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Evaluation of Dosimetry Metrics in Single Isocenter Multiple Targets and Single Isocenter Single Target in the Treatment of Brain Metastases

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Abstract

Purpose: This study compares two LINAC-based techniques for treating multiple brain lesions using quantitative evaluation of plan dosimetric indices.

Material & Methods: Twenty-one patients with a total of 168 targets were selected. All plans were designed with five non-coplanar arcs in the RayStation treatment planning system (TPS). The composite dose of Multiple Isocenter Multiple Targets (MIMT) was compared to that of single isocenter multiple targets (SIMT) by evaluating conformity indices, Paddick gradient-index (PGI), V_8, V_{12}, and Delivery Time (DT). Also, the impact of the number of targets on the dosimetric indices was investigated. Moreover, the effect of energy and Grid Size (GS) on dosimetric indices in SIMT was studied. Two-sample t-tests and Pearson correlation were used to investigate the statistical significance.

Results: A significant difference was observed between MIMT and SIMT in terms of conformity indices. PGI for SIMT is higher than that for MIMT. No significant difference was found between the two methods for V_{12} while a significant difference was observed for V_8. DT was noticeably shorter for SIMT. No correlation between isocenter location and dosimetric indices was observed in SIMT. GS was a significant classifier for conformity indices, but the energy was not. PGI did not demonstrate any statistically significant differences for the same GS.

Conclusion: Shorter DT and improved dosimetric indices indicate that high-quality SIMT plans can be achieved for a limited number of targets (≤6) per plan. Evaluating the impact of energy and GS on dosimetric indices has demonstrated that there is some advantage in using 6MV-FFF with a 1 mm GS beam over 10 MV-FFF and 2 mm GS.

Keywords: Single isocenter multiple targets; Multiple isocenter multiple targets; Quality metrics, Isocenter location; Delivery time; Energy; Grid size; VMAT.

Abbreviations: CC: Correlation Coefficient; DT: delivery Time; FFF: Flattening Free Filter; GS: Grid Size; GTV: Gross Tumor Volume; MIMT: Multiple Isocenter Multiple Target; OAR: Organs at Risk; PCI: Paddick Conformity Index; PGI: Paddick Gradient Index; PTV: Planning target volume; PIV: Prescribed Iso Dose Volume; RTOG_CI: RTOG Conformity Index; SIMT: Single Isocenter Multiple Target; SRS: Stereotactic Radiosurgery; TPS: Treatment Planning System; TV: Tumor Volume; VMAT: Volumetric Intensity Modulated Arc Therapy

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Introduction

Brain Metastases (BM), also called secondary brain tumors, are the most common type of intracranial tumors and are caused by cancer cells spreading via the bloodstream to the brain from different parts of the body. More than 70% of patients with brain metastasis present with multiple lesions [1]. The classic treatment of BM used to be Whole-Brain Irradiation (WBRT), in which a uniform dose is delivered to the total volume of brain tissue, thus ensuring total coverage of all brain metastases; this approach would cause lasting side effects and morbidity. A more modern approach involves advanced radiotherapy techniques such as Stereotactic Radiosurgery (SRS), which have been used widely as an alternative to WBRT. Regardless of the machine delivery technique, an SRS plan delivers a high dose of radiation to a target with a sharp dose falloff and low fractionation. By definition, SRS entails the delivery of one high dose of radiation, whereas hypofractionated Stereotactic Radiotherapy (SRT) regimen delivers up to five relatively high doses of radiation to the target. There are two LINAC-based techniques for treating multiple targets in the brain - the MIMT and the SIMT techniques. In the MIMT technique, the isocenter is placed inside each target and delivers the prescribed dose to the Planning Target Volume (PTV). This can be problematic when targets are not far enough from each other. Moreover, DT and the time the patient is on the treatment table proportionally increase by increasing the number of targets. Furthermore, controlling the dose to organs-at-risk (OAR) can become challenging when arcs overlap between multiple isocenter positions. SIMT can be used to cover all targets by using a single isocenter that is placed at a midpoint, typically the center of mass of all targets in one plan. A meaningful, patient-centered benefit of using this technique is reducing treatment time significantly compared to MIMT [2]. Also, the efficiency is generally improved as patient imaging and couch shifts only need to be done once, and the total number of beams used will be less than MIMT plans. Currently, there are no guidelines regarding the treatment technique, the location of the isocenter, the evaluation of the plan quality, and the impact of Grid Size (GS) and energy on plan quality metrics for multi-target treatment. The goal of this dosimetric study is to compare MIMT and SIMT techniques by evaluating indices including Paddick conformity (PCI), RTOG_ conformity index (RTOG_CI), PGI, DT, and V_8, V_{12} of the brain. Additionally, assessing the effect of the location of the isocenter, GS, and energy on dosimetric indices in the SIMT technique may establish a guideline that can be used in clinics.

Material & methods

Treatment planning

Cranial CT scans of 21 anonymized patients were selected, and a range of 4 to 12 (mean 8) Gross Tumor Volumes (GTV) was drawn for each scan. A 2 mm isotropic margin was added to each target to define the PTV to account for setup error, movement, and any possible geometric variations [3]. The average volume size of PTV was 1.87 cm^3 (range 0.06-20 cm^3). All targets were prescribed to receive 24 Gy in 3 fractions (SRT). Salari et al [4] studied the effect of GS and energy on gamma passing rate in the SIMT technique, reporting that 6MV Flattening Filter-Free (FFF) with a GS of 1mm results in higher plan quality in terms of gamma passing rate. For this reason, all treatment plans were designed using 6 MV-FFF with a maximum dose rate of 1400 MU/min and a GS of 1 mm. All Volumetric Modulated Arc Therapy (VMAT) plans were created in RayStation® TPS (Ver.10.A) (RaySearch Medical Laboratories AB, Stockholm, Sweden) using collapsed cone convolution algorithms (Ver. 5.3) for both techniques. The collimator angle was 30 or 330 [5], gantry angle sampling of 2° between the control points [6], and 5 non-coplanar partial arcs (couch 0°, ±45°, ±90°) to reduce the dose to OARs [7] were used for both MIMT and SIMT. All plans were designed for Varian Edge linac (Varian Medical Systems, Palo Alto, CA) which is equipped with a Varian High Definition 120 multileaf collimator (MLC), with 2.5 mm leaf width in the inner section of 8 cm of the field, and 5 mm leaf width in the outer section of the field. A Boolean operator was used to combine all individual PTV into a single PTV, which was named "PTVs."

MIMT Planning

SRS plans were made for each target and the isocenter was set in the center of the target. The gantry angle was based on minimizing the overlap between arcs for nearby targets as much as possible (Figure 1). Then composite plans, which sum up all individual SRS plans, were made for plan evaluation and comparison. A dose normalization of 100% of the prescribed dose (D_p) at 95% of PTV was adopted, while < 2% of PTV < 130% D_p was accepted.

SIMT Planning

In this technique, a single isocenter is located at the midpoint of all targets to cover all PTVs in one plan (Figure 2). Volumetric dose prescription was adopted, by normalizing 100% D_p to 95% of the volume of all PTVs, while D2%(PTV) <130% D_p was accepted. Nevertheless, we checked the coverage of each individual PTV to ensure none of them were under or over-treated.

Quality metrics

In-house scripts were written in RayStation Scripting Application Programming to calculate and extract data directly from RayStation TPS. The plan quality metrics used in this study include dosimetric indices such as the RTOG_CI, PCI, PGI, and dose-volume metrics V_8 and V_{12} as follows:

RTOG_conformity index

Shaw et al [8] proposed the concept of conformity index by using Equation 1. This concept has been used in radiation therapy oncology group (RTOG) guidelines.

$$RTOG_{CI} = \frac{PIV}{TV} \qquad (1)$$

Where PIV is the volume of the prescription isodose and TV is the tumor volume. The ideal value of RTOG_CI is 1. This index provides information regarding the over-coverage and under-coverage of the target. When the target is overtreated, the value is greater than 1, and if it is undertreated, RTOG_CI is less than 1. However, this ratio does not consider the location of the PIV relative to the TV.

Paddick conformity index

In 2000, Paddick proposed a conformity index (Equation 2) as an alternative to RTOG_CI. This index is based on the volume of the target covered by PIV.

$$PCI = \frac{TV_{PIV}^2}{PIV \times TV} \quad (2)$$

Where TV_{PIV}^2 is the volume of the target covered by the prescribed isodose. This index is equal to 1 for a perfectly conformal plan and does not give any information about whether there is an over-coverage or under-coverage of the target [9].

Conceptually, conformity indices quantify how the isodose conforms to the shape and size of the target. Both conformity indices were calculated per target in this study.

Paddick gradient index

This index, as defined by Paddick and Lippitz [10], quantifies the dose fall-off beyond the target volume. This metric is important to consider for SRS techniques. A steep dose gradient outside the PTV is a hallmark of the SRS technique to reduce the dose spillage to adjacent OAR. For this assessment gradient indices have been proposed to compare different treatment plans with the same conformity. In this study, this index was calculated based on Equation 3.

$$PGI = \frac{PIV_{50\%}}{PIV} \quad (3)$$

$PIV_{50\%}$ refers to the volume of 50% isodose. Generally, PGI ≤ 3 for a single lesion but data are not available for treatment plans with more than one target. It is expected to observe greater values for plans with more than one lesion compared to a single target plan. In practice, for multitarget plans, PGI is usually calculated per plan because of dose bridging between adjacent targets or isodose volumes. Therefore, in this study, PGI was computed per composite plan for MIMT and per plan for SIMT techniques.

V8 & V12

In 2009, Blonigen et al. found that the volume of normal brain tissue receiving 8 Gy (V_8) through 12 Gy (V_{12}) was "significantly predictive of both asymptomatic and symptomatic radiation necrosis in LINAC-based, single-fraction SRS of the brain metastases [11]. Therefore, in this study both V_8 and V_{12} were calculated per plan.

Delivery time(s)

The total time required to deliver a whole plan from the start of the first arc to the end of irradiation was considered as delivery time. These data were extracted directly from RayStation TPS using an in-house script.

Effect of isocenter location in SIMT

Distance to the isocenter was calculated based on the center of each PTV to the isocenter and was extracted from the TPS directly using an in-house script. PTVs were at varying distances from the isocenter with an average of 4.6 cm (range 1.45 to 8.75 cm). Then to determine the effect of isocenter location on dosimetric indices, the correlation between isocenter location and dosimetric indices were analyzed.

Impact of grid size and energy in SIMT

Ten patients with 6 to 10 targets (a total of 92 targets) and an average size of 1.2 cm^3 (range 0.57-2.68 cm^3) were randomly selected. A total of 40 VMAT plans for the Varian Edge Linac using 6 MV and 10 MV Flattening Filter-Free (FFF) beams and GS of 1 mm and 2 mm resulting in four plans per patient were created. All parameters and objectives except dose grid and energy were kept the same in all treatment plans. All targets per plan were treated to the same dose (24 Gy in 3 fractions) and treatment plans were normalized to 95% of each target receiving 100% of the prescribed dose. Next, dosimetric indices including PCI, RTOG_CI for each target, and PGI for each plan were calculated.

Statistical analysis

SPSS Ver.27 was used for performing a two-sample independent t-test for RTOG_CI, PCI, PGI, V8, and V12 to determine any statistically significant difference between MIMT & SIMT. Moreover, the Pearson correlation coefficient (CC) was calculated to find a correlation between target size and quality metrics for both techniques. In addition, the correlation between distance to isocenter and dosimetric indices for SIMT were studied. One-Way ANOVA followed by the Post Hoc Tukey test and a two-sample independent t-test were also performed for statistical analysis of the impact of GS and energy on dosimetric indices in SIMT. A P-value of 0.05 was considered significant as the mean difference.

Results

For all 21 patients, clinically acceptable treatment plans were achieved by both MIMT and SIMT techniques. Figure 3 shows the dose distribution for both methods for patient #14 who had 10 PTVs.

Both PCI & RTOG_CI were computed per target, and PGI, V_{12}, and V_8 were computed per plan for SIMT and per composite plan for MIMT. The result of those calculations is shown in Table 1. As shown here, the RTOG_CI values in MIMT are greater than SIMT (1.377 ± 0.403 vs. 1.267 ± 0.414, $p < 0.05$) which indicates all PTV were over-covered in MIMT. Also, MIMT has smaller PCI in comparison with SIMT (0.74 ± 0.142 vs. 0.78 ± 0.129, $p < 0.05$) (Table 1).

Both RTOG and Paddick indices approached unity as the target volumes increased (Figures 5a & 5b). Despite differences between targets, it appeared that both conformity indices have similar trends in both methods. As it is shown in Figure 4c, PGI tends to be smaller for larger targets in both techniques. Statistical analysis (Table 2) demonstrates very strong and strong correlations between target size and PCI, RTOG_CI, and PGI (0.841, -0.789, -0.725, $p<0.05$) respectively in the SIMT. A similar trend was observed for target size vs PCI and RTOG_CI, (0.675, -0.656, $p<0.05$ respectively) but a moderate correlation between target size and PGI (-0.504, $p<0.05$) was found in MIMT plans. No correlation was observed between target size and V8 (0.051, $p = 0.827$) in SIMT while a strong positive correlation was observed between target size and V8 (0.708, $p<0.05$) in MIMT. A moderate correlation (0.522, $p<0.05$) and very strong correlation (0.802, $p<0.05$) for target volume and V_{12} was observed for SIMT and MIMT, respectively.

The independent sample t-test gave values of 2.577 and -2.463 for PCI and RTOG CI, respectively. These are both beyond the critical values for a two-tailed t-test. $P<0.05$ for both conformity indices highlight a statistically significant difference between the two methods. The gradient index of SIMT is higher than MIMT (5.379 ± 1.58 vs. 4.336 ± 0.781, $p < 0.05$) (Figure 4c). The volumes

that receive 12 Gy and 8 Gy are compared in this study. Both V_{12} and V_8 were larger for SIMT compared to MIMT (Figures 4d & 4e). However, the V_{12} of each plan was comparable between both techniques ($p = 0.247$) while a significant difference was observed for V_8 ($p<0.05$).

Additionally, the Pearson correlation coefficient was performed on SIMT data to find the impact of distance to the isocenter on dosimetric indices, and no correlation was seen between them (Table 3).

Delivery times for all 21 patients with a total of 168 BM with an average of 8 lesions (range 4-12) were analyzed. MIMT plans treated all 168 lesions with 168 isocenters while SIMT plans treated the same 168 targets with 21 isocenters. The MIMT plans averaged 1264 seconds (21.1 minutes) of beam-on time versus the SIMT plans which averaged 252 seconds (4.2 minutes), amounting to an 80% reduction in time for treatment delivery; this is a meaningful difference to the patient, as well as to the radiation therapists.

Figure 5 illustrates box plots (Whisker charts) of PCI, RTOG_CI, and PGI for various energy and GS. Box plot is a graphical rendition of statistical data based on the minimum, first quantile (Q1), median, third quantile (Q3), and maximum. Outliers can be indicated as small circles in this plot. In statistics, an outlier is an observation point that is distant from other observations. However, they do not necessarily indicate an unacceptable data. Our analysis demonstrates that for PCI, there was no statistically significant correlation to energy for a given GS, but a significant correlation was found with GS, with smaller GS yielding higher PCI values ($p = 0.012$). For RTOG_CI, GS was a significant classifier ($p = 0.036$), but the energy was not. Furthermore, statistically significant differences between different energies were found for PGI ($p = 0.024$) but PGI did not demonstrate any statistically significant differences between different GS ($p = 0.209$).

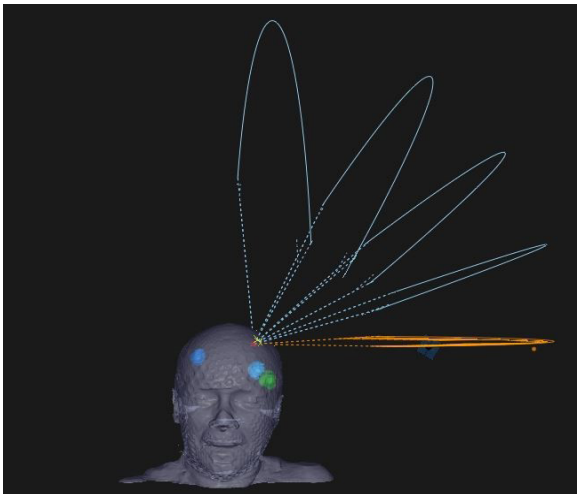

Figure 1: A display of all beams was used to treat one of the PTVs. The gantry angles were tailored to avoid a direct alignment with surrounding PTVs.

The effect of varying number of targets on PGI, V_8, and V_{12} is shown in Figure 6. As it is illustrated these metrics depend on the number of targets and deteriorate (i.e., dose to normal tissues increases) as this number increases. According to our data, we can see that for less than 6 targets, higher plan quality can be achieved using SIMT in terms of low-dose spillage or bath.

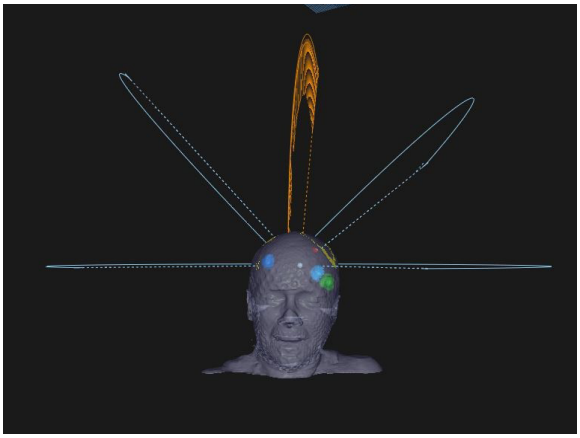

Figure 2: The five couch angles are used to cover all PTVs. They were evenly distributed across the couch motion.

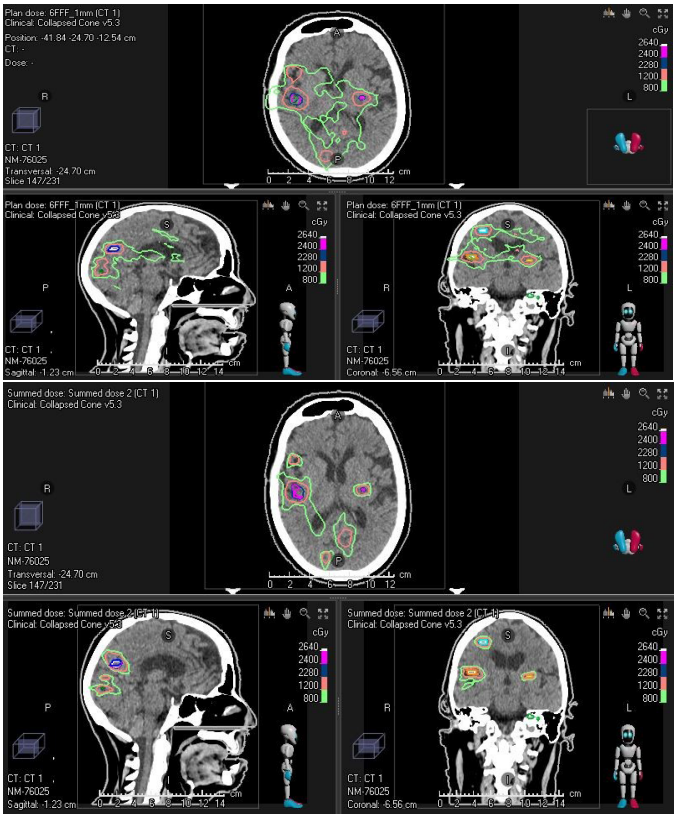

Figure 3: Isodose distribution of a single-isocenter **a)** SIMT, **b)** MIMT for the same patient (patient#14). Isodose lines are 26.4 (105%), 24 (100%), 22.8(95%), 12 (50%), and 8 Gy (33.3%).

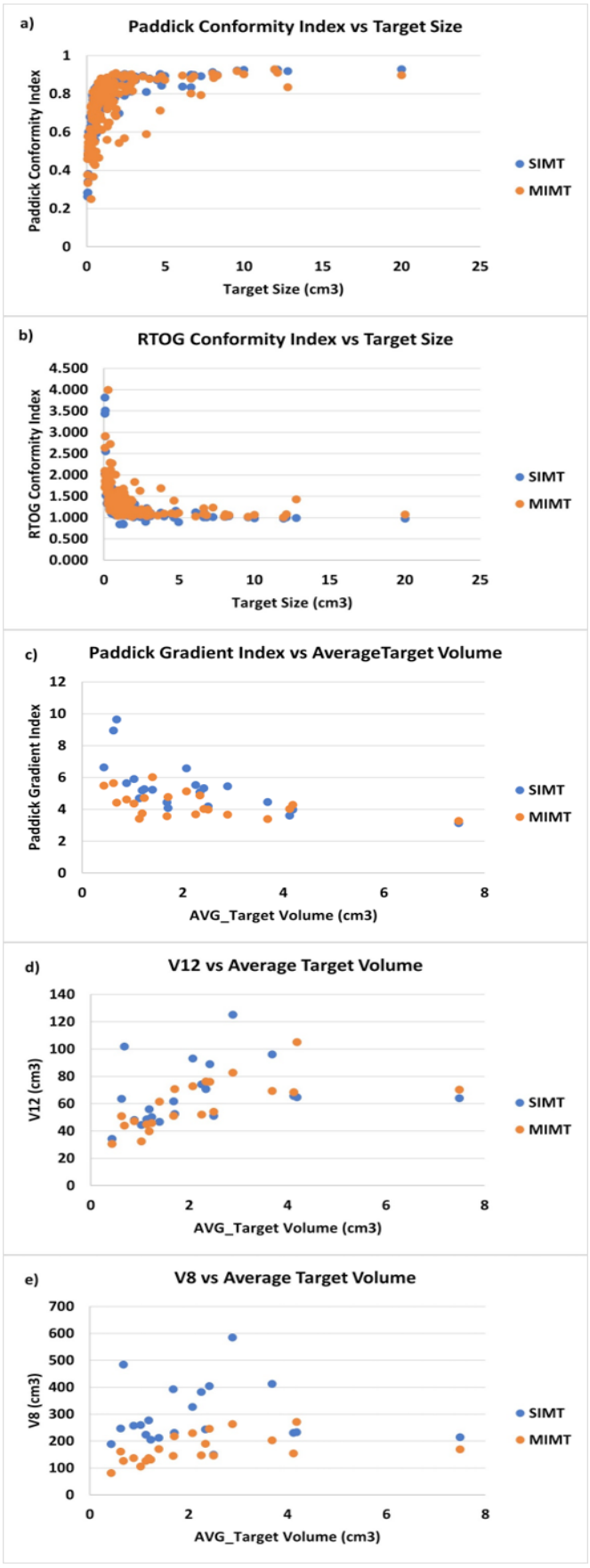

Figure 4: Whisker charts for **a)** PCI, **b)** RTOG_CI, and c) PGI for different energy and grid size. 6FFF and 10 FFF refer to 6MV FFF and 10MV FFF energy respectively. 1mm and 2mm indicate the 1mm and 2mm planned dose grid.

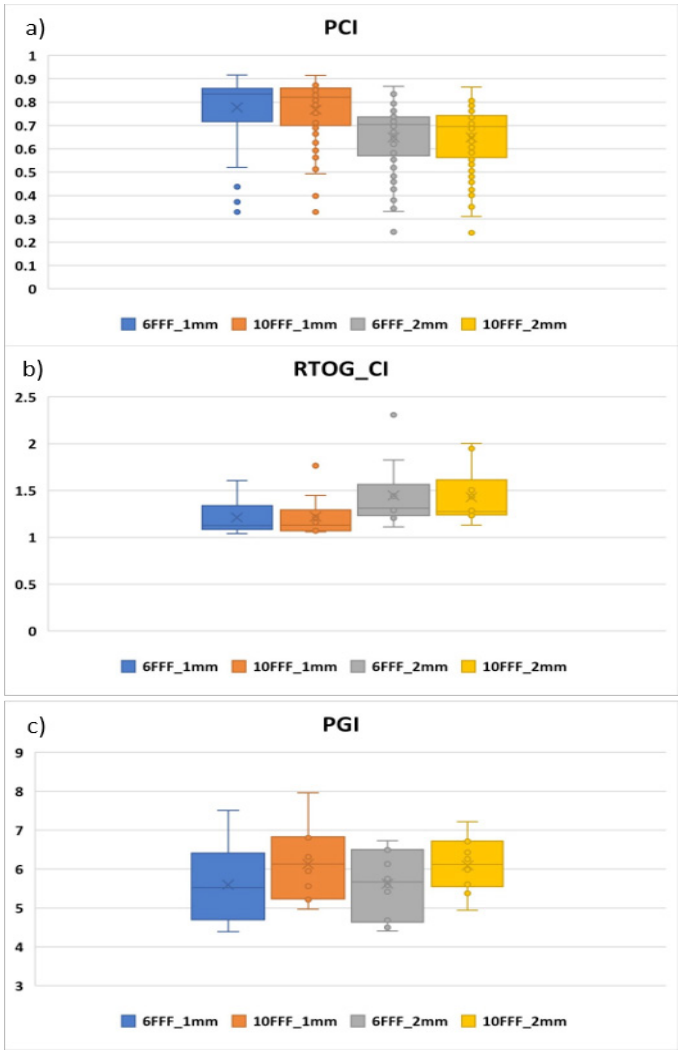

Figure 5: Whisker charts for **a)** PCI, **b)** RTOG_CI, and **c)** PGI for different energy and grid size. 6FFF and 10 FFF refer to 6MV FFF and 10MV FFF energy respectively. 1mm and 2mm indicate the 1mm and 2mm planned dose grid.

Discussion

Several studies have assessed the SIMT technique for treating multiple lesions. In 2007 VanderSperk et al [12] used a single isocenter with 8 to 14 noncoplanar fields and concluded that SIMT is a sensible and well-tolerated treatment for patients with multiple intracranial tumors. They also noted that MIMT might have some dosimetric improvement compared to SIMT but is not clinically significant. Clark et al [13] treated three brain lesions with different techniques including single-arc/single-isocenter, triple-arc (noncoplanar)/single-isocenter, and triple-arc (coplanar)/triple-isocenter configurations, and showed single-isocenter with multiple noncoplanar arcs can be used to deliver conformity equivalent to that of MIMT.

This study compares the dosimetric feasibility of performing MIMT vs SIMT when treating multi-targets in the brain using 5 non-coplanar arcs. One of the main concerns for the SIMT plans is the increased low dose "bath" to the intervening and adjacent normal brain tissue/parenchyma outside the targets. This may be because island blocking happens in SIMT, which yields more dose spillage to surrounding normal tissue compared to MIMT (Fi-

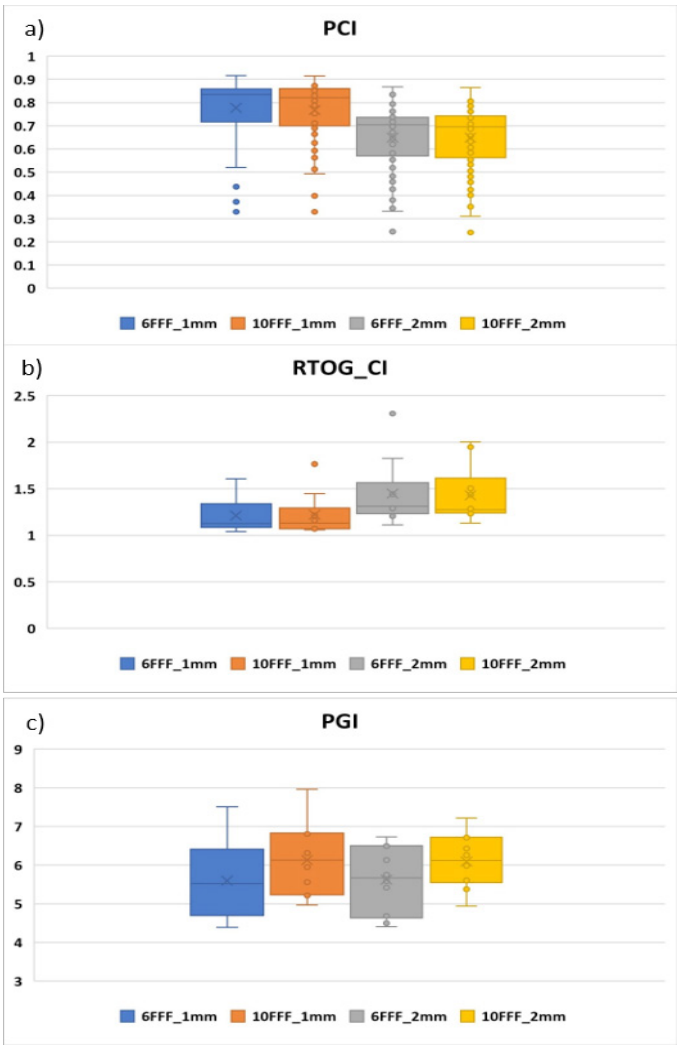

Figure 6: The effect of a varying number of targets on plan evaluation parameters **a)** Paddick Gradient Index, **b)** V12, and **c)** V8.

gure 3) [14,15], or a larger jaw opening increasing the leakage of dose between the leaves [16]. Therefore, a higher low dose (V_8) is expected for SIMT compared to MIMT as we can see in Table 1, Figures 4 and 4e. Wu et al proposed a solution to reduce the stray low dose to normal brain tissue by optimizing couch and collimator angles [16]. In SIMT, PGI has greater values than MIMT, and V_{12} (50% prescription isodose) is comparable between both techniques. Consequently, the higher value of PGI is not because they may have larger 50% isodose volumes but because they have smaller 100% prescription isodose volumes compared to MIMT (Figure 3). This finding is in line with previous studies [13,17].

Furthermore, our findings revealed that PCI and RTOG_CI strongly depend on the volume of the tumor which is in agreement with the results of Prentou et al [14]. They also showed better conformity values are achievable when number of targets is less than 6, and increasing the number of targets causes poor conformity [14]. Also, the result in this study indicates low-dose spillage to normal tissue is greater in SIMT compared to MIMT for plans with more than 6 targets which is independent of the isocenter location.

There are several dosimetric uncertainties regarding the location of the isocenter in SIMT because the isocenter is not inside of any target, and couch rotation error may have a great impact on dose distribution for tiny targets that are further away from the isocenter [18]. Amaya et al (2020) [2] showed that couch rotational error can be rectified by using 6 degrees of freedom couch. Moreover, Aoki et al [19] and Kraft et al [20] studied the effect of distance to isocenter on survival and local rates of targets in SIMT and indicated distance to isocenter is not associated with tumor response. The result of present study also showed that there is no dependency between all quality metrics and location of the isocenter relative to PTV in the SIMT technique.

According to our result, the delivery time of SIMT was 80% shorter than that for MIMT including setup time and image-guidance procedure. The total treatment time can easily be shorter

Table 1: Results of conformity indices, Gradient index, V12, and V8 calculated for both SIMT & SIST treatment plans.

	PCI	RTOG_CI	PGI	V12 (cc)	V8 (cc)
SIMT	0.778 ± 0.129	1.267 ± 0.414	5.379 ± 1.580	66.730 ± 22.671	293.116 ± 110.135
SIST	0.740 ± 0.142	1.377 ±0.403	4.336 ± 0.781	59.256 ± 18.371	169.451 ± 51.683

Table 2: Shows the correlation between target size and quality metrics for both SIMT and SIST techniques.

			PCI	RTOG_CI	PGI	V8	V12
SIMT	Target_Volume	Correlation Coefficient	0.841	-0.789	-0.725	0.051	0.522
		P-Value	1.21E-72	1.05E-53	1.00E-05	0.827	1.00E-04
		N	168	168	21	21	21
SIST	Target_Volume	Correlation Coefficient	0.675	-0.656	-0.504	0.708	0.802
		P-Value	1.00E-03	1.00E-04	1.21E-05	7.80E-05	1.30E-04
		N	168	168	21	21	21

Table 3: The Spearmen Correlation Coefficient between Distance to isocenter and quality metrics for SIMT technique. P<0.05 considers a significant difference.

		PCI	RTOG_CI	PGI	V8	V12
Distance to isocenter	Correlation Coefficient	-0.122	0.116	-0.413	0.2	0.316
	P-Value	0.026	0.035	0.63	0.385	0.163
	N	168	168	21	21	21

than 10-15 minutes, which makes a difference to the patient. The main reason is that setup and imaging only need to be done once with the use of one isocenter to treat all targets. This translates into increased efficiency and throughput in the treatment consoles, and can improve the patient experience and satisfaction, as well as reduce machine utilization. These findings are also comparable with prior studies [17,21,22].

Results of the evaluation of impact of energy and GS on PCI and RTOG_CI indices are shown in Figure 5a& 5b. According to the Pearson correlation test, no significant difference was observed between 6MV FFF and 10 MV FFF for both conformity indices. We believe this is mostly related to the dose-control tuning structures in the inverse optimization process which aims to deliver the prescribed dose to the targets and spare OAR as much as possible. This can be achieved regardless of which energy is used [23,24]. On the other hand, using different GS results in a significant difference in conformity indices. We believe this is related to the way TPS is performing dose calculation. The dose is linearly interpolated between dose points on the calculation grid; therefore, 1 mm GS has more data point than 2 mm GS which can result in less uncertainties in dose calculation. This is more dominant factor for small targets because a small change in the estimated volume can be a large fraction of the structure volume [25].

The gradient index is a measure of how quickly the out-of-field dose decreases away from the target edge. An improved dose gradient is indicative of less peripheral dose which leads to better sparing of the OARs. This is linked to the dosimetric characteristics of the beam. A beam with a higher quality index will be more penetrating and may contribute to a higher peripheral dose. Figure 5c demonstrates a box plot of the PGI ranges, showing more dose spillage around the target as the energy increases. This indicated that the more penetrating beam energy of 10 MV FFF leads to an increase in dose at a distance compared with the 6MV FFF. Our finding related to energy is in line with Laoui et al. [23] who also found an improved dose gradient and normal tissue brain sparing with 6 MV FFF when compared to 10 MV FFF.

Conclusion

The current study evaluated dose-volume metrics (V_8 and V_{12}), delivery times, and relevant dosimetric indices such as PCI, RTOG_CI, and PGI to characterize dose distribution in MIMT and SIMT treatment plans. This study can help planners better inform as to what can be attained using single isocenter or multiple isocenter to treat multiple intracranial lesions. The main aspect of this study is showing the impact of energy and grid size on dosimetric indices which can be used as a guideline regarding using different energies and grid size. According to our data, there is some advantage of using 6MV FFF with 1 mm grid size which results in higher plan quality. Also, our result revealed that the isocenter location does not have any significant impact on quality of the plan. The number of targets seemed to have the largest impact on plan quality in this study, but volume is clearly a factor in improving conformity. We believe that considering all dosimetric indices, together with time considerations, this study reveals an advantage of SIMT planning for ≤6 intracranial targets.

Declarations

Funding: None to Report.

Conflict of Interest: None to Report.

Ethics approval: Approval from the Internal Review Board (IRB) of the University of Toledo (300579-UT) was acquired for this investigation on June 16th, 2021.

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