RESEARCH ARTICLE

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Single-Isocenter Multiple-Target SRS Planning of Five to Ten Brain Metastases Using 5 mm Multileaf Collimator: Relationship between Prescription Dose, Number and Volume of Targets

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Abstract

Objective: To propose an expression relating the number and volume of targets with the prescription dose in determining normal brain volume receiving 12 Gy dose (V12) for five to ten brain metastases treated in linear accelerator-based stereotactic radiosurgery (SRS) planning. To determine the volume of tumor that can be treated within the brain tolerance dose, for different SRS prescription doses. **Methods:** Single-isocenter multiple-target (SIMT) SRS plans were devised for spherical targets that are modeled to simulate 47 tumor scenarios with varying tumor sizes and locations within the brain. Volumetric modulated arc therapy (VMAT) plans were devised using a 5-mm-leaf-width multi-leaf collimator (MLC) with high conformity and dose gradient in the Eclipse treatment planning system for the 21 Gy prescription dose with a 6FFF photon beam. The prescription dose was rescaled to 20 Gy, 18 Gy, 15 Gy and 12Gy to determine the brain V12 volume for a total of 235 SRS plans. **Results:** Linear correlation was observed between the number, volume and prescription dose of the tumor. The expression relating these parameters was constructed to predict the normal brain V12 volume. The maximum tumor volume that can be treated using SIMT SRS with a 5-mm MLC for 5 to 10 number of targets and for a prescription dose of 21 Gy, 20 Gy, 18 Gy and 15 Gy is determined. **Conclusion:** Using the expression obtained, V12 volume can be calculated using the number of tumors and the total volume of tumors from the pre-planning MRI data. The prescription dose and the SRS fractionation size can be determined before radiotherapy treatment planning.

Keywords: Multiple brain metastases- stereotactic radiosurgery- single isocenter multiple target- VMAT

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Introduction

Treatment options for the radiotherapy management of patients with brain metastases (BM) include whole-brain radiotherapy (WBRT), hippocampus-sparing WBRT, stereotactic radiosurgery (SRS) and fractionated stereotactic radiosurgery (fSRS). The advantages of SRS over WBRT are high dose per fraction, higher conformity around the target and higher dose gradient outside the target; hence, the target receives a higher biologically effective dose, and the normal structures are spared (Xue et al., 2015). SRS for the treatment of up to four BM has higher local control, lower toxicity and better neurocognitive function compared with WBRT (Eric et al., 2009, Brown et al., 2016). Recently, ten or more BM SRS treatment has gained increasing interest as the overall survival of patients with five to ten BM treated using SRS is comparable to that of patients with two to four BM (Yamamoto et al., 2014, Ryan et al., 2019, Ferini et al., 2021).

SRS treatment can be carried out using dedicated machines such as Gamma-Knife (Elekta Instrument AB, Sweden) and Cyber-Knife (Accuray, Sunnyvale, California). Conventional medical linear accelerators (LINAC) equipped with a multi-leaf collimator (MLC) deliver an equivalent dose fall-off and have become increasingly common in SRS and fSRS (Lijun et al., 2010). Volumetric modulated arc therapy (VMAT) is a rotational treatment delivery method in LINAC with a single-isocenter multiple-target (SIMT) planning technique, which sequentially treats multiple targets within the brain in a shorter delivery time (Ruggieri et al., 2018). Varian LINAC (Varian Medical System, Palo Alto, California) provides two types of MLC - standard Millennium MLC

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(M120) and High-Definition MLC (HDMLC) - both of which can be used in VMAT SIMT SRS delivery. M120 and HDMLC have minimum leaf width of 0.5 cm and 0.25 cm respectively at the isocenter. Comparison studies showed that the HDMLC has better conformity and dose gradient in SRS treatments than the M120 (Dhabaan et al., 2010, Taylorn et al., 2020). However, the absolute difference in dosimetric parameters between M120 and HDMLC may not be clinically significant (Taylorn et al., 2020). In addition, treatment plans using HDMLC have shown higher optimization complexity, higher MU and higher delivery complexity than M120 plans (Abisheva et al., 2019, Yoshio et al., 2020). Non-coplanar SRS VMAT planning with M120 has been evaluated for clinically acceptable plan quality in treating BM (Yoshio et al., 2020, Hemalatha et al., 2022).

In intracranial SRS planning and delivery, the volume of the normal brain tissue irradiated by a dose of 12 Gy (V12) is considered an important plan quality metric (Brian et al., 2010). V12 is correlated with the occurrence of radionecrosis treated with SRS. For single-fraction SRS to treat BM, V12 including target volume of 5 cc, 10 cc and >15 cc was associated with the risk of symptomatic radionecrosis of approximately 10%, 15% and 20%, respectively. For three-fraction fSRS for BM, normal brain tissue V20 < 20 cc, V18 < 30 cc and V23 < 7 cc were associated with a <10% risk of radionecrosis (Milano et al., 2021, 2022). If the tolerance dose of brainV12 volume is exceeded in SRS planning, risk-adapted SRS dose prescription is adopted, in which the prescription dose is decreased or fSRS is planned.

In this study, we analyzed LINAC-based SRS for five to ten BM, planned in SIMT VMAT planning technique using M120 MLC. This study aims to determine the maximum tumor volume that can be treated for the prescription doses of 21, 20, 18 and 15 Gy for five to ten BM SRS, without exceeding the normal brain tissue tolerance dose of V12< 10 cc.

Materials and Methods

Target Modeling

Radiotherapy planning Computed Tomography images of the brain reconstructed to 1 mm slice thickness taken using a Siemens SOMATOM Definition AS (Siemens Healthcare, Erlangen Germany) 128 slice CT scanner were used in this study. To simulate BM, five to ten spherical targets with different planning target volumes (PTVs), locations and distances between them were modeled in the CT images to obtain 47 CT plans with varying PTV volumes and the number of targets (Table 1). All PTVs in a CT plan were summed to achieve the PTV_{total} for the plan. The PTV_{total} ranged from 0.8 cc to 38.6 cc. Organ-at-risk (OAR) contours of the brain, brainstem, optic chiasm, optic nerves, eyeballs and lenses were drawn. All PTVs and OAR structures were assigned as high-resolution structures.

Treatment Planning

SIMT non-coplanar VMAT treatment planning was carried out in an Eclipse v15.6 (Varian Medical System, Palo Alto) treatment planning system using millennium MLC (M120) to deliver in TrueBeam (Varian Medical System, Palo Alto) LINAC. One coplanar full rotation arc and three non-coplanar half arcs with 45°couch intervals were used for all plans to achieve a higher degree of freedom and planning goals (Figure 1). Collimator angles were carefully selected to minimize the island-blocking problem by inspecting the beam's eye view of each arc. The 6MV flattening filter-free (FFF) beam energy with a maximum dose rate of 1400 MU/min was selected to reduce the treatment delivery time. The beam isocenter was placed at the geometric center of the PTV_{total}. The optimizer was run to provide the maximum coverage to the target, without the upper objective, i.e., the maximum dose constraint. Dose-volume constraints were applied to normal structures and the low dose volume to the normal brain in optimization. Ring structures around the target and normal tissue objective (NTO) were used to achieve a high dose gradient. Dose calculations were carried out using the Acuros XB algorithm with a 1.25-mm calculation resolution. The jaw tracking option was kept ON to reduce the MLC leakage dose (Yuan Y et al, 2018). A total of 47 simulated CT plans with varying PTV_{total} and number of targets (five to ten) were planned for prescription doses of 21, 20, 18, 15 and 12 Gy, thus generating 235 SRS SIMT plans. In evaluation, the prescription isodose line was selected such that 95% of the PTV_{total} receives 100% of the prescription dose (Figure 1).

Plan Analysis

The plans were analyzed in accordance with protocol 90-05 (Shaw E et al., 2000) proposed by the Radiation Therapy Oncology Group (RTOG) based on the conformity index, homogeneity index and gradient index. Clinically acceptable plans were devised, and a dose-volume histogram was evaluated for the V12 normal brain volume including PTV and tabulated against various prescription doses (D), PTV_{total} (V) and number of PTVs (N). Scatter plots were generated using Microsoft Excel (Microsoft Corporation (2018)) to establish and analyze the relationship of the V12 with prescription dose, number of targets and PTV_{total}. Data were first categorized based on the number of targets. The correlation between PTV_{total} and V12 for each N = 5 to 10 was obtained, and then, its dependence on prescription dose was evaluated. The final expression showed the relationship between N, V and D. Using this expression, the maximum volume of PTV and the number of targets that can be treated without exceeding the normal brain tolerance dose was determined.

Statistical Analysis

The scatter plots, linear fits, equations and proportion of variance (R2 value) were obtained using Microsoft Office Excel software (Microsoft, Redmond, WA, USA). Maximum difference and average deviation were computed between planned V12 and calculated V12. Spearman's rank coefficient is used to assess the correlation between planned V12 and calculated V12 data. The formula for computing Spearman's rank correlation coefficient is as follows:

$$rs = \rho R(X), R(Y) = \frac{cov\big(R(x), R(Y)\big)}{\sigma R(X)\sigma R(Y)}$$

where ρ denotes Pearson correlation coefficient applied to the rank variables, cov(R(X),R(Y)) is the covariance of rank variables, σR(X) and σR(Y) are the standard deviations of the rank variables. Spearman's correlation coefficient is simply the Pearson correlation coefficient computed using the rank values instead of the raw values of the two variables, it can uncover non-linear, as well as linear relationships between X and Y, as long as Y is a monotone function of X. In other words, the Spearman assesses how well an arbitrary monotonic function can describe a relationship between two variables, without imposing any assumptions on the frequency distribution of the variables. It is the number of xy pairs and the plotted values are not raw data those are rank-transformed values. The Spearman Coefficient ρ can take a value between +1 to -1 where ρ = +1 means a perfect association of rank, ρ = 0 means no association of rank and ρ = -1 means a perfect negative association between ranks.

Results

For all PTVs, the dose received by 95% volume (D95%) was 100% of the prescription dose. All critical structures drawn were within the tolerance dose. Conformal plans with a high dose fall-off were obtained. The results of plan evaluation indices were presented in our previous study (Hemalatha et al., 2022). The plans were devised for a prescription dose of 21 Gy and re-prescribed for 20, 18, 15 and 12 Gy. The plans were optimized using tighter low-dose constraints and high-dose fall-off in such a way that they were good enough to rescale to other doses with no further room to improve on.

The brain V12 obtained for different numbers, volumes and prescription doses of the targets is presented in Table 1. For the given number of targets, a scatter plot for PTV_{total} vs V12 for 21, 20, 18, 15 and 12 Gy prescription doses was constructed (Figure 2). The maximum PTV_{total} was restricted to 25 cc for the scatter plot as the coefficient of determination (R2) of the linear fit increases beyond 25 cc. Linear correlation was observed between brain V12 and PTV_{total} for the given number of targets. The obtained linear equations that show the relationship between the number of targets and prescription doses are presented in Table 2. When the number of targets and the prescription dose increase, the slope of V12 increases and both show a linear relationship. An expression was calculated for each of the number of targets characterized by PTV_{total} (V) and prescription dose (D) showing a linear fit.

For each prescription dose (D), V12 expressions were obtained for the different number of targets (N):

$V12 = V\,(0.988N^{0.485}) + 0.048\,N + 2.44$ (D = 21 Gy)
$V12 = V\,(0.992N^{0.442}) + 0.04\,N + 2.211$ (D = 20 Gy)
$V12 = V\,(1.027N^{0.341}) + 0.04\,N + 2.061$ (D = 18 Gy)
$V12 = V\,(1.013N^{0.197}) + 0.03\,N + 0.719$ (D =15 Gy)
$V12 = V\,(0.881N^{0.053}) - 0.012\,N + 0.127$ (D = 12 Gy).

The consolidated equation obtained by taking into account the prescription dose was as follows:

$V12 = N\,(0.017DV - 0.2V) + 0.05DV + 0.34(D + V) - 4.043$,

where V12 is the volume of the brain including the target, receiving more than 12 Gy of the dose, N represents the number of targets, D refers to the prescription dose in Gy and V denotes the PTV_{total} in cc. Using this expression, the prescription dose for the given number of tumors, PTV_{total} and V12 tolerance volume can be calculated.

This expression was validated using the V12 values obtained from the 235 plans with different N, V and D. Though the expression was generated for volumes up to 25cc, a PTV_{total} of 38.6 cc was included in the validation process. The average deviation of V12 computed using this expression and the actual value of V12 of the study plan were found to differ by a maximum of 1.8, 1.8, 0.5, 1.2, 0.9 and 1.5 cc for the number of targets of 5, 6, 7, 8, 9 and 10, respectively, with an average deviation of 0.7, 0.5, 0.3, 0.3, 0.8 and 0.4. Spearman's rank correlation

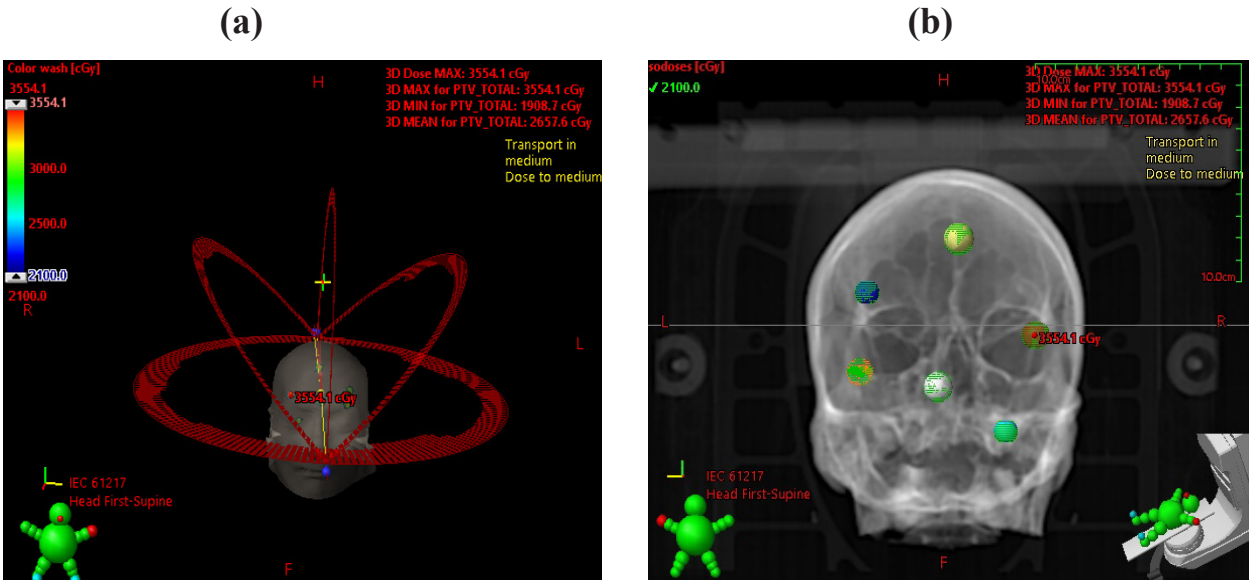

Figure 1. (a) non-coplanar SIMT ARC arrangements (b) AP view of prescription dose coverage for a 6-target SIMT plan.

Table 1. V12 for Different Numbers, Volumes and Prescription Doses of the Targets

No. of targets	PTV_{total}	BrainV12 (cc)				
		21Gy prescription	20Gy prescription	18Gy prescription	15Gy prescription	12Gy prescription
5	2.39	8.51	7.83	6.59	4.67	2.69
	4.49	12.95	11.99	10.07	7.28	4.38
	9.63	24.6	22.98	19.84	14.96	9.75
	12.96	34.11	31.87	27.48	21.11	14.45
	16.31	39.58	36.99	31.91	24.47	16.67
	20.53	46.7	43.7	38.04	29.58	20.61
6	2.03	7.35	6.73	5.48	3.72	2.02
	3.14	10.23	9.41	7.76	5.46	3.2
	6.99	19.43	17.98	15.2	11.06	6.99
	15.57	37.63	35	35.15	22.28	14.58
	21.22	52.82	49.03	41.76	31.44	21.02
7	0.81	4.56	4.09	3.16	1.93	0.8
	2.38	9.36	8.48	6.86	4.54	2.34
	5.04	15.91	14.61	12.11	8.47	4.93
	9.21	26.05	24	20.1	14.6	9.08
	14.32	39.73	36.49	30.41	22.11	14.01
	20.81	56.39	51.82	43.33	31.74	20.34
8	0.84	4.91	4.37	3.37	2.02	0.82
	2.55	9.86	8.92	7.25	4.8	2.5
	5.42	17.29	15.86	13.02	8.07	5.08
	9.59	28.95	26.52	21.99	15.6	9.35
	14.97	43.29	39.55	32.73	23.41	14.35
	21.29	60.45	55.36	45.98	33.47	21.16
9	0.9	6.42	5.73	4.36	2.58	1.06
	2.93	11.57	10.5	8.52	5.66	2.96
	5.85	19.93	18.17	14.93	10.31	6
	11.59	39.15	35.76	29.36	20.78	12.75
	17.14	51.44	47.01	38.77	27.74	12.22
	23.26	70.92	64.82	53.46	38.15	23.61
10	1.25	7.03	6.26	4.49	2.93	1.25
	2.86	11.48	10.4	8.35	5.48	2.82
	6.58	22.51	20.57	16.73	11.5	6.5
	12.93	41.54	37.75	30.77	21.58	13.02
	24.14	75.60	68.81	56.12	39.11	23.96

(Figure 3) between V12 obtained from the plans and the V12 predicted from the expression was $\rho = 0.998$, showing a very strong correlation (Wessa, 2017).

The maximum target volume that can be treated for a given number of tumors, with a prescription dose not exceeding V12 = 10 cc, was calculated using the expression and is presented in Table 3. The standard deviation of the difference between the V12 obtained from the plans and the predicted V12 is also presented in the Table 3.

Discussion

The SRS plans were generated for spherical targets, resulting in conformal plans. The use of ring structures and NTO resulted in a high dose fall-off. SIMT SRS plans for multiple BM with M120 MLC were studied for their clinically acceptable plans as per RTOG recommendations presented in our previous study (Hemalatha et al., 2022). Conformity index = 1 can be achieved for a PTV of 0.1 cc and above while using M120 (Hemalatha et al., 2022). In the present study, to achieve a conformal dose for smaller PTVs, each PTV was given an individual lower objective by analyzing the DVH during the optimization process, so that all PTVs have equal dose coverage (Figure 4). This prevented over-coverage of smaller PTVs while choosing the prescription isodose line.

Studies demonstrating the correlation between PTV,

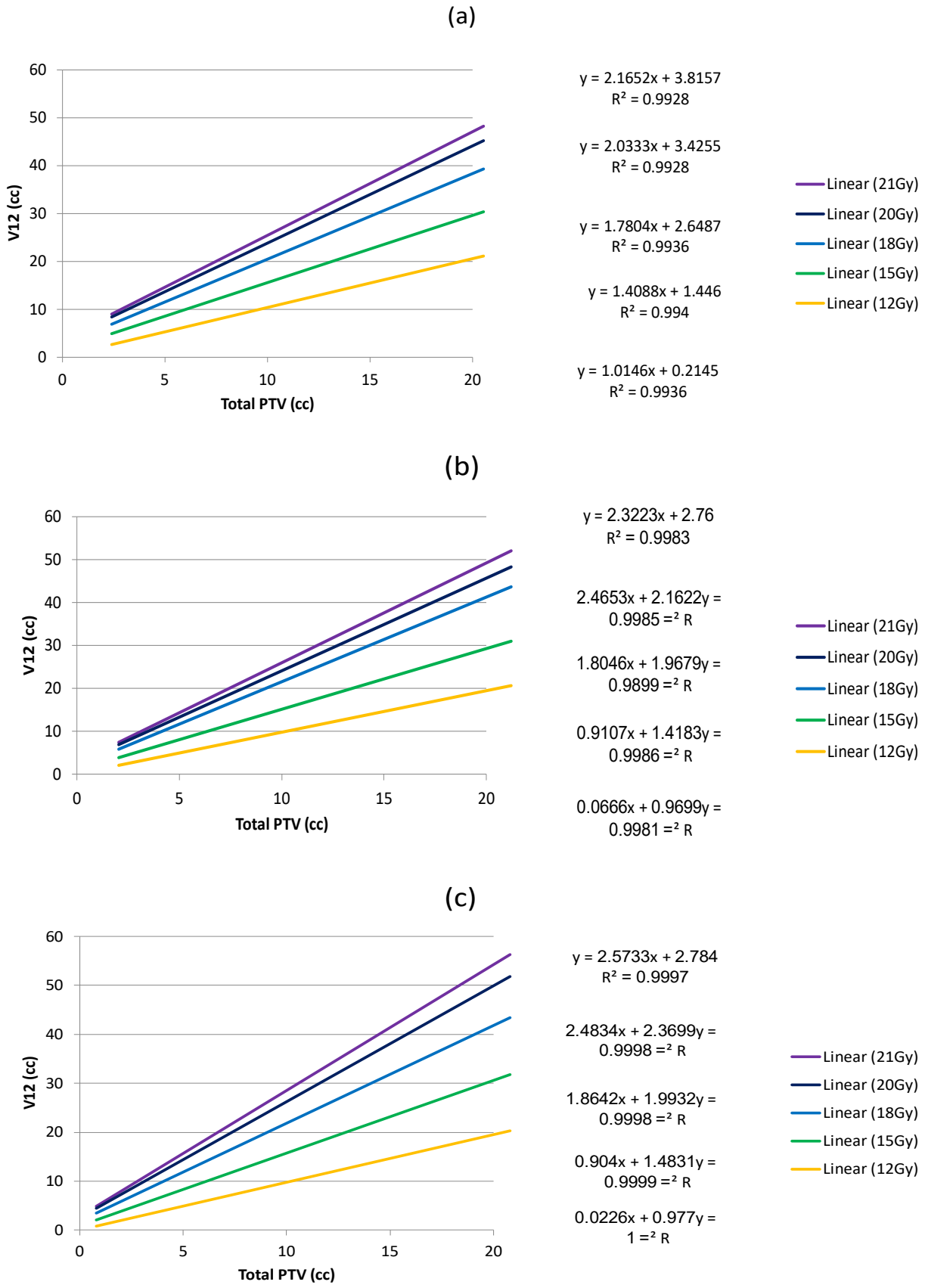

Figure 2. Scatter Plot Showing Trend Line Relating V12 and PTV_{total} for (a) 5 targets (b) 6 Targets (c) 7 targets

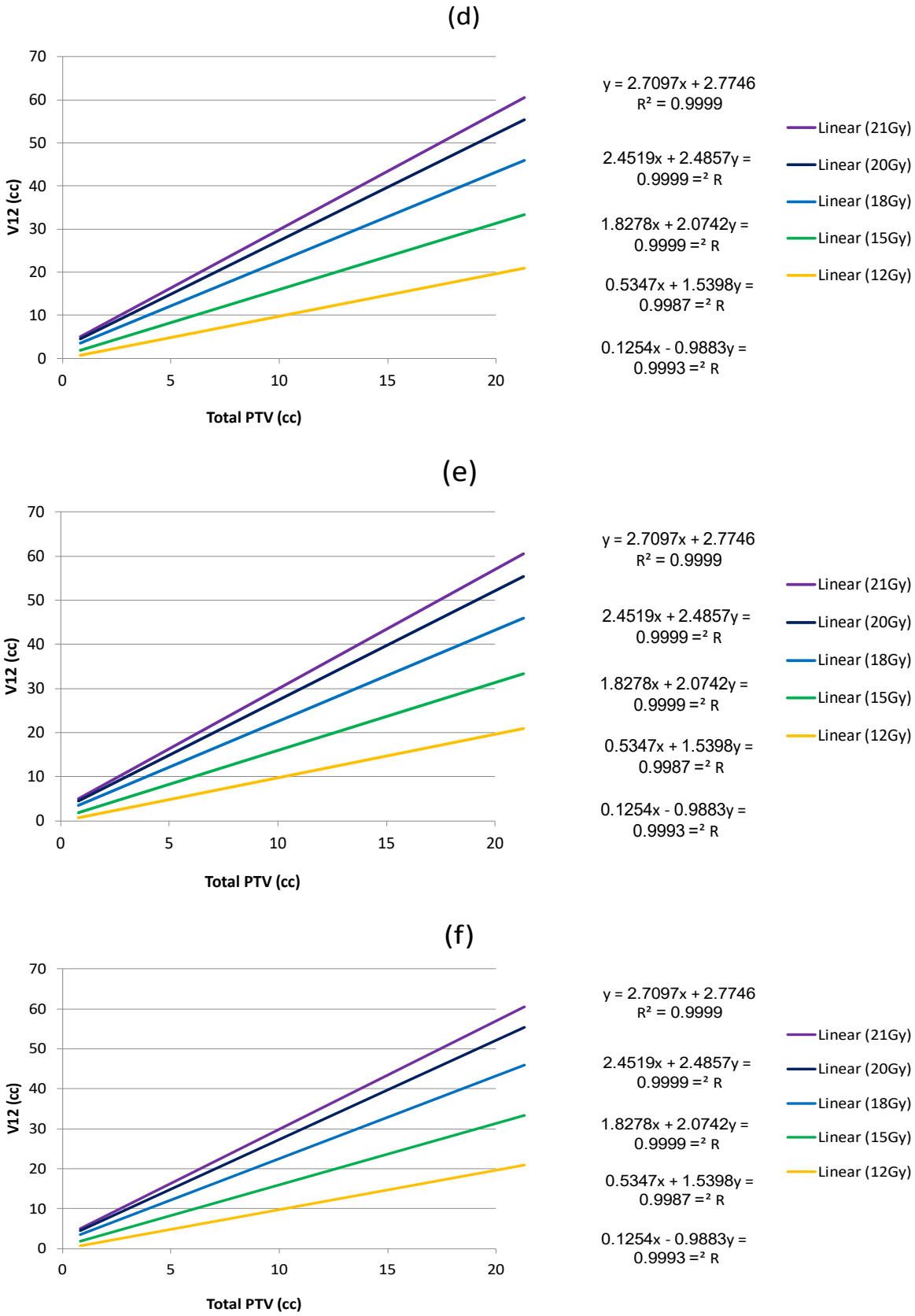

Figure 2. Scatter Plot Showing Trend Line Relating V12 and PTV_{total} for (d) 8 targets (e) 9 targets (f) 10 targets and their linear equations and R^2 values.

Table 2. Linear Equations Relating V12 and PTV_{total}

No. of targets (N)	Prescription dose				
	21 Gy	20 Gy	18 Gy	15 Gy	12 Gy
5	V12 = 2.165V+3.815	V12=2.033V + 3.425	V12=1.780V + 2.648	V12=1.408V + 1.446	V12=1.014V + 0.214
6	V12= 2.322 V + 2.76	V12=2.162V + 2.465	V12=1.967V + 1.804	V12=1.418V + 0.910	V12=0.969V + 0.066
7	V12=2.573V + 2.784	V12=2.369V + 2.483	V12=1.993V + 1.864	V12=1.483V + 0.904	V12=0.977V + 0.022
8	V12=2.709V + 2.774	V12=2.485V + 2.451	V12=2.074V + 1.827	V12=1.539V + 0.534	V12=0.988 V - 0.125
9	V12=2.880V + 3.632	V12=2.638V + 3.215	V12=2.188V + 2.413	V12=1.587V + 1.222	V12=0.920V + 0.304
10	V12=3.002V + 2.956	V12=2.736V + 2.621	V12=2.249V + 1.808	V12=1.581V + 1.017	V12=0.995V + 0.007

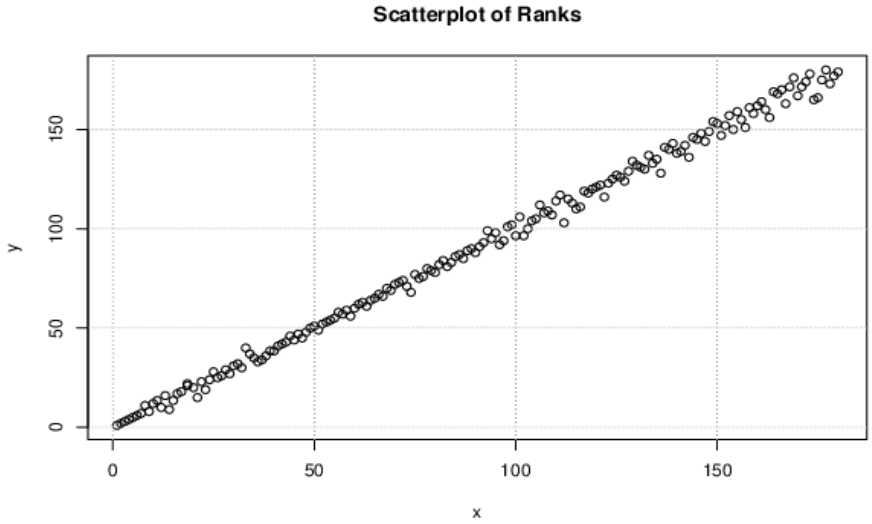

Figure 3. Spearman's Rank Correlation between the Predicted V12 and Plan V12 for 180 Plans Plans for 5 to 10 Number of Targets, PTV_{total} Volume (0.8 cc to 38.6 cc) and Prescription Dose of 21 Gy, 20 Gy, 18 Gy, 15 Gy. X and Y are rank transformed values of planned and calculated V12 value. Correlation of 180 plan V12 and calculated V12 shows $\rho = 0.998$ with 95 % confidence level.

number of tumors and prescription dose for multiple BM are limited. Bohoudi et al., (2016) predicted V12 from a single parameter, - PTV_{total}, and found that it slightly overestimated V12 for small lesions. In the present study, the predicted expression was used on a minimum PTV_{total} volume of 0.81 cc and found to be agreeing with the planned V12 results. Goldbaum et al., (2019) proposed a linear-log relationship for single-isocenter plans for single-lesion SRS using cone arc therapy (CAT) and dynamic conformal arc therapy (DCAT) relating PTV,

Table 3. Maximum PTV_{total} that can be Treated for V12< 10 cc for a Given Number of Targets and Prescription Doses

No. of targets	PTVtotal (cc)				Standard deviation*
	21 Gy	20 Gy	18 Gy	15 Gy	
5	3.2	3.6	4.5	6.6	± 0.95
6	3	3.4	4.2	6.3	± 0.98
7	2.8	3.2	4	6.1	± 0.42
8	2.6	3	3.8	5.9	± 0.41
9	2.5	2.8	3.6	5.7	± 1.0
10	2.3	2.6	3.4	5.5	± 0.55

*The standard deviation of the difference between the V12 from the plans and the predicted V12 is presented in the table

prescription dose and plan type. Rivers et al., (2017) showed no relationship between the number of tumors and the treated brain volume, but their study was a gamma-knife-based analysis and may not apply to LINAC-based non-coplanar SRS treatment. The increase in the mean brain dose and V12 volume with an increase in the number of targets was discussed in our previous study (Hemalatha et al., 2022). Using M120 MLC for treating multiple metastases using SRS, this study demonstrated the correlation between prescription dose, PTV_{total} and the number of targets. An expression for V12 that relates to V, N and D was obtained for SRS of five to ten targets. If the number of tumors and their volume are known while preplanning in an MRI scan, the prescription dose and the choice of SRS or fSRS can be determined before radiotherapy planning.

The use of spherical targets in this study is an effective approach to get highly conformal dose coverage. The results of this study can be applied to irregular targets, if the conformity index, in the order of 1.02 and a gradient measure less than 1.3 cm can be achieved in the irregular target plans. 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). The individual PTV's dose prescription in a multiple metastatic plan depends on the volume of each

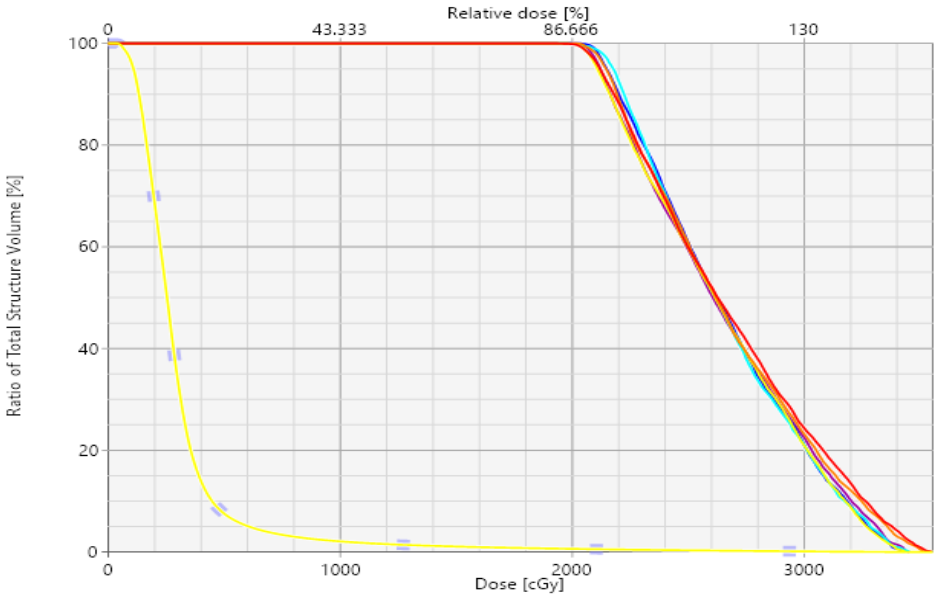

Figure 4. Dose-Volume Histogram Showing All 6 PTVs in a Plan Receiving the Prescription Dose

PTV in a plan. Our study used the same prescription dose for all the PTVs in a plan, irrespective of the individual PTV's volume. The results of this study indicate that the maximum PTV_{total} volume that can be treated is 3.2 cc for 5 targets. This implies that the individual target volume has to be less than 3 cc. Therefore, the use of the same prescription dose in the SRS plans with PTV_{total} volume in the order of 3 cc is in accordance with the practical recommendations and it will not affect the aim of this study and the results in Table 3. As the distance between the PTVs inversely affects the dose gradient between multiple PTVs in a plan, it can be included for the robustness of this study.

In conclusion, V12 determines the risk of radionecrosis in SRS treatment. As shown in this study, V12 can be estimated from the number of tumors and their volume while pre-planning using MRI data. The prescription dose and the choice of fractionation can be determined earlier. V12 predicted for spherical targets can also be implemented for a conformal plan for irregular tumors as a strong correlation is observed between the predicted V12 and V12 obtained from the plans. In the present study, the volume of tumors that can be treated without exceeding the normal brain V12 was determined for different numbers, volumes and prescription doses of the targets using SIMT SRS planning with millennium MLC for five to ten BM.

Author Contribution Statement

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

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General

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Declaration

This article is not been previously submitted in whole or part of an approved student thesis and it was not approved by any scientific body.

Ethical Declaration

Ethical approval is not required as this is a simulation study not used for treatment.

Availability of data

Data sharing is not applicable to this article.

Conflict of Interest

The authors declare no conflict of interest.

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