans, at 56.4%, but the dose difference was only 21.7 cGy (RBE). The maximum dose to these critical organs is the most important parameter; the difference in maximum dose in the right optic nerve in plan C was less than 7.7% but constituted a difference of 111.6 cGy (RBE). This maximum dose was much less than the maximum dose constraint of 5400 cGy (RBE). Except for the right optic nerve, the mean difference in maximum dose for each site was less than 2%.

Figure 4 shows the minimum, maximum, and mean LET in the SFO IMPT plans obtained by the FRBE and VRBE models at different locations. The LET in the brainstem ranged from 1.2 to 7.7 keV/μm (the widest range), while the LET in the left optic nerve ranged from 2.3 to 5.5 keV/μm (the narrowest range). Overall, LET decreased with number of fields because the ends of the beams with high LETs did not concentrate at each site, owing to multiple beam angles.

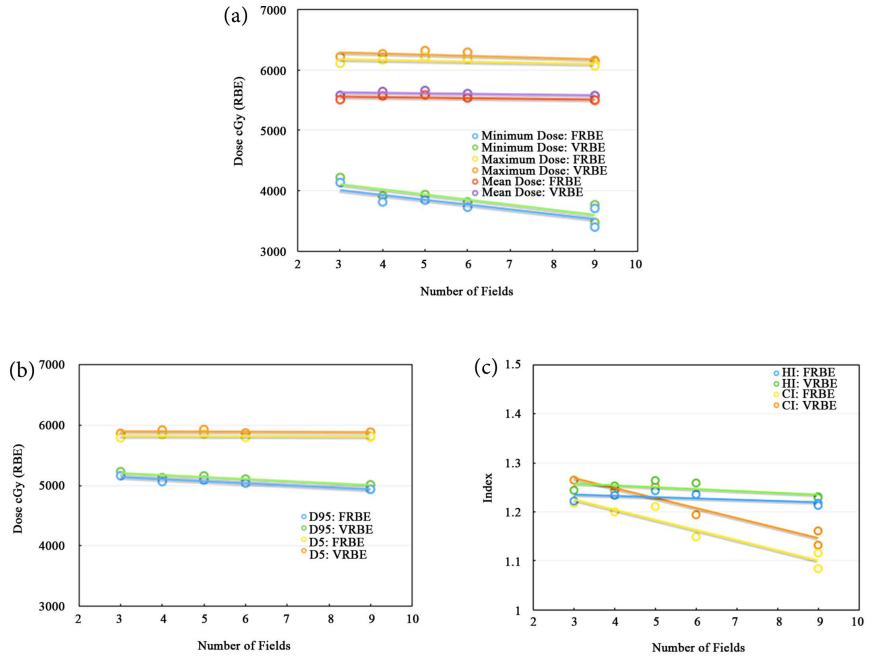

Figure 2. (a) Minimum, maximum, and mean dose; (b) D95 and D5; (c) HI and CI for the CTV obtained by the FRBE and the VRBE models in SFO IMPT plans.

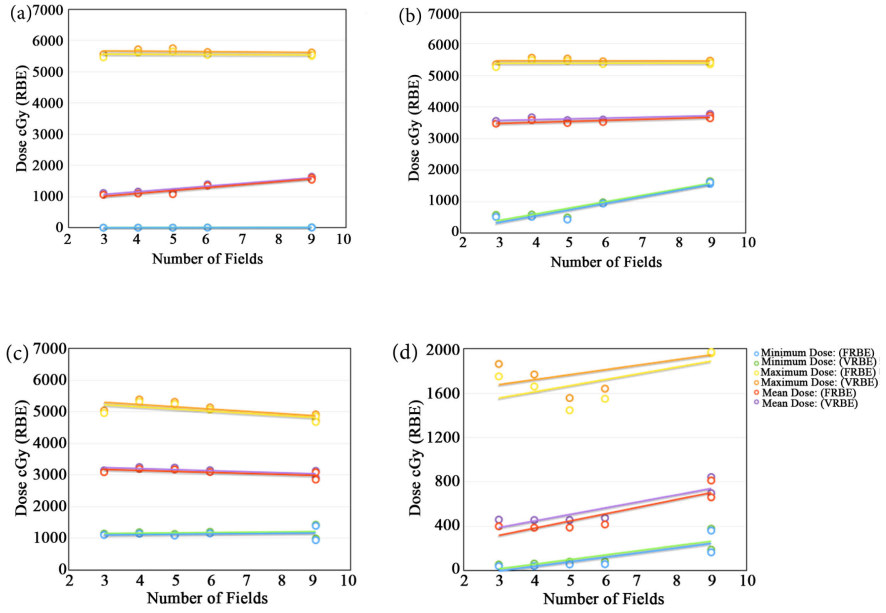

Figure 3. Minimum, maximum, and mean dose in SFO IMPT plans obtained by the FRBE and VRBE models for the (a) brainstem; (b) chiasm; (c) left optic nerve; (d) right optic nerve.

The dosimetric parameters for the CTV in the MFO IMPT plans differed on average between the FRBE and the VRBE models in minimum, maximum, and mean dose by 1.2% ± 0.5%, 1.6% ± 0.5%, and 1.1% ± 0.2%, respectively (**Figure 5**). These differences did not depend on plan. The mean differences between the models in D95 and D5 were 1.2% ± 0.2% and 1.0% ± 0.2%, respectively. The

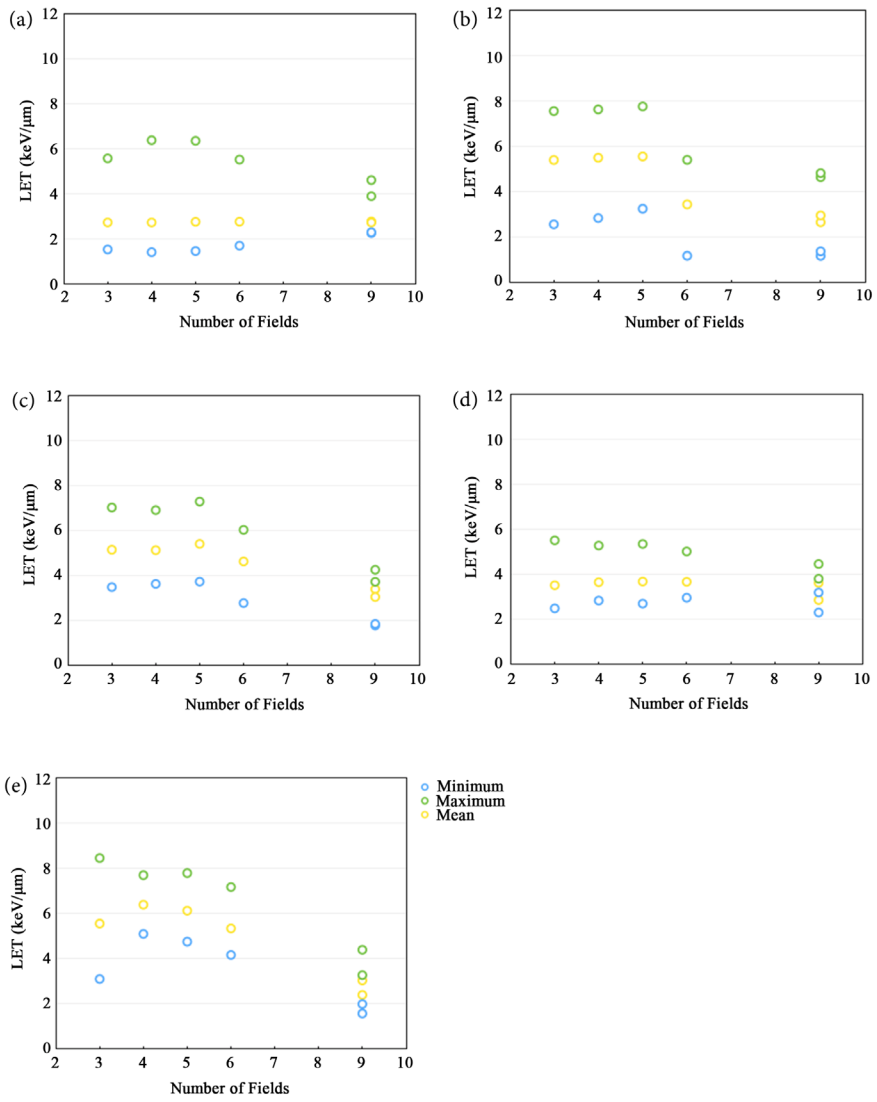

Figure 4. Minimum, maximum, and mean LET in SFO IMPT plans obtained by the FRBE and VRBE models for the (a) CTV; (b) brainstem; (c) chiasm; (d) left optic nerve; (e) right optic nerve.

mean differences between the models in HI and CI were 1.6% ± 0.5% and 4.2% ± 0.5%, respectively. Both indexes in the VRBE model deteriorated compared with those in the FRBE, similar to the indexes in the SFO IMPT plans. There was almost no difference between the results for the SFO plans and the results for the MFO plans.

Minimum, maximum, and mean dose in the MFO IMPT plans obtained by the FRBE and VRBE models for the OARs are shown in **Figure 6**. The differences in minimum dose were larger than the differences in maximum dose and the differences in mean dose for each site, and the differences in each parameter in the right optic nerve were larger than those in other sites. As **Figure 6(d)** shows, differences in each dosimetric parameter decreased with number of fields. Their differences in plan L were minimal in all plans. The difference in

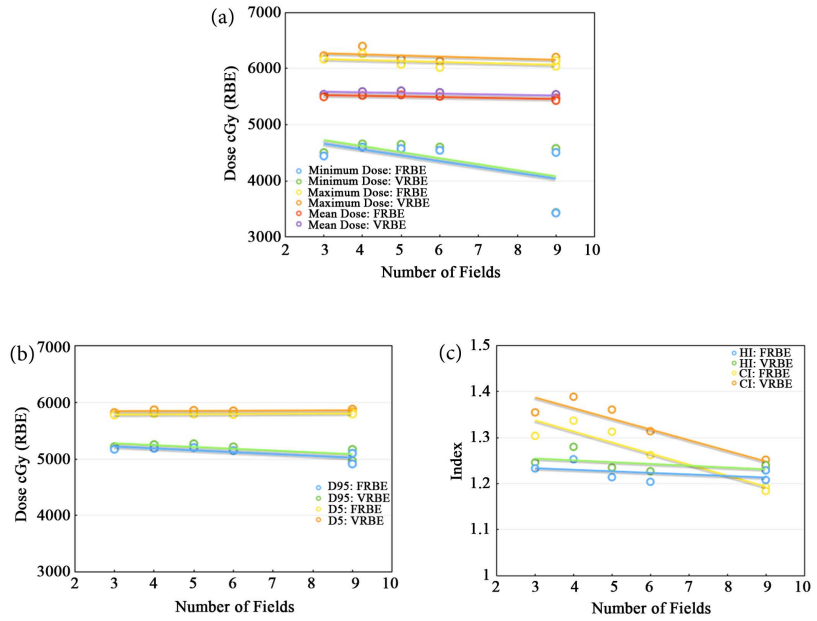

Figure 5. (a) Minimum, maximum, and mean dose; (b) D95 and D5; and (c) HI and CI for the CTV obtained by the FRBE and VRBE models in MFO IMPT plans.

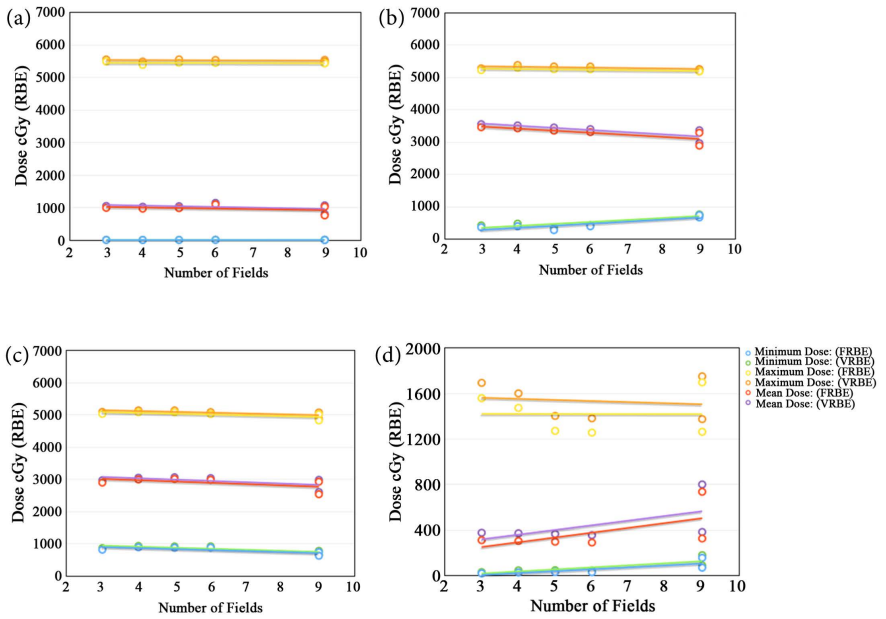

Figure 6. Minimum, maximum, and mean dose obtained by the FRBE and VRBE models in MFO IMPT plans for the (a) brainstem; (b) chiasm; (c) left optic nerve; (d) right optic nerve.

minimum dose to the right optic nerve in plan H was the largest, at 70.4%, but this difference was only 18.1 cGy (RBE). The difference in the important parameter of maximum dose in the right optic nerve in plan I was less than 10.4%, but this difference was only 131.8 cGy (RBE). Except for the right optic nerve, the mean difference in maximum dose was less than 2% for each site, similar to the results of the SFO IMPT plans.

Figure 7 shows the minimum, maximum, and mean LET in the MFO IMPT plans obtained by the FRBE and VRBE models at different locations. The LET in the right optic nerve ranged from 0.2 to 10.5 keV/μm, and the minimum LET of 0.2 was obtained by secondary particles. The LET values in the brainstem and right optic nerve deposited mainly by the end of the beam showed wide ranges. Also, the range of the LET in the MFO plans was larger than that in the SFO plans (Figure 4).

Table 2 summarizes, for better comparison, the mean differences (cGy [RBE], %) between the FRBE and the VRBE models in minimum, maximum and mean dose in the SFO and MFO IMPT plans for the CTV and OARs. For the CTV, the mean differences in minimum, maximum and mean dose were 1% - 2%. For each OAR, the mean difference in maximum dose was the smallest

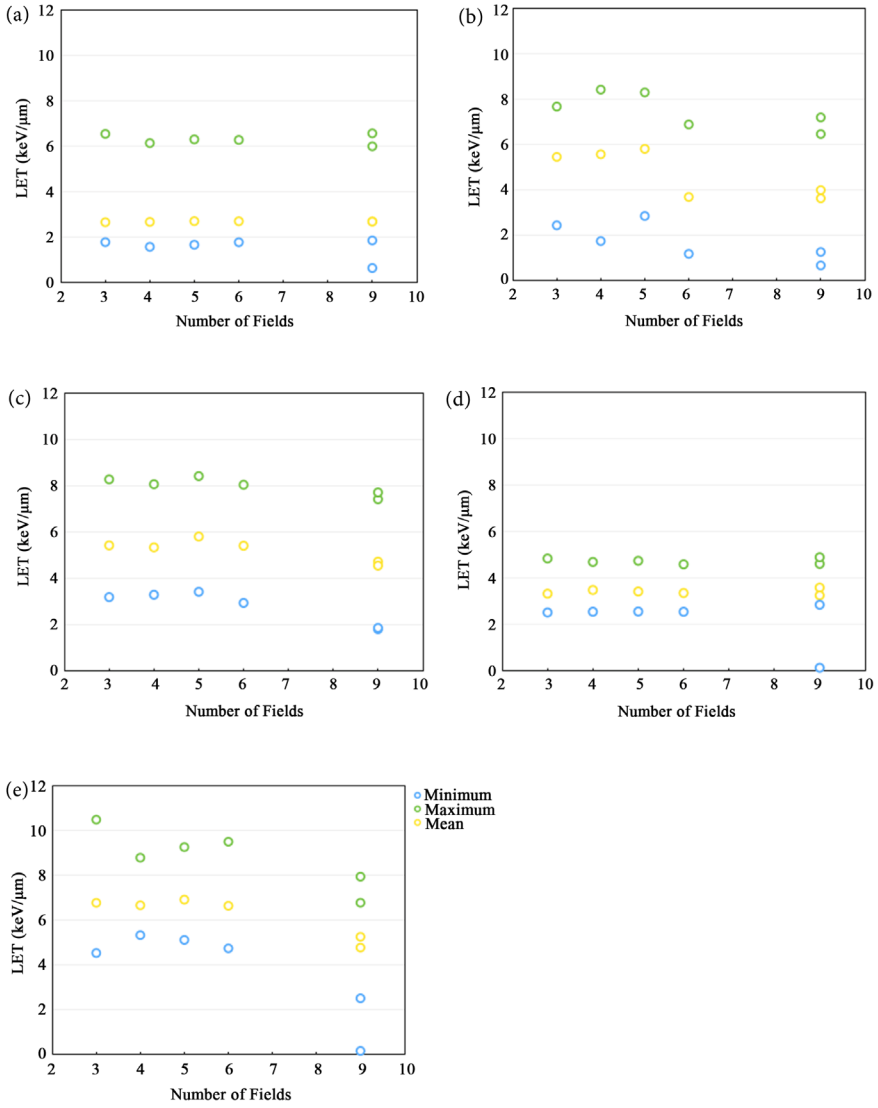

Figure 7. Minimum, maximum, and mean LET in MFO IMPT plans obtained by the FRBE and VRBE models for the (a) CTV; (b) brainstem; (c) chiasm; (d) left optic nerve; (e) right optic nerve.

Table 2. Mean differences between the FRBE and the VRBE models in dosimetric parameters for the SFO and MFO IMPT plans for each site.

IMPT type	Site	Minimum dose		Maximum dose		Mean dose	
		cGy (RBE)	%	cGy (RBE)	%	cGy (RBE)	%
SFO	CTV	84.1 ± 14.4	2.2 ± 0.4	95.1 ± 18.3	1.5 ± 0.3	71.6 ± 0.7	1.3 ± 0.0
	Brainstem	3.7 ± 0.8	42.3 ± 8.6	91.6 ± 1.6	1.6 ± 0.2	48.5 ± 13.2	4.0 ± 1.7
	Chiasma	54.2 ± 15.2	8.5 ± 6.0	75.6 ± 8.1	1.4 ± 0.2	74.2 ± 18.0	2.1 ± 0.5
	Left optic nerve	45.4 ± 7.0	4.1 ± 1.0	67.5 ± 11.6	1.3 ± 0.2	56.3 ± 6.8	1.8 ± 0.2
	Right optic nerve	20.8 ± 4.0	33.9 ± 20.0	88.7 ± 28.2	5.4 ± 2.1	53.8 ± 15.8	12.3 ± 6.0
MFO	CTV	54.0 ± 23.1	1.2 ± 0.5	96.4 ± 29.4	1.6 ± 0.5	61.4 ± 12.8	1.1 ± 0.2
	Brainstem	2.4 ± 1.3	38.9 ± 14.7	81.1 ± 21.0	1.5 ± 0.4	50.3 ± 9.1	5.2 ± 0.9
	Chiasma	56.0 ± 22.5	13.9 ± 7.7	68.4 ± 14.1	1.3 ± 0.3	86.6 ± 8.4	2.6 ± 0.2
	Left optic nerve	40.9 ± 4.6	5.1 ± 0.9	58.4 ± 2.1	1.2 ± 0.1	60.0 ± 8.1	2.1 ± 0.4
	Right optic nerve	16.7 ± 4.3	46.1 ± 21.0	114.1 ± 30.8	8.3 ± 2.6	64.8 ± 4.1	19.3 ± 5.6

among those in minimum, maximum and mean dose. In maximum dose, except for the right optic nerve, the mean differences for all other OARs were less than 2%. On the other hand, the mean difference in minimum dose for each OAR was the largest among them. Namely, minimum dose in all plans for OARs was changed sensitively by the VRBE calculation. Then, the mean differences in each dosimetric parameter for the right optic nerve in the SFO plans were smaller than those in the MFO plans. This is because LETs in the SFO were lower than those in the MFO, as shown in LET comparisons between Figure 4 and Figure 7.

4. Discussion

We observed dose differences between the plans obtained by the FRBE and VRBE models. Doses obtained by the VRBE for the CTV in all plans were 1% - 2% larger than those obtained by the FRBE. The differences between the models in each dosimetric parameter for the CTV in all plans did not depend on number of fields or on plans.

On the other hand, the minimum dose obtained by the VRBE for the right optic nerve in MFO plan H was 70% larger than that obtained by the FRBE, although the mean differences in maximum dose were less than 2% for all other OARs. The differences in each dosimetric parameter between the FRBE and VRBE models in the right optic nerve also decreased with the number of fields (Figure 6(d)). This decrease can be explained by differences in the right optic nerve between the maximum LET and the minimum LET, which decreased with the number of fields (Figure 7).

Thus, biological dose differences depended on location of the OAR, and LET

decreased with number of fields because the ends of the beams with high LETs did not concentrate at each site owing to multiple beam angles. These results may lead to improvements of proton arc therapy with the ultimate multiple-field irradiation [24] [25] [25]. Furthermore, this knowledge may enhance the effectiveness of proton therapy by optimizing true biological dose [9].

In this study, the phenomenological RBE model proposed by Wilkens and Oelfke was used. Dose distributions with the VRBE naturally depend on the RBE calculation model. Although many researchers have also proposed RBE models [27] [28] [29], additional studies will be needed to accurately determine the dependence of RBE on various physical and biologic parameters [30] [31].

Regardless, we were able to evaluate the importance of a VRBE in this study. Dose differences between the FRBE and the VRBE models for the CTV were only about 2%. On the other hand, Kohno *et al.* reported that the conventional pencil beam algorithm (PBA) dose calculation overestimated 400 - 500 cGy (RBE) for minimum physical dose to the CTV relative to the physical dose calculated by the FDC [19]. Mizutani *et al.* also reported that the D95 for PTV obtained by the simplified Monte Carlo method [32] [33] was ~25% smaller than that obtained by conventional pencil beam algorithm (PBA) dose calculation [34]. Thus, for the target volume, these results indicate that the dose errors by the physical dose calculation model would be greater in current proton beam therapy than those calculated by the RBE calculation model. Therefore, we strongly suggest that proton treatment planning and IMPT optimization use a fast Monte Carlo method such as the FDC or the simplified Monte Carlo method in advance.

5. Conclusions

In our evaluation of the dosimetric impacts of FRBE and VRBE models in SFO and MFO IMPT plans with various multi-angle beams using the FDC for a brain cancer patient, doses obtained by the VRBE model for CTV in all plans were about 2% larger than those obtained by the FRBE model. These differences were not large, and the differences among the models in each dosimetric parameter for the CTV in all plans did not depend on plans. On the other hand, for right optic nerve in plan H, minimum and maximum dose obtained by the VRBE model were about 70% and 10% larger than that by the FRBE, and the mean difference in maximum dose for all other OARs was less than 2%.

In conclusion, we found that biological dose with the FRBE had any dose errors in IMPT with various multi-angle beams. Minimum dose in all plans for OARs was changed sensitively by the VRBE calculation. This study indicated that the VRBE should be considered for proton treatment planning to provide an optimal proton beam therapy. However, in order to determine definitely whether there is any clinical evidence in which IMPT plans can benefit from using VRBE, we have to analyze IMPT plans using clinical results for additional patients and at other sites. Then, we also need to develop an RBE model to estimate accurately the VRBE.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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