Radioterapi & Onkologi Indonesia
Journal of the Indonesian Radiation Oncology Society

Patients Outcome with Brain Oligometastases Treated with the SIB-IMRT Technique: Dr. Kariadi General Hospital Experience

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Article informations:

Received: December 2021

Accepted: January 2022

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Abstract

Brain metastases are often considered as the end of life in oncologic diseases. Previously, Whole Brain Radiotherapy (WBRT), with or without radiosurgery, had been the standard of care in the case of single or multiple lesions. Currently, Simultaneous Integrated Boost - Intensity Modulated Radiotherapy (SIB-IMRT) permits the delivery of simultaneous doses within a single therapy to the whole brain and the local lesion. This study summarizes the outcome in cancer patients with brain oligometastases that were treated with the SIB-IMRT technique. Between April 2020 and April 2021, a total of 29 brain oligometastases patients were treated with the SIB-IMRT technique at Dr. Kariadi General Hospital. Twenty patients completed treatment with a whole-brain dose of 37.5 Gy and tumor dose of 45 Gy, both in 15 fractions. Among fifteen who were successfully complete all the radiotherapy session, ten survived at the 6th-month of follow-up time. Four out of ten participants who acquired complete data measurement were included in this study. All four patients improved clinically. Evaluation from imaging revealed mass reductions in two patients, while one patient's metastases were progressing, and the other one showed no changes. Additionally, no patients demonstrated cerebral necrosis as a late side effect.

Keywords: brain metastases, radiotherapy, SIB-IMRT, patient outcome

Introduction

Brain metastasis remains a significant complication faced by cancer patients, with a profound impact on quality of life.[1] Despite its significance, there are still no precise data regarding its incidence and prevalence.[2] A review in 2012 mentioned an older Dutch study that found 8.5% of patients in a neuro-oncology registry spanning ten years were diagnosed with brain metastases.[3] Another review in 2013 noted a population -based study approximated brain metastases' incidence rate reaching 10 per 100,000 (0.01%) individuals.[4] Most recent review in 2020 estimates stated that up to 100,000 patients are diagnosed with brain metastases annually in the United States.[2] These numbers will keep increasing with improved neuroimaging technologies and physicians' and patients' awareness. For example, a Sweden population-based study found that the incidence of brain metastases doubled from 7 in 100,000 to 14 in 100,000 between 1987 and 2006.[5] On the other hand, at Dr. Kariadi General Hospital, there have been 197 (3.17%) cases of brain metastases between 2019 up to October 2021. Given the number of cases in our institution, evaluating how we treated these patients is necessary.

Often regarded as the final stage in the course of oncologic diseases, treatment options for brain metastases are limited. According to a 2020 consensus by the European Society for Radiotherapy and Oncology (ESTRO) and the American Society for Radiation Oncology (ASTRO), oligometastases are often described as the presence of one to three or five metastatic lesions.[6] The prognosis of patients with oligometastases largely depends on the primary site, key factors, and treatment received.[7] Moreover, the median survival is generally worse than patients with a

single metastasis.[8] Whole-brain radiotherapy (WBRT) had long been the standard of care in brain oligometastases, at times with the addition of radiosurgery and other adjunctive such as radiosensitizers, chemotherapy, or molecular-targeted therapy. WBRT has a high rate of failure in local control when given alone.[9] Furthermore, SRS plus WBRT has been shown to worsen the neurocognitive outcome and produce a lesser quality of life in patients.[10, 11] Although, SRS plus WBRT failed to show a survival benefit over treatment with WBRT alone. Nonetheless, SRS alone has risen as the preferred choice in the scenario of brain oligometastases, due to the better neurocognitive outcomes and performance status.[9]

One of the concerns in using radiotherapy for the central nervous system (CNS) is the side effects. Radiotherapy-related side effects in the CNS are divided into early (acute), early-delayed, and late.[12] Cerebral necrosis is considered to be a late side effect. Even with that definition, cerebral necrosis may occur as early as in 3 months, and as late as in 10 years.[13, 14] Necrosis can be seen using Magnetic Resonance Imaging (MRI) as increased contrast enhancement in T1-weighted images and vasogenic edema in T2-weighted images.[13] CT scans can also help to confirm that the abnormality found was included in the radiation port.[15] Generally, the consequences present as neurological deterioration or impairment. Moreover, cerebral necrosis is more likely to occur with higher fractional doses.[16] Cerebral necrosis (radionecrosis) was included in the definition of the Radiation Therapy Oncology Group (RTOG) CNS Grade 4 toxicity. Protocol 90-05 demonstrated that by escalating the dose of single fraction radiosurgery, the incidence of chronic toxicity also increased. In tumor size under 30 mm, a dose of 21 Gy had the highest percentage of patients with chronic toxicity (≤20 mm: 11%; 21-30 mm: 31%). Above 30 mm and under 40 mm, a dose of 18 Gy caused the highest number of chronic toxicity (33%).[17] Nonetheless, the dosage, safety, and advantage of SIB-IMRT in the form of higher overall survival (OS) rate have been demonstrated in recent literature.[18, 19] One prospective trial named "ISIDE-BM -1" investigated the maximum tolerated dose of SIB-IMRT for patients with <5 brain metastases, using a standardized linear accelerator. This study showed that delivering 30 Gy whole-brain and 50 Gy boost doses divided into ten daily fractions is tolerable, with no late toxicity noted.[20] However, the efficacy in the form of local control (LC) has not been established, as phase II of the trial (ISIDE-BM-2) is still in progress. Another retrospective study looked at the efficacy of SIB-IMRT in non-small cell lung cancer (NSCLC) with 1-7 brain metastases and showed that acute toxicities are rare.[21] Nonetheless, long-term toxicities were recorded in

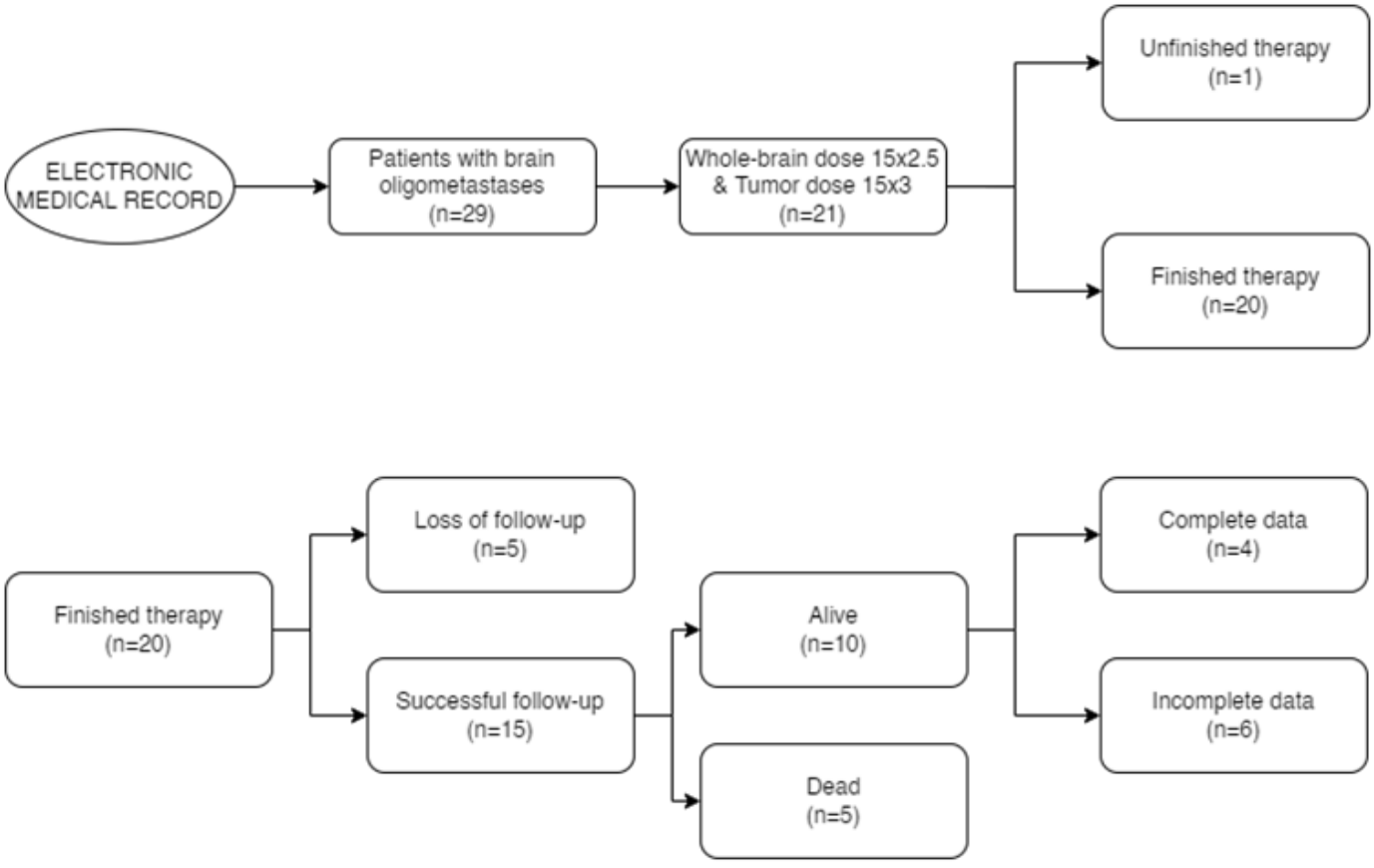

Figure 1. Flowchart of patients' inclusion and exclusion

several patients, notably, memory loss and hearing problems. Note that this study differs from the ISIDE-BM-1 trial in the dose given, in which the whole-brain dose was 37.5 Gy in 15 fractions and dose was 52.5 Gy in 15 fractions.

This paper aims to report of cases in which patients with oligometastases were treated with SIB-IMRT. Hence, we summarize our experience at Dr. Kariadi General Hospital in treating patients with brain oligometastases using the SIB-IMRT technique and their eventual outcomes.

Methods

This study is a retrospective, and non-randomized case series, conducted at Dr. Kariadi General Hospital. We included patients between April 2020 and April 2021 with brain oligometastases treated with SIB-IMRT. In total, there were twenty-nine patients within that period. Twenty-one patients were treated with a whole-brain dose of 37.5 Gy and dose of 45 Gy, both divided into 15 fractions. Twenty patients succeeded in finishing the treatment, and from those we were able to follow-up fifteen patients. Among the fifteen patients, ten were alive at the 6th-month follow-up, and four of them had a complete data to be presented as case series. Last, cerebral necrosis as a late side effect and metastatic lesion progression was evaluated from MRI and CT-scan.

Results

Fifteen patients who were successfully followed up were comprised of six males (40%) and nine females (60%) (**Table 1**). The primary cancer types present are lung (46.67%), breast (40%), bladder (6.67%), and thyroid (6.67%). Among those fifteen patients, ten survived, and five were dead in six months after radiotherapy. The summary of patients' outcomes and the series of cases are outlined in **Table 2** and **Table 3.**

Table 1. Summary of patients' characteristics

N = 15	
Gender	
Men	6 (40%)
Women	9 (60%)
Primary Cancer	
Breast Cancer	6 (40%)
Lung Cancer	7 (46.67%)
Bladder Cancer	1 (6.67%)
Thyroid Cancer	1 (6.67%)
Outcome (6 months post-therapy)	
Survived	10 (66.67%)
Died	5 (33.33%)

Discussion

The most common organs primary cancers frequently metastasize in the brain are breast, skin melanoma, renal, and colorectal.[8] Indeed, the most frequent primary cancer found among our patients in this study were breast (40%) and lung origin (46.67%), with the percentage of patients alive after six months being 71.4% and 40%, respectively. Indeed, a review in 2012 mentioned that the most common primary cancers that metastasize to the brain are lung cancer, breast cancer, and melanoma, which account for 67%-80% of brain metastases.[22] The same review also discussed the higher prevalence of brain metastases in men than women and argued it might be due to the higher prevalence of lung cancer in men. More women than men in the included patients; however, the overall higher prevalence of lung cancer still stands.

In the case of brain oligometastases, several studies agreed that SIB offers a better OS than WBRT alone, especially with its smaller fractional dose.[18, 19, 23] Tiwari and colleagues used 30 Gy in 10-12 fractions for the whole brain and 36-40 Gy in 12-15 fractions for the metastatic lesions.[18] This dosage translates into roughly the same fractional doses we delivered, although with lower total doses. In their study, the primary cancers

Table 2. Summary of outcome in patients with complete data

N = 4	
Clinical Status	
Improved	4 (100%)
Worsenede	0 (0%)
No changes	0 (0%)
Tumor size	
Mass reduction	2 (50%)
No changes	1 (25%)
Progressive	1 (25%)
Cerebral Necrosis	
Present	0 (0%)
Not Present	4 (100%)

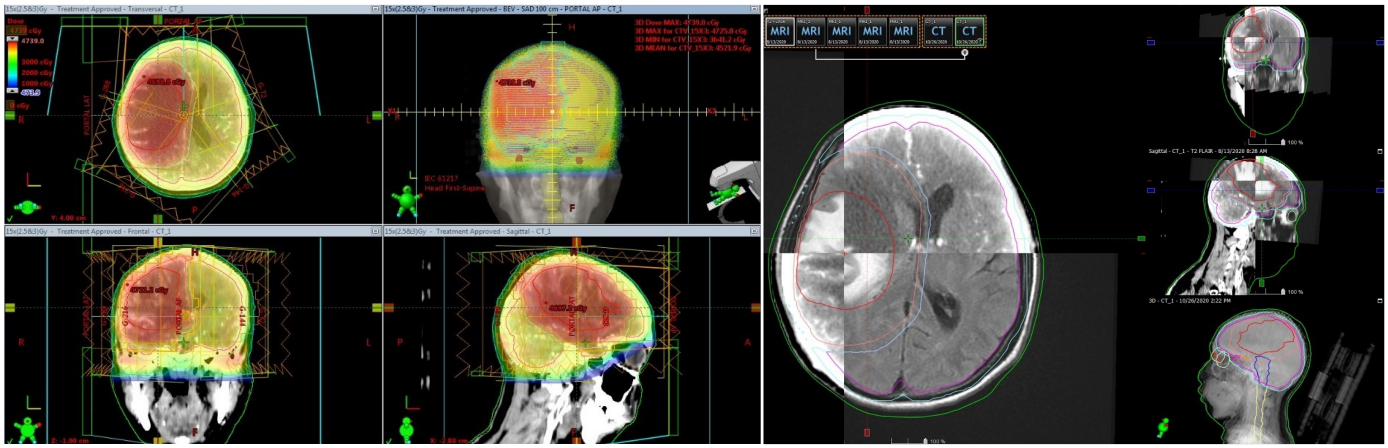

Figure 2. (Left) Planning and (Right) contouring of radiotherapy in patient AN.
The contouring picture shows a fused image of CT and MRI view

were breast and lung. The outcomes were evaluated from imaging, and the results were mass reduction in 82% of patients, 5.9% with progressive tumor growth, and 11.76% with no changes. On the other hand, the ISIDE-BM-1 trial resulted in 11% of patients showing a complete response, 67% with partial response, 22% with no changes in the metastatic lesions, and zero patients with progressivity.[20] Compared with WBRT alone, phase III results of RTOG 9508 showed that at 3 months follow up, 36% experienced a mass reduction, 13% had stable disease, and 10% had mass progression.[24] Although, in the same trial, SRS plus WBRT showed a smaller percentages of stable disease and progressivity, and a higher percentages of mass reduction.

A study by Shao *et al*. gave a total whole-brain and tumor dose of 39.6 Gy and 55 Gy, respectively, divided into 22 fractions, to twenty-six patients.[25] There was no cerebral necrosis seen among all patients, yet acute side effects were still often seen. Those side effects were grade 1 and 2 RTOG CNS toxicity, acute radiation-induced hydrocephalus, and radiation-induced pneumonia. However, most acute side effects improved after treatment, with the median survival time for SIB being 36 months. Another study by Lars *et al.* retrospectively analyzed the incidence of cerebral necrosis in 340 patients treated with SRS alone or WBRT plus SRS in the span of 10 years.[26] The dose of SRS was performed according to the maximum dose demonstrated in the RTOG 9005. With the same WBRT as our study, both SRS and SRS plus WBRT showed the presence of cerebral necrosis in a small percentage of patients. These studies demonstrated the advantage of using SIB in reducing fractional dose and treatment time, thus diminishing late side effects, and improving patients' survival. All that is in exchange for a higher total dose and acute side effects, which in most cases can be managed with pharmacological modalities. Moreover, the proportion of patients developing cerebral necrosis smaller in SIB than in

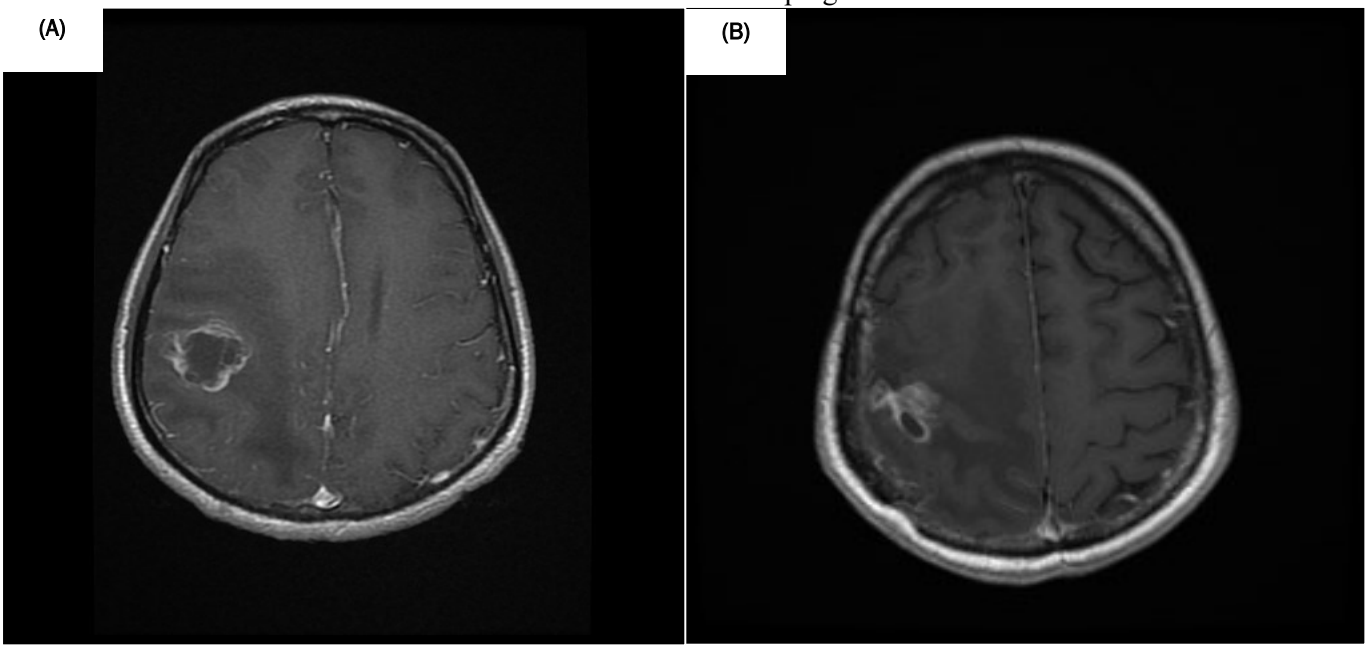

Figure 3. (A) Pre-radiation and (B) six-month post-radiation brain MRI scan of patient AN,
showing a reduction in size of the metastatic lesion

Tabel 3. Case Series Summary

	1st Patient	2nd Patient	3rd Patient	4th Patient
Gender	Female	Female	Male	Male
Primary Cancer	Invasive Ductal Carcinoma	Paget's Disease with Intraductal Carcinoma	Papillary Adenocarcinoma	Papillary Adenocarcinoma
Immunohistochemistry	ER (-); PR (-); HER2 (+3); Ki67 >20%	ER (-); PR (-); HER2 (+1)	EGFR (+) Exon 21 mutation; GFAP (-); Cytokeratin (+); CK20 (-); CK7 (+); TTF1 (+); Napsin A (+)	CK20 (-); CK7 (+); TTF1 (+); Napsin A (+)
Pre-radiotherapy KPS	40	60	50	50
Post-radiotherapy KPS	60	60	70	80
Clinical status pre-radiotherapy	Occipital headache; Nausea and vomiting; Bedridden; Low appetite Using wheelchair;	Headache; Nausea and vomiting; Sleeping difficulty; Using wheelchair;	Severe headache; Vomiting; Left hemiparesis; Left hemiparesthesia; Left facial droop;	Headache; Epigastric pain; Seizure; Right hemiparesis;
Clinical status post-radiotherapy	Intermittent headache; Using wheelchair;	Headache; Sleeping difficulty; Upper-back pain (VAS 2); Using wheelchair;	No headache; No vomiting;	Improved headache; Improve right-sided muscle strength; Numb feeling in occipital
Clinical status at 6 months' post-radiotherapy	Compos mentis; No complaints; KPS 90;	Compos mentis; KPS 90;	Worsening left-sided muscle strength; KPS 70;	Post-chemotherapy; No nausea and vomiting; Lip-twitching; KPS 80;

Table 4. Comparison of Local Control

	Tiwari *et al.* (2015)	ISIDE-BM-1 (2017)	Dion *et al.* (2021)	Phase III RTOG 9508	
N	**19**	**30**	**4**	**135**	**135**
Dose	WBRT 30 Gy/10-12 Fr; SIB 36-40 Gy/12-15 Fr	WBRT 30 Gy/10 Fr; SIB 35-50 Gy/10 Fr	WBRT 37.5 Gy/15 Fr SIB 45 Gy/15 Fr	WBRT 37.5 Gy/15 Fr	SRS according to RTOG 9005 + WBRT
Local Control					
No changes	11.76%	22%	25%	13%	8%
Progressive	5.9%	0%	25%	10%	6%
Mass reduction	82%	11% (complete response) 67% (partial response)	50%	5% (complete response); 31% (partial response)	9% (complete response); 32% (partial response)

SRS alone or SRS plus WBRT.

The side effects of radiotherapy specific to the brain can be divided into acute, sub-acute, and late. These injuries commonly manifest as acute edema due to capillary leakiness and cerebral necrosis caused by direct injury to oligodendrocytes and endothelial cell damage.[16] Edema occurs almost immediately, while necrosis may arise after 3-6 months.[13] These generally present as cognitive and neurosensory impairments. Indeed, a lower radiation dose has been reported to possess a better cognitive outcome than a high dose.[13] It is known that radiation as low as 50 Gy could induce damage. Furthermore, risk escalation of cerebral necrosis is linked to higher fractional doses.[16] Predictability of its incidence in fractionated dose <2.5 Gy with biologically effective dose (BED) of 100-140 Gy is 5% and 10% with BED of 140-170.[27] The mechanism on how it occurs has been reviewed thoroughly in literature and outside the scope of this study.

A consequence of inflammatory response may occur sub-acutely, a term called *pseudoprogression*. The definition and clinical diagnosis of pseudoprogression highly vary between authors. It can be considered as a new enlarged area of contrast agent enhancement in the absence of tumor growth, which will dwindle without intervention.[28] One review mentioned that around 23% of patients would experience true pseudoprogression within a month of radiotherapy.[29] This phenomenon could potentially explain patients in this case series whose imaging demonstrated tumor progression yet improved clinically or decreased tumor size in subsequent imaging. A phase 1 trial ISIDE-BT-1 performed study using IMRT with concurrent and sequential delivery of temozolomide in patients with glioblastoma. Out of 15 patients, no pseudoprogression was observed at 3 months' follow-up. Another report by Cha *et al.* mentioned a 25% occurrence of pseudoprogression among malignant gliomas patients treated with SIB-IMRT at 3 months follow up. Due to the difficulty and the necessity of biopsy to prove true progression from pseudoprogression, it is essential to observe the tumor response continuously.

Conclusions

Our study summarizes the experience of Dr. Kariadi General Hospital in treating patients with brain oligometastases using SIB-IMRT with a whole-brain dose of 37.5 Gy and tumor dose of 45 Gy, both given in 15 fractions. The survival rate in our case series is 66.67% (10 out of 15) six months post-therapy. All of the patients did not develop cerebral necrosis. Among four patients with complete data, all improved clinically. In addition, one patient (25%) showed progressivity of the metastatic lesions on imaging, with one patient's (25%) imaging remaining the same, while the last two (50%) had a size reduction. However, the certainty of tumor progressions being true progression or pseudoprogression remains elusive to us, as the gold -standard proof would require biopsy. Here, we demonstrated the advantage, safety, and outcome of using SIB-IMRT with a smaller fractional dose.

WBRT can be given concurrently with chemotherapy in brain metastatic GTN cases. Higher total dose is associated with higher 5-year local control rates.

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Table 5. Comparison of Cerebral Necrosis after Treatment

	Shao *et al.* (2018)	Dion *et al.* (2021)	Lars *et al.* (2014)	
N	**26**	**4**	**111**	**102**
Dose	WBRT 40 Gy/22Fr SIB 50 Gy/22 Fr	WBRT 37.5 Gy/15 Fr SIB 45 Gy/15 Fr	SRS according to RTOG 9005	SRS + WBRT 35-37.5 Gy/14-15 Fr
Cerebral necrosis				
Present	0%	0%	4.5%	2.9%
Not present	100%	100%	95.5%	97.1%

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