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Planning Target Volume Margin in Linac-Based Stereotactic Radiosurgery for Brain Metastases

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Abstract

Background: The treatment of brain metastases with radiotherapy has shifted to the use of Stereotactic Radio-surgery (SRS). The technical issue of expanding the treatment volume around the Gross Tumor Volume (GTV) is a current debate. Radiotherapy centers use variable GTV-PTV margins, ranging from one to 2 mm. **Material and Methods**: We performed a dosimetric comparison in plans of twenty patients using three margins: PTV zero, PTV1, and PTV2. We also developed imaginary Peel volumes. These volumes are described as follows: Peel1 = PTV1 − GTV, Peel2 = PTV2 − GTV. **Results:** Our results showed that the mean PTV volume differed significantly across the different margins ($p = 0.000$). The V12 of the brain significantly varied as a function of PTV margin ($p = 0.000$). The target coverage and plan quality indices were not significantly different. The Peel volume dosimetric analysis showed that the mean dose was significantly higher in the nearby normal brain tissue: Peel1 ($p = 0.022$) and Peel 2 ($p = 0.013$). **Conclusion:** According to our dosimetric analysis, expanding the GTV into a PTV by 1 mm margin is more convenient than 2 mm.

Keywords

SRS, Brain Metastases, PTV

1. Introduction

With the advent of several targeted therapies, selected patients with metastatic disease have now a rather long-term survival. In such cases, the remote affection

of cognition becomes a clinical concern. Consequently, brain metastases are treated with more localized and ablative, radiation techniques rather than irradiating the whole brain e.g. IMRT (Intensity-Modulated Radio-Therapy) [1]. SRS (Stereotactic Radio-surgery) is a more focused technique, which radiation oncologists currently suggest for most patients with limited brain metastases [2]. The platforms used in SRS include Gamma Knife or CyberKnife, and Linac-based SRS [1].

The target volumes of SRS usually include the GTV (Gross Tumor Volume), with an expansion into PTV (Planning Target Volume). Expanding the GTV into a PTV is still debatable. One extreme of the debate is that some studies showed no benefit from adding margin at all *i.e.* zero margin (GTV = PTV) [3]. The other extreme comprises studies that have shown benefit from expanding the GTV into PTV. Some centers expand the GTV-PTV margin as 2 mm, while others use only 1 mm as an expansion of GTV into PTV [3] [4].

In the contemporary planning process, there is always an obvious need to decrease the volume of irradiated normal brain tissue, the volume receives 12 Gy (V12) should be constrained to 10 cc [5]. Also, the geometric calculation shows that expanding a GTV of a 20 mm diameter lesion by another 2 mm peel, will produce a 74% larger PTV [6]. Such an increase in treated volume would reflect on the V12 e.g. irradiating either the GTV or PTV to 20 Gy with a dynamic arc SRS will incrementally increases V12 by one third, from 15.4 cc to 21.4 cc [7].

In this study, we explored the dosimetric differences between different GTV-PTV margins. We performed a comparison of three plan aims: no margin (PTV zero = GTV), 1 mm margin (PTV1 = GTV + 1mm) and 2 mm margin (PTV2 = GTV + 2 mm). We separately analyzed the dosimetry of the proximity brain tissue by creating two imaginary volumes. We called them peel volumes. We developed the Peel volumes from the GTV as follows: Peel1 = PTV1-GTV, Peel2 = PTV2-GTV (**Figure 1**).

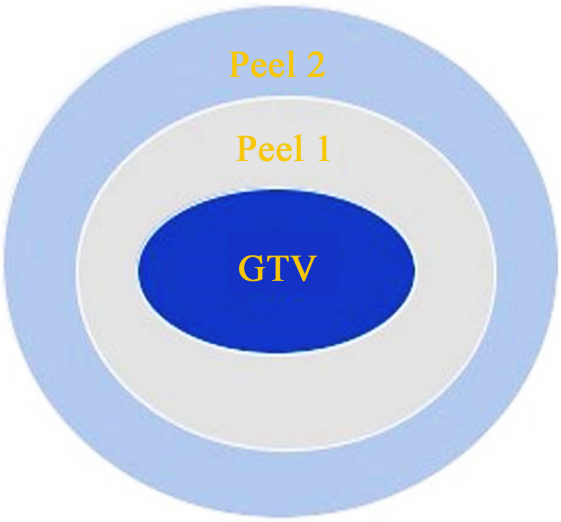

Figure 1. Peel Volumes: Peel1 = PTV1 minus GTV, |Peel2 = PTV2 minus GTV.

2. Patient and Method

We revised the plans of twenty patients with single brain metastases, from the July 2022 to October 2023 who received SRS for brain metastases at the International Medical Center (IMC) Cairo, Egypt. We described the eligibility criteria as follows:

2.1. The Inclusion Criteria

- Pathologically proven an extra cranial primary tumor;
- Brain metastases diagnosed by MRI with contrast, and have a high-definition MRI for planning;
- Single brain metastases;
- Performance status of 80% or more on Kornowski scale;
- Age more than 18 years and less than 70 years;
- Patients who can tolerate a treatment time of 20-30 minutes on a radiation machine.

2.2. The Exclusion Criteria

- No available patient file records;
- No available treatment plan of SRS;
- Patients received SRS in different institutions;
- Plans of SRS are evaluated according to different quality indices.

2.3. Fixation and Simulation

Fixation applied by a 4 mm rigid mask. As per the departmental protocol of SRS, patients uniformly had a CT brain without contrast, with 1 mm cuts. In addition, patients had a High-Definition (HD) MRI brain protocol: 1mm cuts, zero angle, and zero collimator. Then the radiation oncology team perform a supervised fusion of both images: CT brain and HD MRI brain.

2.4. Delineation

We defined the Gross Tumor Volume (GTV) as the radiologically visible tumor, contoured using image-specific window settings to maximize discrimination of the tumor from the surrounding normal tissues. We use all imaging modalities available; to guide delineation of the GTV, including the planning of CT and HD-MRI fused images. Clinical Target Volume (CTV) is the GTV with no margin for microscopic disease extension.

2.5. Dose prescription

As per the departmental practice, the dose prescription followed the classic RTOG 90 - 50 study [8]: 18 Gy for tumors < 20 mm, 15 Gy for that 21 - 30 mm, and 12 Gy for that 31 - 40 mm in maximum diameter. Universal 1 mm GTV-PTV margin applied to the actual treatment plans.

2.6. Planning

Patients received their treatment using GTV-PTV margin of 1 mm. Experimentally, we re-planned the same treatment plans, using 2 more margins, 0 and 2 mm. Therefore, for every case, we created three plans, one standard and two experimental. A standardplanaims to cover GTV + 1 mm (PTV1). The other two experimental plans are; one aims to cover the GTV only (PTV zero), and another plan aims to cover the GTV and 2 mm (PTV2). We performed all treatment plans using Eclipse v 15.6 planning system. Achieve adequate target coverage using SRS whilst sparing OARs is the aim of each treatment plan. The beam configuration may be coplanar or non-coplanar, depending on the size and location of the lesion. We performed all dose calculations using the Eclipse planning system with the Acuros algorithm. A universal plan acceptance values for coverage were applied to all three plans for each patient as follows: Coverage of PTV ≥ 95%, with other plan indices *i.e.* Conformity, Paddick, Selectivity, Gradient, all aim to approach the value of 1. Peel volumes were created from the GTV as follows: Peel1 = PTV1 − GTV, Peel2 = PTV2 − GTV (Fig 1). Then we collected the mean, max, and min isodose for the peel volumes in the created three plans.

2.7. Ethical Considerations

This review received approval from the International Medical Center Committee (Egypt Center of Research and Regenerative Medicine [E.C.R.R.M] under the Ministry of Defense) OHRP Reg. IORG0010559 - 1R800012517 (the Decision number 8/03-2022 and granted on 26/6/2022). All these approvals adhered to the ethical standards established in the 1964 Declaration of Helsinki. All individuals provided informed consent before undergoing therapy.

2.8. Statistical Analysis

A Two-Way Analysis of Variance by Ranks was performed using the Related samples Friedman's test (SPSSv20). Using this test, we examined the null hypothesis and we calculated the overall significance. As per the definition of the related samples Friedman's test, if the null hypothesis is rejected, then a paired comparison could be performed. No paired comparison could be performed if the null hypothesis is not rejected. We considered the p-value as significant if less than 0.05.

3. Results

We categorized the twenty GTV volumes: 1) according to the maximum diameter as per the RTOG 90-058, and 2) by the volume of the GTV in cc (Table 1). We found that the mean PTV1 is 6.11(SD: ±4.68), which significantly (p = 0.006) shrinks to 77% of the mean PTV2 7.88 (SD: ±5.67). Besides, using a 1 mm margin vs. 2 mm reduces the increase in the mean V12 by more than half *i.e.* 17% for PTV1: 5.45 (SD: ±2.18) vs. 37% for PTV2: 6.35 (SD: ±2.77) (Table 2). For the peel analysis, the mean isodose of Peel1 significantly (p = 0.022) in-

creased by 2% when the margin increased from 1 mm to 2 mm *i.e.* 102.99% (SD: ±2.09) vs 104.96% (SD: ±2.30). In addition, the Peel2 mean dose was significantly (p = 0.013) increased by 3% *i.e.* 98.92 (SD: ±2.38) vs. 102.85 (SD: ±5.79) (Table 3).

Table 1. GTV volume description.

Stratification of GTV Volume	GTV volume	No of patients	Prescribed Dose (Gy) (Mean)
GTV: Max diameter RTOG 90 - 50	Up to 20 mm	12	23 Gy
	21 - 30 mm	7	19 Gy
	31 - 40 mm	1	18 Gy
GTV volume categories: Volume in cc	GTV vol: Up to 1cc	5	24 Gy
	GTV vol 1.1 - 3 cc	3	24 Gy
	GTV vol 3.1 - 5 cc	6	20 Gy
	GTV vol 5.1 - 10 cc	4	19 Gy
	GTV larger than 10 cc	2	18 Gy

Table 2. PTV volume, target coverage and plan indices.

	PTV0	PTV1	PTV2	Friedman's test	
		Mean ± SD		Overall p value	Paired comparison
PTV volume	4.24 ± 3.60	6.11 ± 4.68	7.88 ± 5.67	0.000	PTV0 vs PTVl: p = 0.005 PTV0 vs PTV2: p = 0.000 PTV1 vs PTV2: p = 0.006
GTV min Isodose	94.13 ± 2.62	94.93 ± 5.20	95.90 ± 5.26	0.101	NA
GTV max Isodose	110.58 ± 3.95	111.97 ± 5.56	110.31 ± 5.00	0.392	NA
PTV Min Isodose	92.74 ± 6.61	92.24 ± 2.60	94.09 ± 3.32	0. 252	NA
PTV Mean Isodose	103.24 ± 2.46	103.84 ± 2.30	103.92 ± 2.37	0. 040	PTV0 vs PTVl: p = 0.173 PTV0 vs PTV2: p = 0.053 PTV1 vs PTV2: p = 1.000
Brain V12	4.63 ± 2.32	5.45 ± 2.18	6.35 ± 2.77	0. 000	PTV0 vs PTVl: p = 0.022 PTV0 vs PTV2: p = 0.000 PTV1 vs PTV2: p = 0.022
Conformity Index	1.03 ± 0.10	1.00 ± 0. 06	1.00 ± .049	0.170	NA
Target Coverage Ratio	0.94 ± 0.03	0.95 ± 0.02	0.95 ± 0.02	0.444	NA
Selectivity Index	0.91 ± 0.06	0.95 ± 0.042	0.95 ± 0.039	0.000	PTV0 vs PTVl: p = 0.005 PTV0 vs PTV2:p = 0.004 PTV1 vs PTV2:p = 1.000
Paddick Index	0.86 ± 0.071	0.90 ± 0.044	0.90 ± 0.047	0.002	PTV0 vs PTVl: p = 0.010 PTV0 vs PTV2:p = 0.008 PTV1 vs PTV2:p = 1.000
Gradient 50%	4.22 ± 1.07	3.64 ± 0.764	3.38 ± 0.690	0.000	PTV0 vs PTVl: p = 0.005 PTV0 vs PTV2:p = 0.000 PTV1 vs PTV2:p = 0.081
Efficiency Index	0.43 ± 0.36	0.31 ± 0.15	0.33 ± 0.57	0.000	PTV0 vs PTVl: p = 0.013 PTV0 vs PTV2:p = 0.000 PTV1 vs PTV2:p = 0.098
Homogeneity Index	1.10 ± 0.039	1.11 ± 0.046	1.103 ± 0.049	0.342	NA

NA: Not Applicable, PTV: Plan Target Volume.

Table 3. Peel1 and peel2 dosimetric.

	PTV0	PTV1	PTV2	Friedman's test	
		Mean ± SD		Overall p	Paired comparison
PEEL1 Max Isodose	105.45 ± 2.89	109.70 ± 3.37	110.84 ± 4.43	0.000	PTV0 vs PTVl: p = 0.000 PTV0 vs PTV2:p = 0.000 PTV1 vs PTV2:p = 0.618
PEEL1 Mean Isodose	92.86 ± 4.06	102.99 ± 2.09	104.96 ± 2.30	0.000	PTV0 vs PTVl: p = 0.005 PTV0 vs PTV2:p = 0.000 PTV1 vs PTV2:p = 0.022
PEEL2 Max Isodose	106.43 ± 2.36	110.71 ± 3.61	111.53 ± 4.70	0.000	PTV0 vs PTVl: p = 0.000 PTV0 vs PTV2:p = 0.000 PTV1 vs PTV2:p = 1.000
PEEL2 Mean Isodose	87.55 ± 4.61	98.92 ± 2.38	102.85 ± 5.79	0.000	PTV0 vs PTVl: p = 0.013 PTV0 vs PTV2:p = 0.000 PTV1 vs PTV2:p = 0.013

PTV: Plan Target Volume.

4. Discussion

In one of the introductions of their published study, Kirkpatrick JP *et al.*7 stated the problem of margin in SRS as follows:

"*In the absence of radiation-induced adverse events, one would select a generous expansion margin about the GTV… However, increasing the volume of tissue receiving a high dose of radiation may increase the risk of normal tissue toxicity*"

Evidently, two main justifications call for the need to expand the GTV into another relatively larger volume to be treated *i.e.* PTV. The first reason is to compensate for the sum of errors that was described originally by Herk *et al.* However, such margin described by Herk needed to be adapted to the special nature of SRS *i.e.* fewer fractions, even single fractions in most cases of brain metastases. The BIR (British Institute of Radiology) published such modifications in their last report in 2020. The fewer fractions lead to the fact that the day-to-day motion will not exist. Thus, errors will be more of systematic nature. This few number of fractions, as low as single fraction, coincides with what our study applied. All our patients received one single fraction of SRS. Thus, all the errors are systematic, and only the exception is the intra-fraction motion. The second justification is the post-mortem evidence, projected by the research of Baumert BG *et al.* [9]. They pathologically reviewed the infiltrative nature of the brain metastases in autopsy. They found that infiltration beyond the radiological border in 63% of the evaluated 45 cases. They suggested adding a margin of 1 mm to the visible lesion. This supports what the BIR stated that a zero margin would reduce the dose coverage to the target periphery due to geometrical uncertainties. The explanation is that although the PTV0 plans showed significantly better dose profiles, the discussed geometric uncertainties are against its routine use. The BIR report supported the use of a narrow margin that would be "an appropriate trade-off to ensure lower doses to normal tissue especially if sup-

ported past clinical evidence" [10]. To align with this evidence in our study, we used the zero margin (PTV zero) only as an internal control for the dosimetric comparison. Thus, the following results compared the PTV1 vs the PTV2, as compared to the internal control of PTV zero. The dosimetric analysis of the mean PTV volume shrinks by 77% when 1 mm is used as margin vs 2 mm ($p = 0.006$). Additionally, using a 1 mm margin vs. 2 mm reduces the increase in the mean V12 by more than half. This shrinkage of margin to 1 mm vs 2 mm didn't significantly influence main parameters used to evaluate the SRS plans. Such parameters include: The target coverage, the conformity index (CI), the Homogeneity Index (HI), the Selectivity Index, Paddick index, the Efficiency Index and the 50% Gradient (**Table 2**). The Peel volume dosimetric analysis showed the mean dose was significantly higher in the nearby normal brain tissue e.g. Peel 1, when a 2 mm margin is used vs 1 mm ($p = 0.022$), the same significant increase was seen in Peel2 ($p=0.013$). Nevertheless, such an increase did not extend to the max dose: Peel 1 ($p=0.618$) and Peel 2 ($p = 1.000$) (**Table 3**). Such results of our study favor the practice of use of 1 mm margin rather than 2 mm as it is it shows less delivered doses to the normal brain tissue. This comes in line with what was found by Noel *et al*. in a retrospective study that the local control after a median follow-up of two years significantly (90% vs 51%, $p = 0.0008$) improved in the group treated with GTV-PTV margin of 1 mm without a significant difference in toxicity4. Although this study sets the pavement for a successive large prospective study, it still has some limitations. The primary limitations of this study include the small sample size of 20 patients and the retrospective design. Additionally, the study population was restricted to patients with single brain metastases, which may limit the generalizability of the findings to those with multiple lesions. Furthermore, the study did not evaluate long-term clinical endpoints, such as local control or toxicity profiles, associated with the different PTV margin sizes. Prospective data collection and analysis of clinical outcomes would strengthen the conclusions drawn from this dosimetric comparison of PTV margin sizes.

5. Conclusion

According to our dosimetric analysis, expanding the GTV into a PTV by 1 mm margin is more convenient than 2 mm.

Conflicts of Interest

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

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