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Impact of Planning Target Volume Margins in Stereotactic Radiosurgery for Brain Metastasis: A Review

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Margin inclusion or exclusion remains the most critical and controversial aspect of stereotactic radiosurgery (SRS) for metastatic brain tumors. This review aimed to examine the available literature on the impact of margins in SRS of brain metastasis and to assess the response of some medical physicists on the use of these margins. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses method was used to review articles published in PubMed, Embase, and Science Direct databases from January 2012 to December 2022 using the following keywords: planning target volume, brain metastasis, margin, and stereotactic radiosurgery. A simple survey consisting of five questions was completed by ten medical physicists with experience in SRS treatment planning. The results were analyzed using IBM SPSS Statistics version 26.0. Of the 1,445 articles identified, only 38 articles were chosen. Of these, eight papers were deemed relevant to the focus of this review. These papers showed an increase in the risk of radionecrosis, whereas differences in local control were variable as the margin increased. In the survey, the response rate to whether or not to use margins in SRS, a critical question, was 50%. Margin addition increases the risk of radio necrosis. The local control rate varies among treatment modalities and cannot be generalized. From the survey, no consensus was reached regarding the use of these margins. This calls for further deliberations among professionals directly involved in SRS.

Keywords: Planning target volume, Stereotactic radiosurgery, Margins, Brain metastasis

Introduction

Brain metastases are the most common intracranial malignancies in adults, and 20%–40% of cancer patients develop this condition [1-4]. Brain metastases can be managed using whole-brain radiotherapy, surgery, or stereotactic radiosurgery (SRS). Among these options, SRS is considered the most optimal treatment with high local tumor control and less toxicity [5-9]. SRS is a minimally invasive to noninvasive method involving external beam radiation therapy based on the principle of using a focal technique to deliver high doses of radiation into one or few fractions using multiple convergent beams of high-energy photons to a distinct target volume while sparing healthy surrounding tissues [10-12]. To deliver ablative doses of radiation to brain targets, SRS requires precise placement and immobilization. In the era of fractionated SRS using both linear accelerator (LINAC) and gamma knife (GK) radiosurgery, inter- and intrafraction uncertainties are becoming increasingly critical [2,13,14].

Local control depends both on the dose supplied and the margin to the therapeutic target volume [15]. The margin is typically attributed to planning/treatment delivery uncertainties, such as setup, imaging, and target contouring. Planning target volume (PTV) can be determined by expanding the clinical target volume (CTV) margin [16,17].

A PTV margin can be added to the CTV to prevent geographic misses and allow for geometric errors in radiation therapy [17]. Contrastingly, conventional SRS involves rigid immobilization fixation of a single fraction with GK using a 0 mm PTV with no margin, similar to surgical excision of brain targets [18,19]. Previous studies have reported contradictory results for using the PTV margin to account for geometric uncertainty. Noël et al. [20] selected a PTV margin of 1 mm for SRS and found that this improved local control without affecting complication rates. Nataf et al. [21] conducted a similar clinical study with 93 metastases cases treated using a 2 and 0 mm PTV margin on a LINAC-based SRS. They showed a 19.6% and 7.1% severe risk of necrosis, respectively, with no impact on local control. As increasing PTV margins significantly impacts the volume of a normal brain and results in a dosage linked with the risk of radio necrosis, these margins should be optimized. Although these papers provide sufficient insight, they were published before 2010.

Target expansion for SRS is a novel procedure; hence, its potential negative impacts must be thoroughly examined. In addition to correcting for systematic and random uncertainties, the process of PTV margin expansion may have additional effects on the irradiated volume, risk of radiation necrosis, and overall treatment time [22-24]. Considering this, this review evaluated the impact and consensus of adding PTV margins during radiosurgery of brain metastases.

Methods

A literature search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted using the PubMed, Science Direct, and Embase databases of the National Library of Medicine. The key search phrases used were planning target volume, margin, stereotactic radiosurgery, and brain metastases. At least three keywords were used and separated by AND. The search was restricted to articles in English published between January 2012 and December 2022. Initially, the articles were evaluated using information extracted from their titles and abstracts. Whenever necessary, complete papers were collected for further evaluation. Other potential articles were included using the references of the selected papers. The main inclusion criteria were that the studies must precisely define the impact of the PTV margin on SRS for brain metastases and be published within the timeframe. We omitted review papers, abstracts, and case reports.

A questionnaire with five questions was drafted on specific sections related to margin addition for treating brain metastases with SRS. Ten medical physicists experienced in SRS treatment planning completed it. The results were analyzed using the IBM SPSS Statistics version 26.0 (IBM Corp.) using simple bar graphs and descriptive statistics.

Results

We identified 1,445 publications based on the initial search results using the keywords mentioned above. Of these, 38 articles were chosen for further review based on their titles and abstracts. After further scrutiny, only eight full-text research papers were found to fulfill the inclusion criteria of this study. The process of selecting the papers was conducted in accordance with the PRISMA guidelines (Fig. 1) [25]. The references of the articles chosen did not yield any more papers. Table 1 shows the characteristics of each paper.

Of these eight articles, four were LINAC-based, three involved GK and only one was conducted with the CyberKnife. Ma et al. [26] were the first to assess the impact of millimeter margin addition using GK. They used the radiation necrosis incidence model developed by Flickinger to investigate the effects of different margins used in GK-SRS. A set of margins ranging from 0.5 to 3.0 mm was theoretically analyzed. This study revealed that using a 2-mm margin, on average, increased the 12 Gy volume by 55%±16%. This correlated to a higher necrosis rate between 6% and 25%. Only one of the 15 lesions investigated in this study was below 1 cm in diameter. Treating lesions below 1 cm in diameter has a low risk of radionecrosis [19]. Feuvret et al.

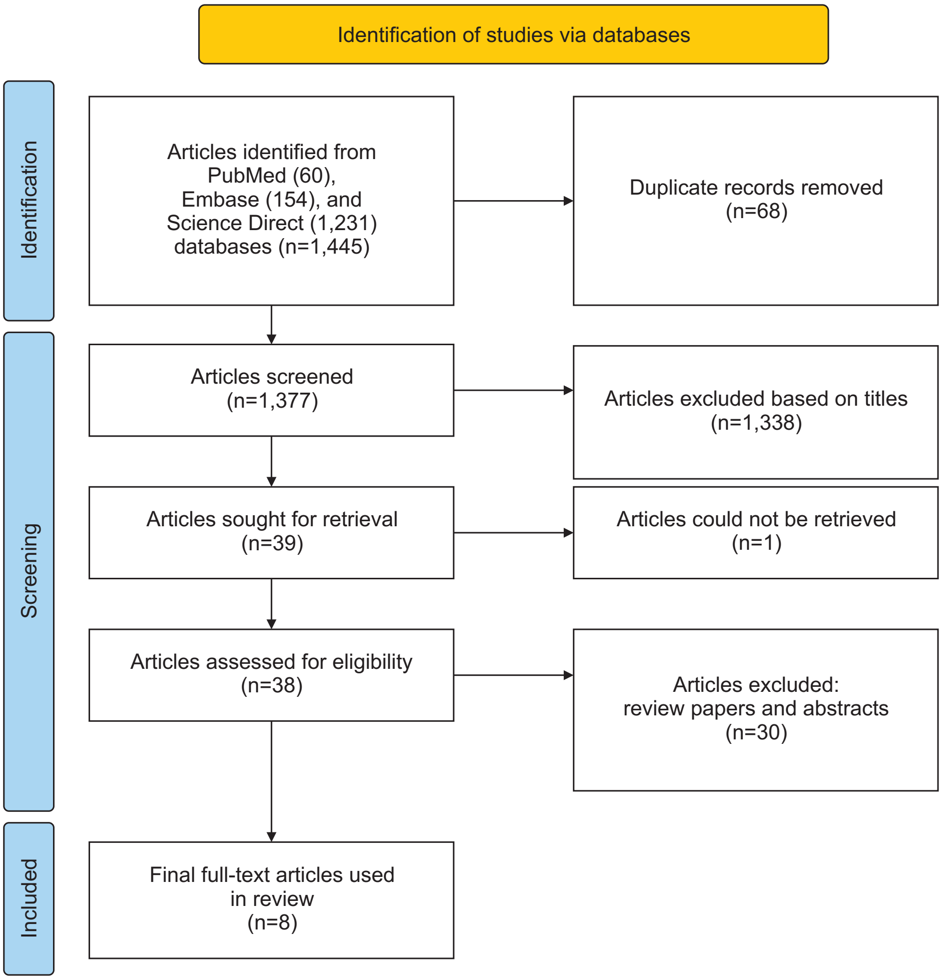

Fig. 1. Summary of the PRISMA flow [25].

[27] conducted GK radiosurgery with 24 brain metastases using a margin of 1 mm. They found that the local control rates achieved for 6 months, 1 year, and 2 years were 68%, 58%, and 48%, respectively, while regarding toxicity, acute grade 1–2 occurred in 6 patients and late grade 2 in only 1 patient.

Jhaveri et al. [17] also investigated the impact using a 1 mm margin compared to that over 1 mm on 133 patients with resected brain metastases in a LINAC-based SRS. They found statistically significant symptomatic radionecrosis rates in the group with >1 mm margin than those with 1 mm margin (26.6% and 20.9% and 9.1% and 6.0%, P=0.028) for 1 and 2 years, respectively. This study showed no improvement in local control when the PTV margin was increased beyond 1.0 mm, although the risk of symptomatic radionecrosis increased.

In a retrospective study, Sneed et al. [28] treated 2,200 lesions in 435 patients with a dose of 20 Gy without a margin on the GK. They reported a one-year likelihood of severe radiation effects of 1% or less and a median patient survival time of 17.4 months. A prospective randomized trial by Kirkpatrick et al. [29] identified 80 metastases in 49 patients and used a PTV margin of 1 or 3 mm. Although they found no differences between the two cohorts regarding local control, the cohort with the 3 mm margin had an increased incidence of radionecrosis.

The only dosimetric study found was by Agazaryan et al. [30]. They created 48 treatment plans using the Elements Multiple Brain Mets (Brainlab) treatment planning software for SRS with various margins of 0, 1, and 2 mm on eight patients with multiple targets. Upon assessing the impact of the margins dosimetrically on V5, V8, V10, and V12 Gy, they found that these volumes significantly increased by a factor of 2 and 3 when the margin was increased from 0 to 1 mm

Table 1. Characteristics of the eight articles included in this study

Reference	Treatment modality used	No. of brain metastases	PTV margin (mm)	Treatment regime	Key finding
Feuvret et al., 2014 [27]	Gamma knife	24	1	14 Gy in a single fraction	For 6 months, local control achieved was 68%, for 1 year 58%, and for 2 years 48%, while regarding toxicity, the acute grade 1–2 was seen in 6 patients. Late grade 2 in only one patient
Ma et al., 2014 [26]	Gamma knife	15	0.5–3.0	18 Gy in a single fraction	Caution must be applied when adding margins because margins beyond the GTV adversely affect normal brain sparing
Sneed et al., 2015 [28]	Gamma knife	2,200	0	20 Gy in a single fraction	Less than 1% of toxicity in a year
Kirkpatrick et al., 2015 [29]	LINAC	80	1, 3	15–24 Gy	No significant in local control between the two margins used, but 3 mm showed increased toxicity
Badloe et al., 2021 [15]	LINAC	121	0, 2	21 Gy in a single fraction (0 mm) 8 Gy in three fractions (2 mm)	Local control rates were similar between the 22 and 0 mm margin sets (82% vs. 79%, *P*=1, respectively)
Choi et al., 2012 [31]	CyberKnife	112	2	20 Gy in a single fraction (12–30 Gy in 1–5 fractions)	The local control was enhanced with the 2-mm margin without increasing toxicity compared with the 0-mm margin. There was also no difference in survival rates
Jhaveri et al., 2018 [17]	LINAC	133	1	Based on the Radiation Therapy Oncology Group (RTOG) 9005 Protocol	A PTV margin beyond 1 mm appears to increase the risk of radionecrosis but is not associated with improved local control
Agazaryan et al., 2021 [30]	LINAC	8	0, 1, 2	16–18 Gy	When margins were increased from 0 to 1 mm and from 0 to 2 mm, the volume receiving V12 Gy approximately doubled and tripled, respectively

PTV, planning target volume; LINAC, linear accelerator; GTV, gross tumor volume.

and from 0 to 2 mm, respectively. Based on these findings, they switched their institutional protocol to using margins from 2 to 1 mm, with a future goal of reducing it further.

Choi et al. [31] discovered that adding a 2 mm margin around the postsurgical cavity of brain metastasis for SRS enhanced local control without toxicity compared to that without any margin. Similarly, Badloe et al. [15] found that the local control rate was almost the same between the 2 and 0 mm margin sets (82% vs. 79%, *P*=1, respectively).

Figs. 2 and 3 summarize the responses of the ten medical physicists experienced in treating and planning SRS. With a 100% response rate, the most controversial questions that did not have consensus were those involving the addition of CTV expansion margin to the gross tumor volume (GTV) and the use of CTV-PTV margins in the treatment. Five of the ten physicists, representing 50%, responded that the maximum and optimal margin expansion should be limited to 1 mm. Moreover, in Fig. 3, the lack of response to using 1.5 mm as an optimal PTV margin might be because a 1.5-mm PTV margin is difficult to create when using the LINAC-based SRS treatment planning system.

Discussion

In this review, the impact of the inclusion or exclusion of PTV margins was assessed. We also conducted a simple survey among ten medical physicists regarding the use and optimal PTV margin during SRS treatment planning for brain metastasis. In the radiation oncology community, margins are traditionally added to the CTV during treatment planning to compensate for geometrical uncertainties [32-34]. The ICRU 91 Report recommends using a stringent definition of target volumes (GTV, CTV) by critically reviewing the imaging modalities [35]. With the growing use

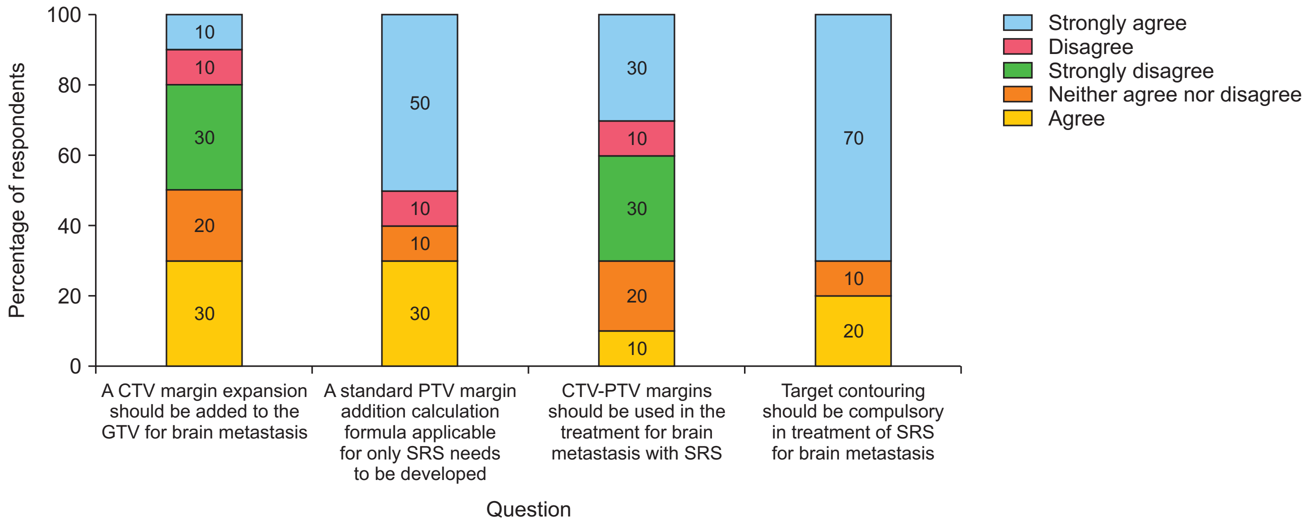

Fig. 2. Graphical response of respondents for four of the questions. CTV, clinical target volume; GTV, gross tumor volume; PTV, planning target volume; SRS, stereotactic radiosurgery.

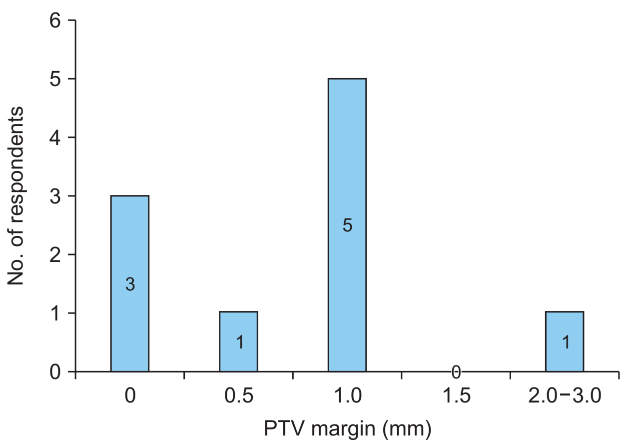

Fig. 3. Bar graph distributions of respondents' answers to the fifth question: what the maximum and optimal planning target volume (PTV) margin should be to be accepted and applied in stereotactic radiosurgery treatment?

of SRS for managing brain metastases, clinicians, especially those using a GK for treatment, do not add any margins to the GTV/CTV to form a PTV [36]. These differences in the use of margins among centers treating patients with SRS globally might make clinical trials difficult. Furthermore, the studies specifically reporting the impact of PTV margins during SRS are insufficient, consistent with that shown by Badakhshi et al. [37]. Only eight relevant studies conducted from January 2012 to December 2022 investigating the impact of adding PTV margin during SRS of brain metastases were included.

Although the GK is the gold standard for brain metastasis management, other common treatment modalities include LINAC-based systems and the CyberKnife [38]. Most of the studies included in this review involved LINAC-based systems, suggesting the increased use of these systems. Pudsey et al. [39] also found an increase in using LINAC-based systems for SRS.

Although these treatment modalities are linked with some delivery uncertainty, it is critical to consider imaging accuracy, patient setup uncertainties, and immobilization devices when determining the margin to be used. During commissioning, equipment limits need to be characterized, considering the degree of likely geometric errors for a quality assurance program [40,41]. Plan verification and routine end-to-end tests, if mandatory, need to be performed to ensure that the prescribed dose is correctly given to the exact target [42].

Based on the eight studies reviewed, we can deduce that including margins increases the target volume, directly impacting two main parameters: the risk of radionecrosis and tumor control. Radionecrosis is a late side effect, and its clinical presentation differs depending on the affected area of the brain [23]. This risk increases linearly with increasing margin, but the percentage change seems very high when a margin ≥2 mm is used compared to those without a margin [43,44]. These differences were lower in the studies involving GK.

For example, if the volume of a target is 0.268 cc, after adding a margin of 1 mm, it becomes 0.524 cc, doubling the volume. If an equal prescribed dose is applied to these two targets, there will be increased exposure to the normal brain in the one with an increased margin, escalating the risk of radiation necrosis [19]. This may be especially significant when several lesions are closely treated in the same session. Although the absence of a PTV margin in treatment delivery might indicate inadequate coverage of the tumor and an increased risk for treatment failure, it might provide adequate local control [18,24,45].

Lawrence et al. [22] discovered a higher manifestation of radiation necrosis on the corpus callosum and brain stem. Further, their analysis confirmed that the risk of complications increases with target volume size and that toxicity increases rapidly when V12 is >5–10 cm^3. These results demonstrate that radionecrosis development is significantly influenced by the volume of the brain receiving 12 Gy [43]. Therefore, considering the impact of increasing PTV margins on this parameter is crucial, as outlined by the studies shown in Table 1.

PTV margins can significantly impact the local control during SRS of brain metastases. As the target volume increases, the amount of radiation dose needed to achieve local control increases geometrically [29]. Studies using LINAC systems showed no significant differences in the local control rates between SRS with and without margins. However, in studies involving a CyberKnife, the local control rate was higher when a margin of 2 mm was used compared to those without margins. GK radiosurgery also results in higher local control. Therefore, the local control rate varies among the three modalities and cannot be generalized.

There was no consensus among the responses from the ten medical physicists with experience in SRS regarding the addition of either GTV-CTV or CTV-PTV margins during SRS of brain metastases. The response to adding margins by 50% of the physicists (5/10) was similar to that of a survey by Grishchuk et al. [19]. This survey was completed by 14 members of the International Stereotactic Radiosurgery Society guidelines committee. In this paper, 50% strongly disagreed with a CTV expansion to the GTV, which remains controversial in the SRS community. An International Organization for Medical Physics (IOMP) webinar titled CTV-PTV margins in SRS: "Do we need them?" which was delivered in June 2021 by a senior Physicist of the Icon Cancer Centre, Gold Coast, Queensland in Australia, also demonstrated no consensus among participants who completed a simple survey [46]. From Fig. 3, 50% of the participants agreed to a maximum and optimal of 1 mm to be added. This aligns with the findings by Minniti et al. [47], who evaluated 31 patients with 204 brain metastases planned with single isocenter multiple target dynamic conformal arc SRS from October 2016 to September 2018 and recommended using a 1-mm GTV-to-PTV margin. Furthermore, many SRS centers in the United Kingdom use 1 mm as the maximum PTV margin [48]. This was contrary to the 2 mm margin commonly used by many SRS centers in Australia and New Zealand [39]. Due to the lack of consensus regarding this aspect of SRS treatment for brain metastasis, there is an opportunity to develop recommendations through clinical trials. Therefore, the use of PTV margins should be carefully considered during SRS to avoid potential adverse impacts on patients when a larger treated volume is used. To minimize therapeutic complications caused by margin usage, techniques such as changing the prescribed dosage or increasing the fractionation can be used [49].

Conclusion

From this review, the addition of PTV margin, a novel concept in SRS treatment, was shown to increase the treated volume linearly, thus increasing the volume receiving the amount of 12 Gy delivered using either the GK, CyberKnife, or LINAC system. This also increases the risk of radionecrosis. The local control rate varies among the three treatment modalities and cannot be generalized. Furthermore, no consensus was reached regarding margin use in SRS, although some advocate that it should be applied cautiously. This calls for further consultation among a large group of professionals directly involved in radiosurgery treatment for brain metastases.

Limitations

The limitation of this review includes the possible exclusion of studies written in languages other than English as we only incorporated English-language primary research.

Another limitation is the small number of medical physicists who participated in the survey.

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Conflicts of Interest

The authors have nothing to disclose.

Availability of Data and Materials

All relevant data are within the paper and its Supporting Information files.

Author Contributions

Conceptualization: Emmanuel Fiagbedzi, Francis Hasford. Data curation: Emmanuel Fiagbedzi, Samuel Nii Tagoe. Formal analysis: Emmanuel Fiagbedzi, Francis Hasford, Samuel Nii Tagoe. Writing – original draft: Emmanuel Fiagbedzi, Francis Hasford. Writing – review & editing: Emmanuel Fiagbedzi, Francis Hasford, Samuel Nii Tagoe.

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