RESEARCH ARTICLE

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# A Comprehensive Evaluation of Single Isocenter Multiple Target SRS Plans and the Analytical Relationship between Plan Quality Indices with the Number and Volume of Targets

**Hemalatha Priyadarsini V[1,2,3], Murali R[2]*, Arunai Nambi Raj N[2], Saravanan S[3]**

## Abstract

**Objective:** To study the relationship of plan quality indices with the number and volume of target for 5 to 10 brain metastases treated with LINAC-based Single Isocenter Multiple Target (SIMT) Stereotactic radiosurgery (SRS) planning and to determine the maximum volume of spherical targets treated without exceeding the normal tissue tolerances. **Methods:** Spherical targets of 5 to 10 numbers per plan, with individual target volumes ranging from 0.025 cc to 11.5 cc, were simulated with randomly drawn planning target volumes (PTVs) within the brain. SIMT SRS plans were generated for the 21 Gy prescription dose with a 6 MV Flattening Filter Free photon beam. Target coverage, organ at risk sparing, plan quality indices, $R_{50\%}$, and gradient measure were studied. Mean brain dose, $V_{12}$ for Brain minus PTV (BmP), $V_{10}$, $V_{12}$, $V_{15}$, $V_{18}$, $V_{20}$, and $V_{24}$ for brain volume were evaluated. Equations relating the gradient index, mean brain dose, and $V_{12}$ (BmP) to the given number and volume of the targets were constructed. **Results:** PTV coverage $D_{98}$ was 98.77 ± 1.37 %. The mean $CI_{RTOG}$, $Q_{RTOG}$, $HI_{RTOG}$, $CI_P$, GI, and $R_{50\%}$ of the individual targets were 1.02 ± 0.08, 0.94 ± 0.02, 1.49 ± 0.11, 0.91 ± 0.06, 4.74 ± 2.3, and 4.95 ± 2.67, respectively. The gradient measure achieved was in the range of 0.49 to 1.35 cm. The mean brain dose was in the range of 1.62 to 6.69 Gy. The mean $V_{12}$ (BmP) per target obtained was 3.85 ± 2.83 cc. **Conclusion:** Equations relating the number and volume of targets to the gradient measure, mean brain dose, $V_{12}$ (BmP), and $V_{10\text{-}24}$ can serve as a baseline for multiple brain metastases SIMT planning. The target volume for 5, 6, 7, 8, 9, and 10 targets that can be treated without exceeding $V_{12}$ (BmP) is 6, 5, 4.7, 4, 3.7, and 3.4 cc, respectively, for the 21 Gy prescription dose.

**Keywords:** multiple brain metastases- Stereotactic Radiosurgery- single-isocenter multiple-target- Linac based SRS

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## Introduction

Brain metastases (BM) are very common in cancer patients. For patients with nonresectable or multiple metastases, whole-brain radiotherapy (WBRT) was the primary treatment for symptom palliation; however, it is associated with neurocognitive function decline (Suh et al., 2011). Stereotactic Radiosurgery (SRS) is found to increase the local control and overall survival with improved neurocognitive outcomes compared to WBRT alone, thus improving the quality of life of the patients (Chang et al., 2009).

SRS is a non-invasive procedure that uses ionizing radiation to treat intracranial and extracranial lesions with a high dose of radiation delivered in a single fraction of treatment. The rapid dose fall-off of SRS spares the healthy brain tissues and becomes the treatment of choice for 1 to 3 BM of less than 3 cm diameter (Linskey et al., 2010). Patients with 5 to 10 BM also have a comparable survival rate to that of patients with 2 to 4 BM (Yamamoto et al., 2014), and some patients can be long-term survivors (Kondziolka et al., 2005). SRS improves survival and may be the best treatment choice for multiple BM when the quality of life is considered the most important outcome (Tsao et al., 2012).

Linear Accelerator (LINAC) -based SRS is gaining more interest in multiple lesion radiosurgery, as it is widely available and capable of treating small lesions intracranially as well as extracranially with a shorter treatment time. Traditionally, LINAC-based SRS for the treatment of multiple BM has used a multi-isocenter setup, aligning each isocenter around the individual metastatic lesions, which increases the treatment time (Ruggieri et al., 2018). The single-isocenter multiple targets SIMT technique with multiple non-coplanar arcs has been studied extensively, which provides optimal dose distribution with exceptional treatment delivery efficiency (Clark et al., 2012; Hoffmeier et al., 2019). The treatment

*[1]Tamil Nadu Medical Services Corporation Ltd, 417, Pantheon road, Egmore, Chennai, Tamil Nadu, India. [2]Department of Physics, School of Advanced Sciences, Vellore Institute of Technology, Vellore, Tamil Nadu, India. [3]Department of Radiation Oncology, Government Royapettah Hospital, 1, West Cott road, Royapettah, Chennai, Tamil Nadu, India. *For Correspondence: murali.r@vit.ac.in*

machine having MLC with a smaller leaf width is preferred for better dosimetric indices in SRS planning (Abisheva et al., 2019). We studied the dosimetric indices of SIMT Volumetric Modulated Arc Therapy (VMAT) plans using 5 mm leaf width MLC for 5 to 10 BM of various volume ranges and compared with other published results of established methods. Plan quality indices were analysed for their dependence on the number of targets, total volume of Planning Target Volume (PTV), and isocenter distance from individual PTVs. The purpose of this study is to find out the optimal PTV volume to treat 5 to 10 BM of varying sizes and locations without exceeding normal tissue tolerances in LINAC-based SIMT planning with 5 mm leaf width MLC. Equations were also derived to predict normal tissue doses and gradient measure upfront for the given number and volume of PTV.

## Materials and Methods

*Treatment Planning CT*

Planning CT of 1 mm slice thickness taken in Siemens SOMATOM® Definition AS 128 slice CT scanner using the predefined RT Head protocol was used in this study. For SIMT treatment planning, spherical targets of 5 to 10 numbers per plan were created. Targets were created in the order of increasing total PTV volume from 0.81cc to 38.65 cc to simulate 47 patient tumor scenarios (Table 1). A total of 347 individual target volumes ranging from 0.025 cc to 11.5 cc were simulated with randomly drawn PTVs within the brain. The average volume of individual PTV was 2.01 ± 2.07 cc and median 1.28 cc. PTVs were located at least 0.5 cm from the brainstem and optical apparatus. The distance from the isocenter to individual PTV varied from 0.49 cm to 5.63 cm. The average distance of an individual PTV from the isocenter for 5, 6, 7, 8, 9, and 10 targets were 3.64 ± 1.58, 4.25 ± 0.85, 3.34 ± 1.28, 3.48 ± 1.26, 3.53 ± 1.31, and 3.66 ± 1.17, respectively. The typical distribution of PTVs used in this study is shown in Figure 1.

Normal structures such as brain, brain excluding PTV (BmP), brainstem, eyes, eye lenses, optic nerves, optic chiasm, cochlea, and spine were contoured. Boolean operation was used to sum all the PTVs in an individual plan to obtain $PTV_{total}$ volume. All the PTVs and small Organ At Risk (OAR) structures were drawn as high-resolution segment structures.

*Treatment Planning*

SIMT plans were done in Eclipse v15.6 (Varian Medical Systems, Palo Alto) Treatment Planning System (TPS) to deliver in TrueBeam LINAC equipped with a millennium MLC of 5 mm leaf width in center 20 cm and 1cm leaf width in outer 10 cm on either side of both MLC banks which constitute 40 cm total width.

RapidArcTM plans were generated with SRS arc field with a Flattening Filter Free (FFF) 6 MV photon beam of dose rate 1400 MU/min (Figure 2). The isocenter of the plans was kept at the geometric center of $PTV_{total}$. One full arc in coplanar and three non-coplanar partial arcs with couch angles 45°, 90°, and 315° were used. Collimator angles were selected manually depending on the target structures to avoid dose bridging as much as possible. All field sizes were fit to $PTV_{total}$ with a 0.5 cm margin. Acuros XB algorithm with 1.25 mm calculation resolution with heterogeneity correction ON and dose to medium reporting was used. Three annular ring structures of 3, 7, and 13 mm width around each PTV were created to control high dose spillage. In optimization, the normal tissue objective was kept in the manual mode with high priority, with distance from target border 0.1 cm, start dose 100 %, end dose 10 %, and fall-off 1, for rapid dose fall-off outside PTVs. Lower objectives for individual PTVs were given, and the upper objective was not given to get the advantage of steep dose fall-off. The mean dose objective was given to normal brain for low dose optimization. Dose constraints for all other normal structures were also given. In optimizer, the structure resolution was kept at 1.25 mm for all plans. Jaw tracking was enabled.

The prescription dose for treating multiple BMs depends on the size of the lesions, proximity of the lesions with critical organs, or adjacent lesions. SRS dose prescription in practice is 18-24 Gy, 15-24 Gy and 12-18 Gy for PTV volume < 2 cc, 2 to < 3 cc, and 3 to < 4 cc, respectively (Shaw E et al., 2000). In this study, SIMT plans using VMAT were generated for a prescription dose of 21 Gy in a single fraction to all the PTVs regardless of their volume for comparing the dosimetric indices. The Prescription Isodose Line (PIL) was chosen such that the minimum dose to individual PTV in a plan should not be less than 19 Gy.

*Plan Evaluation*

To evaluate target coverage, minimum dose to PTV ($D_{min}$), maximum dose to PTV ($D_{max}$), mean dose to PTV ($D_{mean}$), dose received by 2% volume ($D_2$), dose received by 95% volume ($D_{95}$), dose received by 98% volume ($D_{98}$), and dose received by 99% volume ($D_{99}$) were used. Dose to the brainstem, optic chiasm, optic nerves, eyes, eye lens, and cochlea was noted. Quality of plans was evaluated as per Radiation Therapy Oncology Group (RTOG) QA guidelines (Shaw E et al., 1993) with the following indices, Conformity Index ($CI_{RTOG}$), Quality of coverage ($Q_{RTOG}$), and Homogeneity Index ($HI_{RTOG}$). In addition, Paddick conformity index ($CI_p$) and Gradient Index (GI) of individual PTVs were also calculated. $R_{50\%}$ to study the intermediate-dose fall-off was evaluated to compare with the published results. The PTV volume and indices were calculated based on the dose-volume histogram.

The influence of the number and volume of PTV and their distance from the isocenter on indices was evaluated. Gradient Measure (GM) reported in Eclipse TPS was addressed. For the brain, the mean and the volume receiving 10 Gy, 12 Gy, 15 Gy, 18 Gy, 20 Gy, and 24 Gy given as $V_{10}$, $V_{12}$, $V_{15}$, $V_{18}$, $V_{20}$, and $V_{24}$, respectively, were analyzed. The value of prescription isodose percentage and MU for each plan were noted.

*Definitions*

$CI_{RTOG}$ assees the degree of congruence between the prescription isodose and the PTV volume. $CI_{RTOG} = 1$ is ideal conformity. If $CI_{RTOG} < 1$, the target is under-covered, and if $CI_{RTOG} > 1$, then the target is over-covered. $CI_{RTOG}$

is given by,

$$CI_{RTOG} = V_{RI} / TV$$

where $V_{RI}$ is the volume encompassed by the prescription isodose and TV is the Target Volume. The Quality of coverage is given by

$$Q_{RTOG} = I_{min}/RI$$

where $I_{min}$ is the minimum dose received by the target and RI is the prescription isodose. If 90% isodose covers all of the target volume ($Q_{RTOG} \geq 0.9$), treatment is considered to comply with the RTOG protocol. The heterogeneity index is given by

$$HI_{RTOG} = I_{max}/RI$$

where $I_{max}$ is the maximum dose in the target and RI is the prescription isodose. $HI_{RTOG}$ measures the uniformity of dose inside the target, which may not be of high priority in SRS planning, as dose heterogeneity can be compromised at the cost of high dose fall-off.

Paddick conformity index ($CI_P$) was proposed to avoid false perfect scores in certain circumstances (Paddick, 2000):

$$CI_P = TV_{PIV}^2 / (TV \times V_{RI})$$

where $TV_{PIV}$ is the target volume covered by the prescription isodose, TV is the target volume, and $V_{RI}$ is the total volume covered by the prescription isodose. $CI_P = 1$ is the ideal conformity. $CI_P < 1$ means lack of conformity, but $CI_P$ cannot tell whether the lack of conformity is due to under-coverage or over-coverage (Paddick, 2000). GI is used to measure the dose gradient outside the target and is given by

$$GI = V_{RI\ half} / V_{RI}$$

where $V_{RIhalf}$ is the volume at half of the prescription isodose. A lower value of GI is expected to reduce normal tissue complications. GI < 3 reflects a reasonably good plan configuration as discussed by Paddick I et al, 2006. $R_{50\%}$ is used to measure the intermediate fall-off in SBRT and is becoming popular in intracranial SRS plan evaluations recently (Desai et al., 2021).

$$R_{50\%} = V_{RI\ half}/PTV$$

where PTV is the volume of PTV GM is defined as the difference between the equivalent sphere radius of the prescription isodose and half-prescription isodose:

$$GM = r_{EqSphVIDC50\%} - r_{EqSphVIDC100\%}\ (cm)$$

where $r_{EqSphVIDC50\%}$ and $r_{EqSphVIDC100\%}$ are the radii of spheres that are equal in volume to the actual volume of 50% isodose coverage and volume of 100% isodose coverage, respectively. $R_{50\%}$ and GM for multiple BM were characterized in this study as a limited number of published data were available for the same for multiple BM SRS planning.

*Statistical Evaluation*

Descriptive statistical analysis was performed using the mean, median, SD, and box plots, wherever needed. Scatter plots were drawn to study the relationship between indices. Linear and polynomial fits were derived, and the proportion of variance with equations was obtained. Spearman's correlation coefficient (ρ) was used to investigate the existence of a correlation between variables. If $\rho \geq \pm 0.70$, there is a strong positive or negative correlation between variables, and if $\rho = \pm 0.3$ to $\pm 0.70$, there is a weak correlation between variables. If ρ is between -0.3 and 0.3, there is no correlation (Mukaka, 2012).

## Results

*1. Target coverage and OAR sparing*

For a total of 47 plans, the mean, standard deviation, and median of $D_{min}$, $D_{max}$, $D_{mean}$, $D_2$, $D_{95}$, $D_{98}$, $D_{99}$, and $D_{100}$ of $PTV_{total}$ are presented in Table 2. The OAR maximum dose was summarised using a box plot (Figure 3).

*2. Plan quality indices*

Mean $CI_{RTOG}$, $Q_{RTOG}$, $HI_{RTOG}$, $CI_P$, GI, and $R_{50\%}$ of the individual targets evaluated were 1.02 ± 0.08, 0.94 ± 0.02, 1.49 ± 0.11, 0.91 ± 0.06, 4.74 ± 2.3, and 4.95 ± 2.67, respectively. All indices were found to be within the recommendation. The box plots of indices of individual targets are shown in Figures 4 (a) and (b).

*3. Factors influencing the indices:*

*3.1. Individual PTV volume*

When analyzing 347 individual targets by grouping them according to their volume (Figure 5), $Q_{RTOG}$ and $HI_{RTOG}$ were independent of individual PTV volume. The mean value of $CI_P$ and $CI_{RTOG}$ of PTV volume of 0.025 to 0.05 cc were 0.67 and 1.2, respectively, which shows

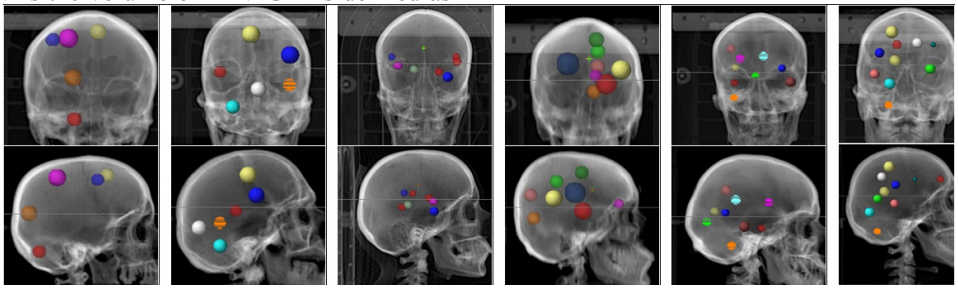

Figure 1. AP and Lateral View of Target Placements

Table 1. Number of Plans and Range of PTV Volumes, Their Mean and SD Used in This Study

| No. of targets | No. of plans | Volume of $PTV_{total}$ (cc) | Range of individual PTV volume (cc) | Mean PTV volume and SD (cc) |
|---|---|---|---|---|
| 5 | 9 | 1.53 | 0.18 – 0.38 | 0.30 ± 0.07 |
| | | 2.49 | 0.25 – 0.87 | 0.50 ± 0.21 |
| | | 4.49 | 0.57 – 1.60 | 0.90 ± 0.38 |
| | | 9.57 | 1.26 – 3.06 | 1.91 ± 0.65 |
| | | 12.96 | 0.29 – 3.39 | 2.59 ± 1.16 |
| | | 16.31 | 0.70 – 4.88 | 2.86 ± 1.49 |
| | | 20.41 | 0.56 – 5.23 | 4.08 ± 1.76 |
| | | 28.93 | 3.03 – 11.59 | 5.78 ± 3.13 |
| | | 36.95 | 4.85 – 10.43 | 7.39 ± 2.40 |
| 6 | 8 | 0.87 | 0.06 – 0.16 | 0.14 ± 0.04 |
| | | 2.03 | 0.06 – 0.51 | 0.34 ± 0.16 |
| | | 3.14 | 0.27 – 0.96 | 0.52 ± 0.23 |
| | | 6.99 | 0.74 – 1.76 | 1.16 ± 0.33 |
| | | 15.57 | 0.48 – 4.35 | 2.59 ± 1.14 |
| | | 21.22 | 1.78 – 5.42 | 3.54 ± 1.42 |
| | | 27.41 | 3.15 – 5.43 | 4.57 ± 1.01 |
| | | 38.34 | 6.36 – 6.42 | 6.39 ±0.02 |
| 7 | 8 | 0.81 | 0.06 – 0.29 | 0.12 ± 0.08 |
| | | 2.38 | 0.17 – 0.43 | 0.34 ± 0.09 |
| | | 5.04 | 0.41 – 1.19 | 0.72 ± 0.23 |
| | | 9.21 | 0.51 – 2.32 | 1.31 ± 0.54 |
| | | 14.32 | 0.51 – 3.39 | 2.04 ± 0.90 |
| | | 20.81 | 0.51 – 4.31 | 2.97 ± 1.15 |
| | | 27.63 | 1.13 – 6.42 | 3.95 ± 2.04 |
| | | 36.03 | 1.75 – 7.16 | 5.15 ± 2.00 |
| 8 | 7 | 0.84 | 0.025 – 0.29 | 0.10 ± 0.08 |
| | | 2.55 | 0.16 – 0.43 | 0.32 ± 0.10 |
| | | 5.42 | 0.38 – 1.19 | 0.68 ± 0.25 |
| | | 9.59 | 0.38 – 2.32 | 1.20 ± 0.59 |
| | | 14.97 | 0.51 – 3.39 | 1.87 ± 0.96 |
| | | 21.77 | 3.00 – 4.31 | 2.72 ± 1.26 |
| | | 33.97 | 0.51 – 7.16 | 4.24 ± 2.44 |
| 9 | 8 | 0.9 | 0.025 – 0.29 | 0.10 ± 0.07 |
| | | 2.93 | 0.66 – 0.43 | 4.24 ± 0.10 |
| | | 5.85 | 0.38 – 1.19 | 0.65 ± 0.24 |
| | | 11.59 | 0.38 – 2.32 | 1.29 ± 0.61 |
| | | 17.14 | 0.51 – 3.39 | 1.90 ± 0.91 |
| | | 23.98 | 0.51 – 4.31 | 2.66 ± 1.20 |
| | | 28.36 | 1.66 – 6.76 | 3.15 ± 1.50 |
| | | 37.8 | 0.51 – 7.16 | 4.20 ± 2.55 |
| 10 | 7 | 1.25 | 0.08 – 0.51 | 0.12 ± 0.13 |
| | | 2.86 | 0.17 – 0.51 | 0.29 ± 0.12 |
| | | 6.58 | 0.26 – 1.15 | 0.66 ± 0.27 |
| | | 12.83 | 0.16 – 2.48 | 1.28 ± 0.65 |
| | | 24.12 | 1.75 – 3.16 | 2.41 ± 0.54 |
| | | 29.04 | 0.16 – 7.16 | 2.90 ± 1.88 |
| | | 38.66 | 1.78 – 7.16 | 3.86 ± 1.41 |

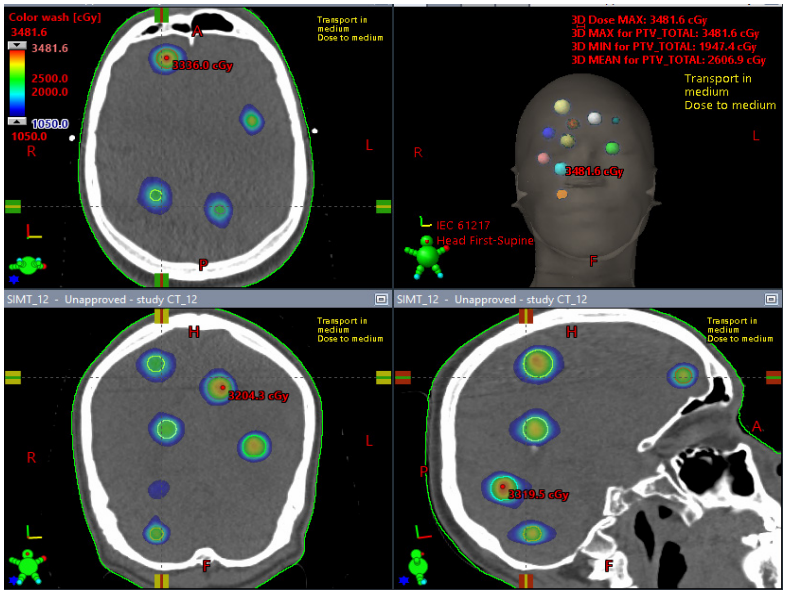


Figure 2. SIMT VMAT Plan in the Eclipse v15.6 Treatment Planning System Showing Absolute Dose Distribution Around PTV. Dose color wash showing doses above 10.5 Gy

that PTVs were over-covered by the prescription isodose line encompassing the surrounding normal brain tissue. For 0.05- 0.1 cc target volume (target diameter 0.46 to 0.58 cm), mean $CI_{RTOG}$ and $CI_P$ were 1.08 and 0.79, respectively, showing better conformity. The volume of PTV above 0.1 cc (target diameter >0.58 cm) showed near-ideal $CI_{RTOG}$ and $CI_P$. The spearman correlation of volume of individual PTV with conformity index $CI_{RTOG}$ ($\rho$ = -0.27)

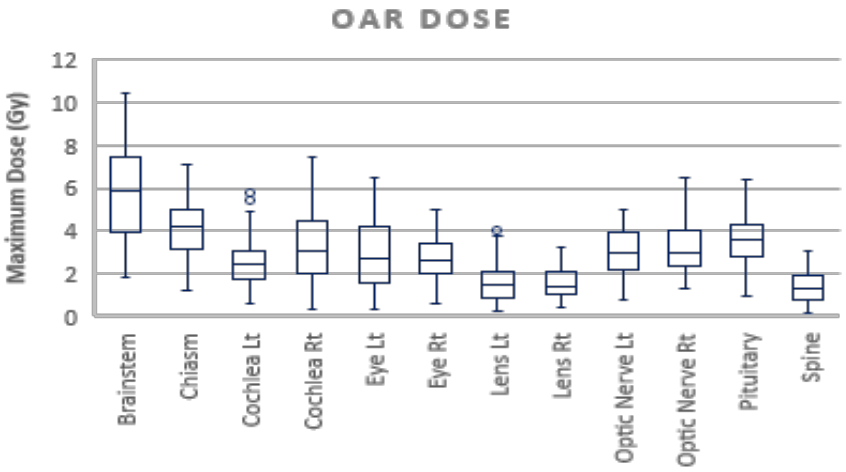


Figure 3. Box plot Dmax of various OARs summarized for all 47 plans

Table 2. Descriptive Statistics of Coverage of $PTV_{total}$ Volume for all 47 Plans

| $PTV_{total}$ | $D_{min}$ | $D_{max}$ | $D_{mean}$ | $D_2$ | $D_{95}$ | $D_{98}$ | $D_{99}$ | $D_{100}$ |
|---|---|---|---|---|---|---|---|---|
| Mean (%) | 91.47 | 159.28 | 122.89 | 149.95 | 100.93 | 98.77 | 97.41 | 91.48 |
| Standard Deviation (%) | 0.86 | 8.46 | 7.11 | 7.66 | 1.47 | 1.37 | 1.21 | 0.96 |
| Median (%) | 91.24 | 160.38 | 122 | 150.76 | 100.67 | 98.57 | 97.38 | 91.24 |

Table 3. Comparison of Indices with Published Results

| | Narayanasamy G et al | Liu H et al | This study | Acceptable range (Torrens M et al.,2014) |
|---|---|---|---|---|
| $CI_{RTOG}$ | 1.7 ± 0.6 | 1.23 ± 0.32 | 1.02 ± 0.08 | 1.0 – 2.0 |
| $CI_P$ | - | 0.77 ± 0.12 | 0.91 ± 0.06 | 0.85 – 1 |
| GI | 5.1 ± 1.9 | - | 4.74 ± 2.3 | < 3.0 |
| $R_{50\%}$ | 5 ± 1.9 | - | 4.95 ± 2.67 | < 3.0 |
| $HI_{RTOG}$ | 1.3 ± 0.1 | - | 1.49 ± 0.11 | 1.0 – 2.0 |

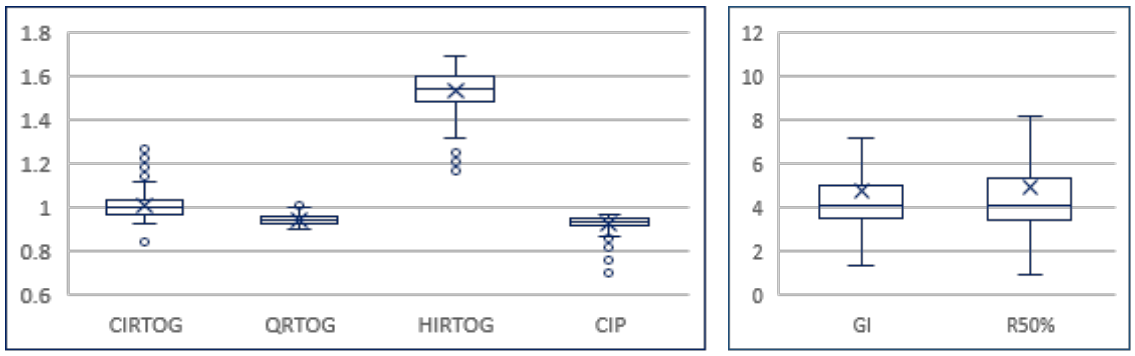


Figure 4. Box Plot of (a) $CT_{RTOG}$, $Q_{RTOG}$, $HI_{RTOG}$, $CI_P$ and (b) GI & $R_{50\%}$

and $CI_P$ (ρ = -0.27) did not show any correlation. The volume of individual PTV with gradient index showed a strong negative correlation (ρ = -0.72) for the volume of 0.025 – 1.5 cc and above 1.5 cc of PTVs volume, the correlation was weak negative (ρ = -0.55). The GI plot and $R_{50\%}$ plot overlap each other because, in all the plans, the prescription isodose volume ($V_{RI}$) was nearly equal to the PTV volume (PTV).

*3.2. Number of targets*

The PTVs were grouped to analyze the influence of the number of targets on indices. Coverage and quality indices were independent of the number of targets. Mean $HI_{RTOG}$ decreases with an increase in the number of targets. The mean GI and GM increase with the increase in the number of targets, as shown in Figure 6.

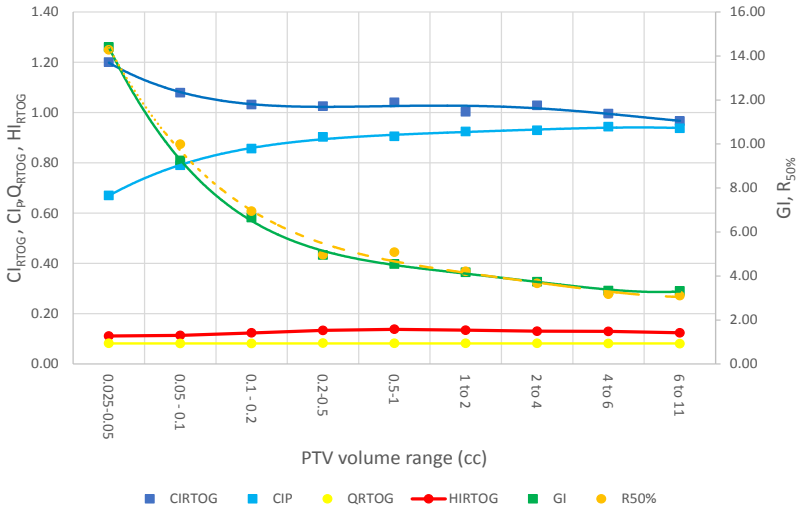


Figure 5. $CI_{RTOG}$, $CI_P$, GI, and $R_{50\%}$ of the individual PTV Volume Range

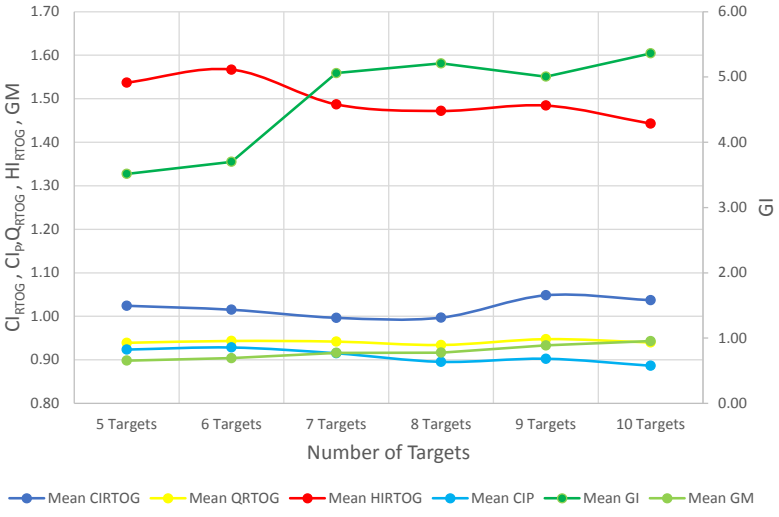


Figure 6. Influence of Number of Targets on Mean GI of Individual PTVs

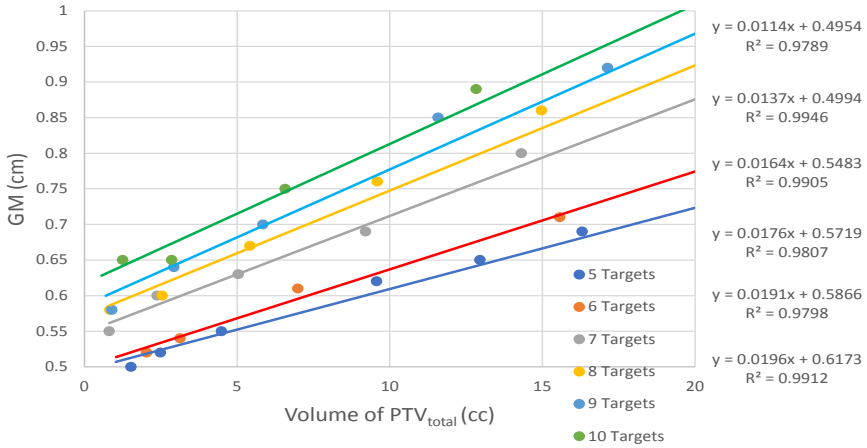


Figure 7. GM Increases with Increase in PTV$_{total}$ Volume and Number of Targets

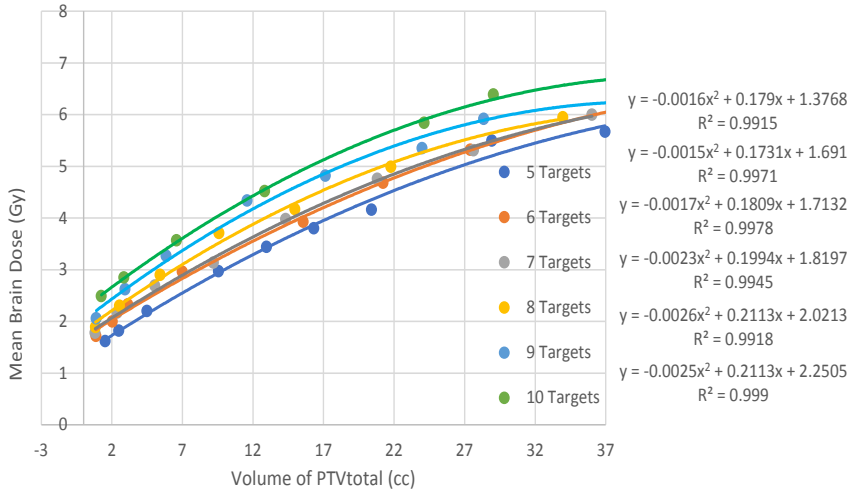


Figure 8. Trendline Showing Increase in Mean Brain Dose with the Increase in PTV$_{total}$ Volume and Number of Targets. Each dot represents the mean brain dose of a single plan.

*3.3. PTV distance from isocenter*

There was no correlation between isocenter to PTV distance and $CI_{RTOG}$ ($\rho = 0.14$), $CI_{P}$ ($\rho = 0.01$) and GI ($\rho = -0.03$). The distance of the PTV from the isocenter did not affect the conformity and gradient index.

*4. Gradient measure*

GM was reported in Eclipse TPS for the target volume for PTV$_{total}$; therefore, GM is discussed separately. With the increase in PTV$_{total}$ volume and the number of targets, the GM increases and forms a linear fit (Figure 7). The minimum GM achieved in this study was 0.49 cm, which corresponds to PTV$_{total}$ of 0.87cc and 6 targets. The maximum GM was 1.35 cm for PTV$_{total}$ of 38.66 cc and 10 targets. The achievable GM for a given number of targets and PTV$_{total}$ volume within the studied range can

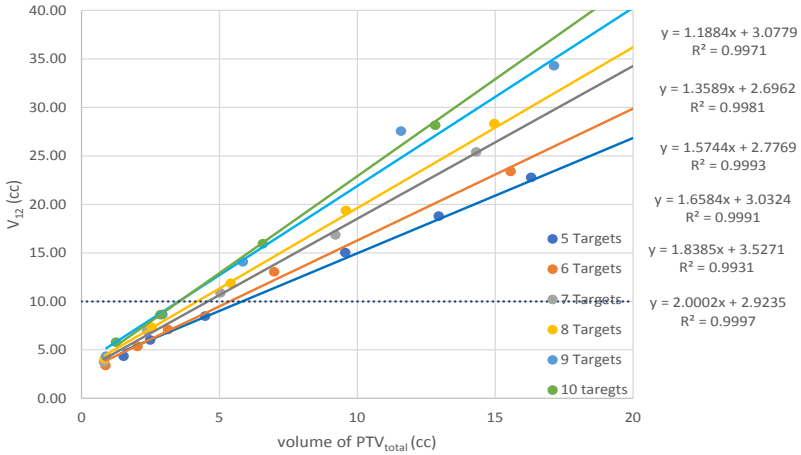


Figure 9. Trendline Showing an Increase in $V_{12}$ (BmP) with the Increase in PTV$_{total}$ Volume and Number of Targets

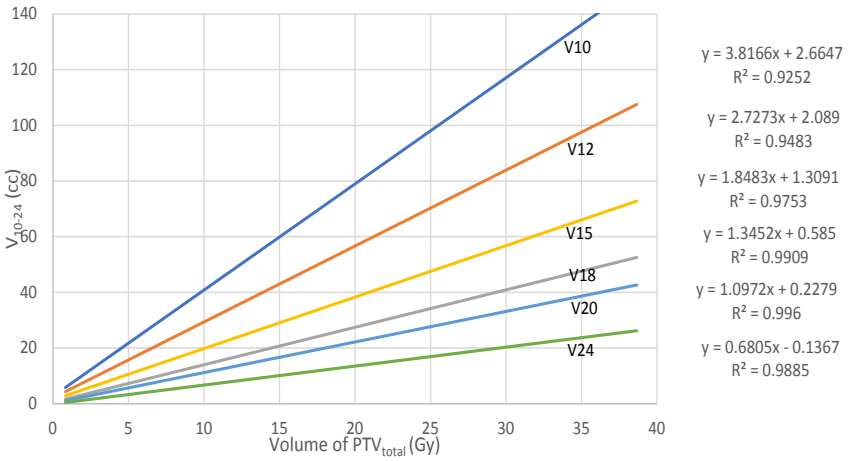


Figure 10. Trendline Showing That the Volume of the Brain Receiving 10 to 24 Gy Increases with the Increase in $PTV_{total}$ Volume

be calculated using equation 1.

$$GM = (0.0022 \times n \times PTV_{total}) + (0.2835 * n^{0.333}) \quad (1)$$

where n stands for the number of targets.

*5. Brain mean dose and $V_{12}$*

The dose to the normal brain is the limiting factor in SRS plans as tolerance of other critical organs were is well achievable, if the target is a non-brainstem tumor or not adjacent to optical apparatus. In this study, the minimum mean brain dose achievable was 1.62 Gy for $PTV_{total}$ of 1.52 cc for 5 targets. The mean brain dose was found to increase with the increase in the volume of $PTV_{total}$ as well as the number of targets (Figure 8). The maximum mean brain dose was 6.69 Gy for $PTV_{total}$ of 38.66 cc for 10 targets. Equation (2) represents the change in mean brain dose with respect to the number of targets (n) and $PTV_{total}$ volume:

$$\text{Mean brain dose} = n[(-0.00025 \times PTV_{total}^{2}) + (0.1 \times n^{-0.693} \times PTV_{total}) + (0.5 \times n^{-0.3535})] \quad (2)$$

$V_{12}$ (BmP) was found to depend on both total PTV volume and the number of lesions (Figure 9). The increase in $V_{12}$ with respect to the increase in the number of targets (n) and $PTV_{total}$ is represented by equation 3.

$$V_{12}\,(BmP) = (0.3535 \times PTV_{total} \times n^{0.75}) + (2.5 \times n^{0.1334}) \quad (3)$$

Figure 10 shows the trendline of $V_{10}$, $V_{12}$, $V_{15}$, $V_{18}$, $V_{20}$, and $V_{24}$ for brain volume for all the plans. Equation 4 relates to brain volume including PTV receiving $d_n$ dose.

$$Vd_n = d_n\,[(2.1 \times PTV_{total} \times e^{-0.182dn}) + (6.72 \times e^{-0.306dn}] \quad (4)$$

where $Vd_n$ is the volume receiving $d_n$ of dose ($d_n$ = 10, 12, 15, 18, 20, or 24 Gy)

*6. Prescription isodose line and MU*

The prescription isodose lines were in the range of 99%-78%. The maximum prescription line used was for the minimum $PTV_{total}$, volume and it decreased with an increase in $PTV_{total}$ volume (Figure 11). MU required for VMAT planning for the number of PTVs and volume of $PTV_{total}$ is shown in Figure 12. On average, MU increases with an increase in the number of targets and decreases with an increase in $PTV_{total}$ volume.

## Discussion

For PTV coverage, as the prescription isodose line was chosen such that all the PTVs in a plan should get a minimum dose of 19 Gy (90.5%), $Q_{RTOG}$ was well achieved. At the same time, the value of $D_{max}$ and other indices of each target were carefully evaluated, and they were in concurrence with RTOG guidelines. Despite as

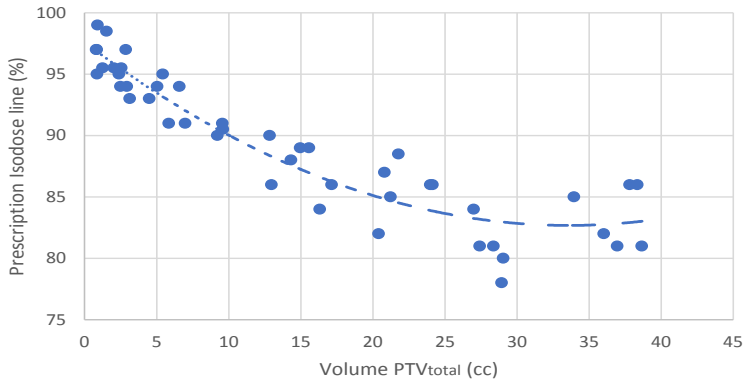


Figure 11. Scatter Plot Showing a Decrease in PIL with an Increase in $PTV_{total}$ Volume

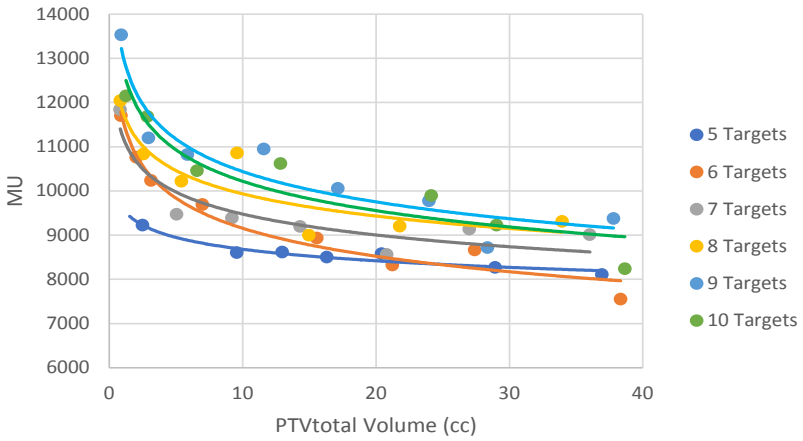


Figure 12. MU Required to Deliver SIMT VMAT Plan for the Given Number and Volume of $PTV_{total}$

many as 10 targets and a high dose of 21 Gy for a large $PTV_{total}$ volume (38.66 cc) was planned, the maximum dose to critical organs was low and within tolerance. OAR doses of this study were comparable to that of the HDMLC non-coplanar VMAT technique of Li et al., (2019). Plan quality indices were compared with the published indices by Narayanasamy et al., (2017) and Liu et al., (2019) (Table 3). Better conformity of this study compared to their published results is due to the sphericality of the targets chosen.

In the studied range of 0.025 to 11 cc individual PTV volumes, the optimum PTV volume that can be treated using an MLC of 5 mm leaf width MLC, in a multiple BM SIMT plan is 0.1 to 11 cc (PTV diameter ≥ 0.58 cm) in terms of better conformity. GI plot for individual PTV volume shows that a better gradient was achieved for PTVs volume greater than 0.3 cc (PTV diameter ≥ 0.83 cm). For PTV volume below 0.3 cc, GI showed a steep increase.

Studies by Xue et al., (2015) and Rivers et al., (2017) in Gamma Knife treatment found that the total PTV volume was the influencing factor of the normal brain mean dose, and the number of targets did not influence the same. We observed in Linac-based SIMT planning that the normal brain dose tends to increase with the number of targets. For instance, as shown in 7, 5 cc of $PTV_{total}$ with 5 targets results in a mean brain dose of 2.23 Gy, whereas the same volume of $PTV_{total}$ with 10 targets is 3.2 Gy. In this study, we found that despite a higher dose to large PTV volume, the dose to the brain was low in SIMT SRS planning, thus helping in avoiding the decline in neurocognitive functions, unlike WBRT. Given the $PTV_{total}$ volume and the number of targets, equation (2) can help to predict the expected mean dose of the brain to tweak the prescription dose up-front and to keep the radiation-induced normal tissue complication as minimum as possible.

Brain volume receiving 12 Gy ($V_{12}$) is an important predictive factor for potential brain necrosis complications. The tolerance of healthy brain tissue treated is given by $V_{12}$ < 10 cc for single lesion SRS (Limon et al., 2017). If the tolerance dose of brain $V_{12}$ volume is exceeded, risk-adapted SRS dose prescription is widely adopted, by lowering the prescription dose or changing to Stereotactic Fractionated Radiotherapy (SFRT) (Kim et al., 2011). The dose and fractionations for treating multiple BM are decided based on how well the normal brain is getting spared.

Chea et al., (2021) found that 5cc of target can be treated without exceeding $V_{12}$ volume of the healthy brain for a 18 Gy prescription dose. Rescaling SIMT plans in this study to the prescription dose of 18 Gy reveals that 9 cc of $PTV_{total}$ can be treated without exceeding healthy brain $V_{12}$ for 5 targets. For 10 targets, it was 6 cc. $PTV_{total}$ volume that can be treated without exceeding healthy brain $V_{12}$ (BmP) volume was 6, 5, 4.7, 4, 3.7, and 3.4 cc for 5, 6, 7, 8, 9, and 10 targets, respectively, for a 21 Gy prescription dose. However, for brain including PTV, $V_{12}$ was 3.2, 3.0, 2.7, 2.5, 2.3, and 2.3 cc for the same number of targets and 21 Gy prescription dose. Mean $V_{12}$ (BmP) per lesion obtained for spherical targets was 3.85 ± 2.83 cc for all 47 plans for a prescription dose of 21 Gy compared to that of Ruggieri R et al., 2018, who achieved 4.9 ± 3.5 cc.

Equation 1 estimates the gradient measure for the given $PTV_{total}$ volume for multiple BM SIMT planning, and its average deviation was 0.03 cm from the actual values obtained in planning. Equation 2 for the mean brain dose agreed well, with an average deviation of 0.11 Gy. $V_{12}$ for BmP calculated using Equation 3 showed an average deviation of 0.46 cc up to 25 cc of $PTV_{total}$ and 5.9 cc for above 25 cc of $PTV_{total}$ volume. Average deviation of Equation 4 from the calculated dose for $V_{10}$, $V_{12}$, $V_{15}$, V18, $V_{20}$, and $V_{24}$ was 5.04, 2.95, 1.94, 0.76, 0.22, and 0.47 cc, respectively. All the four equations were in accordance with their respective values obtained from the total 47 plans.

In conclusion, SIMT VMAT with 5 mm leaf width MLC is capable of delivering the SRS target dose without compromising OAR tolerance for 5 to 10 BM. A systematic approach was followed relating the volume and number of targets to obtain equations for gradient measure, mean brain dose, healthy brain $V_{12}$, and $V_{10\text{-}24}$, which can serve as a baseline for multiple BM SIMT planning for the prescription dose of 21 Gy. With the addition of target complexity, these formulas can become more robust. The maximum volume determined that can be treated guides in determining the dose and fractionation for the given number and volume of targets, before planning for multiple BM SRS treatments.

## Author Contribution Statement

Study concept, data collection, analysis, interpretation of results, and draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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*Ethical Declaration*

Ethical approval is not required as this is a simulation study and not used for patient treatments.

*Data Availability*

The data of this study are available on request.

*Conflict of Interest*

The authors declare no conflict of interest.

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