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CLINICAL STUDY

Comparison of two-stage Gamma Knife radiosurgery outcomes for large brain metastases among primary cancers

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Abstract

Purpose Stereotactic radiosurgery (SRS) is typically considered for patients who cannot undergo surgical resection for large (> 10 cm^3) brain metastases (BMs). Staged SRS requires adaptive planning during each stage of the irradiation period for improved tumor control and reduced radiation damage. However, there has been no study on the tumor reduction rates of this method. We evaluated the outcomes of two-stage SRS across multiple primary cancer types.

Methods We analyzed 178 patients with 182 large BMs initially treated with two-stage SRS. The primary cancers included breast (BC), non-small cell lung (NSCLC), and gastrointestinal tract cancers (GIC). We analyzed the overall survival (OS), neurological death, systemic death (SD), tumor progression (TP), tumor recurrence (TR), radiation necrosis (RN), and the tumor reduction rate during both stages.

Results The median survival time after the first Gamma Knife surgery (GKS) procedure was 6.6 months. Compared with patients with BC and NSCLC, patients with GIC had shorter OS and a higher incidence of SD. Compared with patients with NSCLC and GIC, patients with BC had significantly higher tumor reduction rates in both sessions. TP rates were similar among primary cancer types. There was no association of the tumor reduction rate with tumor control. The overall cumulative incidence of RN was 4.2%; further, the RN rates were similar among primary cancer types.

Conclusions Two-stage SRS should be considered for BC and NSCLC if surgical resection is not indicated. For BMs from GIC, staged SRS should be carefully considered and adapted to each unique case given its lower tumor reduction rate and shorter OS.

Keywords Two-stage stereotactic radiosurgery · Gamma knife · Large brain metastases · Primary cancer · Adaptive radiosurgery · Tumor reduction rate

Introduction

Approximately 20–40% of patients with cancer develop brain metastases (BMs) [1]. Local control of BMs has become a critical issue since the evolution of chemotherapy. Further, molecular targeting drugs, immune checkpoint inhibitors, and radiotherapy have improved the life expectancy of patients with cancer. Large BMs (> 10 cm^3) can typically be treated through surgery and/or whole-brain radiation therapy (WBRT) [2–7]. However, patient selection for operative intervention is limited by age, Karnofsky performance status (KPS), tumor location, extracranial disease status, and patient preference [8]. Tumor size is negatively correlated with the tumor control rate [9] and positively correlated with the neurotoxicity risk. Larger BMs should have a decreased prescribed dose; however, low prescribed doses (< 15 Gy) are associated with poor outcomes [10]. Tumor control and radiation damage are challenging in patients with large BMs who cannot undergo craniotomy or WBRT. In these cases, stereotactic radiosurgery (SRS) is an effective option [5, 11–15]. Moreover, SRS by Gamma Knife limits the indication for treatment depending on the metastatic tumor volume [10, 16, 17].

Recently, staged SRS has been developed to deliver a sufficient prescribed radiation dose while reducing the

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neurotoxicity risk; moreover, previous studies have reported its effectiveness [18–25]. No differences in the outcome have been reported for three-stage and two-stage SRS [24]. In staged SRS, the tumor volume is calculated to allow adaptive planning at the time of second fractions. This leads to reduced prescription volume and neurotoxicity.

To the best of our knowledge, there have been no reports on the tumor reduction rates achieved with staged SRS according to the primary cancer type. We aimed to clarify the role of staged SRS in cancer treatment with regard to the tumor volume reduction rate and tumor control and compared its effectiveness according to primary cancer type to allow the suggestion of appropriate treatment strategies.

Methods

Patient population

The institutional review board of Chiba Cerebral and Cardiovascular Center IRB (IRB number: #456) approved this retrospective study. The main inclusion criteria were as follows: (1) newly diagnosed BMs, (2) tumor volume > 10 cm^3, (3) BC, non-small cell lung cancer (NSCLC), or GIC as the primary cancer type. We enrolled 178 patients with 182 lesions treated with two-stage SRS between April 2008 and March 2019 at Chiba Cerebral and Cardiovascular Center and Tsukiji Neurological Clinic. In all patients, a Leksell G frame (Elekta Instrument, Stockholm, Sweden) was secured with screw pins under local anesthesia with adequate sedation, as appropriate. For each dose planning, we obtained gadolinium (Gd)-enhanced T1-weighted magnetic resonance (MR) images. We determined the prescription dose and treatment interval based on a previous report [24]. Neither the Extend system with Perfexion nor the mask system with ICON was used in this series. We did not set margins for the gross, clinical, or planning target volumes. All patients underwent staged SRS alone and not in combination with concurrent WBRT.

Definition of clinical outcomes

Overall survival (OS) was defined as the interval between the first SRS procedure and death. Tumor progression was defined as a 20% increase in the maximum diameter of the Gd-enhanced lesion since the first SRS [24, 26]. Neurologic death (ND) was defined as death by intracranial disease progression, including tumor recurrence, as well as leptomeningeal and cerebral dissemination. Systemic death was defined as death due to primary lesion progression. Tumor recurrence (TR) and radiation necrosis (RN) were determined using various imaging findings on MR imaging, single-photon emission computed tomography, and methionine positron emission tomography as previously described, as well as the clinical course [27–30]. The reduction rate was calculated based on the difference in the tumor volume measured by Gamma Plan™ at the first and second SRS. We assessed changes in the tumor burden based on the revised RECIST guideline [31] using final MR imaging and were classified as Partial Response (PR), Progression Disease (PD), or Stable Disease (SD).

Statistical analysis

We obtained patient characteristics regarding sex, age at diagnosis, primary cancer, KPS score, tumor volume, prescribed dose, duration between first and second SRS. Moreover, we used presented continuous variables as median values and categorical factors as percentages. We estimated OS using the Kaplan–Meier method. Tumor control, including TP and TR, was calculated using Gray analysis with competing risk being considered. We considered death as a competing risk for TP, death or RN as a competing risk for TR, and death or TR as a competing risk for RN. The reduction rate was analyzed using a one-way analysis of variance. All statistical analyses were performed using EZR version 1.40 (Saitama Medical Center, Jichii Medical university). A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

Table 1 shows the clinical characteristics of the patients, which were compared among the primary cancer types. Compared to patients with BC and NSCLC, patients with GIC had significantly worse KPS scores ($p = 0.001$), more frequent neurological symptoms ($p = 0.022$), and worse modified recursive partitioning analysis classes [32] ($p = 0.0001$). There were no significant differences in the age; extracranial disease status, including systemic disease status and extracranial metastases; tumor volume; prescribed dose; and duration from first to second Gamma Knife surgery (GKS) procedure among the three primary cancer types. The period from the date of primary cancer diagnosis to delivery of the first SRS fraction was 36.8 ± 54.2 months.

Clinical outcomes

Table 2 shows the comparison of the clinical outcomes among the primary cancer types. The median follow-up duration after the first GKS procedure for the 178 cases was 5.4 months (range 2.5–12.4 months). The median survival time (MST) after the first GKS procedure was 6.6 months. The MST from the first GKS in the patients aged above

Table 1 Comparison of clinical characteristics among the three primary cancers

Categories	Breast	GI tract	Lung	p value*
No. of patients	37	47	94	
Age (years)				
Median range	63 (29–90)	69 (35–90)	69 (40–86)	0.07
IQR	57–72	63–76	63–72	
Mean	63.2	68.7	67.3	
KPS score				
≥ 70%	30 (81.1)	34 (72.3)	89 (94.7)	0.001
Sex				
M/F	0/37	30/17	68/26	< 0.0001
Extracranial active				
No (%)	10 (27.0)	6 (12.8)	12 (12.8)	0.133
TV (cm^3)				
Median range	12.9 (10.0–30.1)	15.5 (10.0–35.8)	14.4 (10.0–69.0)	0.416
IQR	11.7–17.5	12.9–20.4	11.6–19.6	
Mean	15.3	17.1	16.9	
Neurological symptoms				
Yes (%)	32 (86.5)	41 (87.2)	71 (75.5)	0.022
MRPA				
I + IIa (%)	7 (18.9)	4 (8.5)	29 (30.9)	0.0001
IIb (%)	9 (24.3)	14 (29.8)	40 (42.6)	
IIc + III (%)	21 (56.8)	29 (61.7)	25 (26.6)	
Prescribed dose (Gy)				
Median range	13.0 (12.5–14.0)	13.0 (10.0–14.0)	13.0 (10.0–14.0)	0.324
IQR	12.5–13.0	12.5–13.0	12.5–13.0	
Mean	13	12.9	12.8	
First–second GKS duration (day)				
Median range	22 (7–38)	21 (11–32)	15 (7–38)	0.11
IQR	14–30	14–28	14–27	
Mean	22.2	21.3	19.3	

Values represent the number of patients (%) unless otherwise specified

IQR interquartile range, *KPS* Karnofsky performance status, *GKS* Gamma Knife radiosurgery, *TV* tumor volume, *MRPA* modified recursive partitioning analysis the one-way ANOVA was used for continuous variables and Fisher's exact test for pairs of categorical variables

65 years was significantly shorter than that in patients aged under 65 years old ($p < 0.01$). The OS from the first GKS differed among the primary cancer types (Fig. 1a, $p = 0.002$). Patients with GIC showed a significantly higher systemic death rate compared with those with BC and NSCLC ($p = 0.002$). A total of 141 patients (79.8%) died before the final data analysis; among them, 20 had experienced ND, including 8 with BC, 3 with GIC, and 9 with lung cancer. The overall cumulative incidence of ND was 11.2% in all patients. The ND causes were determined as carcinomatous meningitis in 10 (50.0%) cases, recurrence of the GKS-treated lesion in 8 (40.0%) cases, and progression of the untreated lesion in 2 (10.0%) cases. We confirmed the response of 122 lesions (67.0%) on final MR imaging. Among 31 cases of BMs from BC, 17(54.8%), 6 (19.4%), and 8 (25.8%) were classified as PR, SD, and PD, respectively. Among 62 lesions with BMs from NSCLC, 32 (51.6%), 16 (25.8%), and 14 (22.6%) were classified as PR, SD, and PD, respectively. Among 29 lesions with BMs from GI tract cancers, 10 (34.5%), 9 (31.0%), and 10 (34.5%) were classified as PR, SD, and PD, respectively. Moreover, there were 60 (33.0%) lesions which we could not obtain information since the image at the second fraction was the last follow-up image. The overall cumulative incidence of PD was 26.2% and the PD rates were similar among the primary cancer types ($p = 0.221$).

Tumor control

Thirty-three patients (18.5%) presented with TP; among them, 8, 10, and 15, had BC, GIC, and lung cancer, respectively. Moreover, among the aforementioned patients, 19,

Table 2 Comparison of the clinical outcome

Categories	Breast	GI tract	Lung	p value*
Reduction rate (%)				
Mean ± SD	40.4 ± 4.19	21.1 ± 3.65	25.8 ± 2.60	0.002
Overall survival (months)				
Survival rate (%)				
Median (95% CI)	9.0 (5.5–13.6)	5.3 (3.5–5.9)	9.4 (4.6–11.1)	0.002
6 months	57.1	33.4	59.3	
1 year	42.9	15.9	36.8	
Neurological death (%)				
6 months	5.9	4.7	2.5	0.235
1 year	11.8	7.5	3.9	
Tumor progression (%)				
6 months	0	13.7	5.9	0.615
1 year	2.9	21.5	9.7	
Tumor recurrence (%)				
6 months	0	4.7	2.5	0.439
1 year	2.9	12.5	6.3	
Radiation necrosis (%)				
6 months	0	9	3.4	0.452
1 year	0	9	3.4	

The reduction rate was analyzed by one-way ANOVA. OS was analyzed by the Log-rank test. Neurological death, tumor progression, tumor recurrence, and radiation necrosis were analyzed by the Gray test

11, 2, and 1 underwent repeated SRS, observation, surgical removal, and WBRT, respectively. The cumulative incidence of TP was 6.8% in all the patients, 0.0% in patients with BC, 14.3% in patients with GIC, and 6.0% in patients with NSCLC at 6 months after the first GKS procedure. The TP rate was not significantly different among the three primary cancer types. There were no cases with mixed/undetermined lesions. Twenty-two patients (12.4%) were associated with TR; among them, 7, 6, and 9 were patients with BC, GIC, and lung cancer, respectively. The cumulative incidence of TR was 2.5% in all the patients at 6 months after the first GKS procedure. The TR rate did not differ significantly among the primary cancer types (Table 2).

The cumulative RN incidence in all the patients was 4.2%. The RN rate was not significantly different among the three primary cancers. RN occurred in 11 patients (6.2%); among them, there were 1, 4, and 6 patients with BC, GIC, and lung cancer, respectively. Further, among the 11 patients with RN, 3, 5, and 3 patients demonstrated Common Terminology Criteria for Adverse Events grade 3 toxicity, grade 2 toxicity, and grade 1 toxicity, respectively. There was no relationship between the reduction rate and the RN rate. Only 7 patients presented with a tumor volume of > 30 cc; among them, there were 1, 3, and 3 patients with BC, GIC, and NSCLC, respectively. All the cases were associated with systemic death. There were no cases with TP and RN. Among the patients with a tumor volume > 20 cc, 4.6% and 13.0% presented with RN and TP at 1 year. In the patients with a tumor volume > 20 cc, 2.8% and 5.7% presented with RN and TP at 1 year. The p values for RN and TP were 0.958 and 0.282, respectively.

Tumor volume reduction during the treatment protocol

The median tumor volume reduction rate after the second GKS procedure was 26.6% (interquartile range [IQR] 7.4–44.8%) in all the patients, 46.1% (IQR 14.1–68.8%) in patients with BC, 18.2% (IQR 3.4–37.0%) in patients with GIC, and 26.6% (IQR 7.2–38.3%) in patients with NSCLC. The tumor volume reduction rate differed significantly among the primary cancer types (p = 0.002) (Fig. 1b). Compared with patients with NSCLC and GIC, the patients with BC had a significantly higher tumor reduction rate. Forty lesions showed volume decreases of < 5% after the second GKS procedure. The primary pathologies of these 40 low-responders were BC in 5 (13.5%), GIC in 12 (24.5%), and NSCLC in 23 (24.0%) with a significant among-group difference (p = 0.011). Among the low-responders, we observed TP in 7 lesions, TR in 4 lesions, and RN in 3 lesions. There was ND due to carcinomatous meningitis and recurrence of the GKS-treated lesion in 1 and 2 patients, respectively.

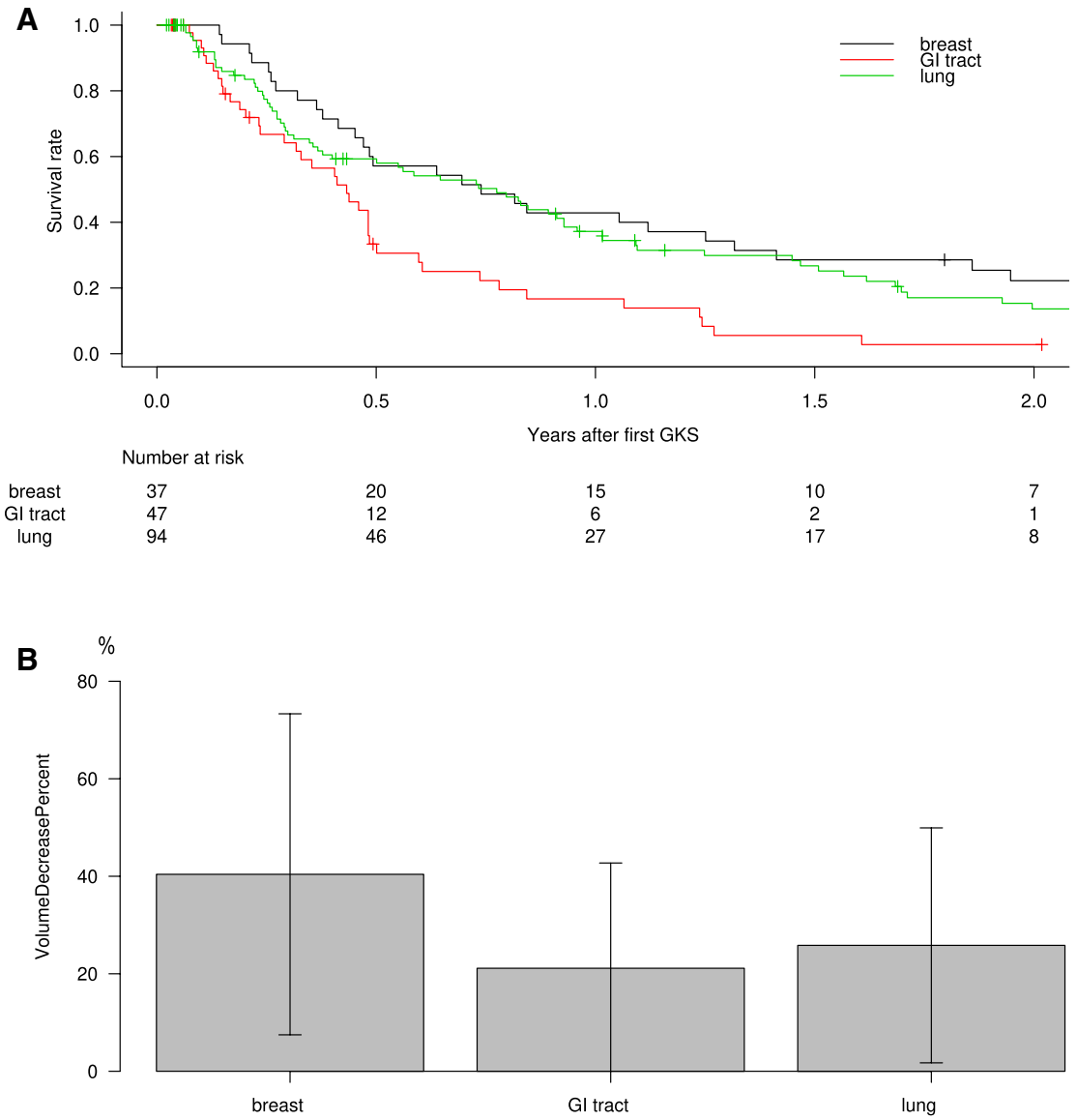

Fig. 1 **a** Kaplan–Meier curves showing overall survival of the patients with different primary cancer types. The median survival time of all the patients was 6.6 months (95% CI 5.3–9.3). The median survival time of the patients with BC, NSCLC, and GIC was 8.9 months (95% CI 5.4–15.0), 9.3 months (95% CI 4.5–11.1), and 5.2 months (95% CI 3.5–5.8), respectively. The overall 6- and 12-month OS rates after the first SRS in all the patients, patients with BC; NSCLC; and GIC were 52% and 33%; 57.1% and 42.9%; 59.3% and 36.8%; and 33.4% and 15.9%; respectively. **b** The reduction rate was analyzed by one-way analysis of variance. The median tumor volume reduction rate was 46.1%, 18.2%, and 26.6% in patients with BC, GIC, and NSCLC, respectively. BMs from BC showed significantly higher reduction rates than those from GIC ($p = 0.001$) and NSCLC ($p = 0.007$)

Prognostic factors for clinical outcomes

Table 3 shows the proportion hazards model for OS. A low KPS score (< 60), active extracranial disease status, GIC, and large tumor volume (> 20 cm^3) were identified as unfavorable prognostic factors that independently predicted the OS rates. Table 4 shows the proportion hazards model for TR. The tumor reduction rate was not a prognostic factor for TR. We found that older age (> 65-years old) was a favorable prognostic factor that independently predicted the TR rate. The cumulative incidence of TR at 12 months after the first GKS procedure was 5.4% and 10.1% in patients aged above and below 65 years, respectively ($p < 0.01$).

Therapeutic factors, including the duration between the first and second GKS or the prescribed dose, were not identified as prognostic factors that could predict either TP or TR.

Table 3 Analysis of clinical factors predicting survival after the first Gamma Knife surgery (cox proportional hazards model)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (more than 65/less than 65)	1.640 (1.160–2.317)	0.005	1.314 (0.916–1.886)	0.138
KPS score (less than 60%/more than 70%)	2.497 (1.562–3.992)	0.0001	2.151 (1.318–3.509)	0.002
Neurological symptoms (symptomatic/asymptomatic)	1.182 (0.780–1.793)	0.431		
Extracranial active (active/non active)	3.245 (1.843–5.714)	< 0.0001	2.867 (1.614–5.092)	0.0003
Primary cancer				
Breast/GI tract	0.441 (0.270–0.722)	0.001	0.541 (0.330–0.886)	0.015
Breast/lung	0.799 (0.524–1.218)	0.297		
Lung/GI tract	0.553 (0.369–0.828)	0.004	0.686 (0.447–1.053)	0.085
TV (more than $20cm^3$/less than $20cm^{3)}$	2.483 (1.664–3.706)	< 0.0001	1.8330 (1.212–2.772)	0.004

KPS Karnofsky performance status, *TV* tumor volume

Table 4 Analysis of clinical factors predicting tumor recurrence (Cox proportional hazards model)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (more than 65/less than 65)	0.223 (0.087–0.573)	0.002	0.266 (0.102–0.698)	0.007
KPS score (less than 60%/more than 70%)	0.527 (0.121–2.288)	0.390		
Duration from the first to second GKS (more than 21 days/less than 21 days)	2.002 (0.849–4.722)	0.110		
Extracranial active (non-active/active)	0.378 (0.160–0.894)	0.027	0.513 (0.218–1.211)	0.130
Primary lesion				
GI tract/breast	0.737 (0.252–2.156)	0.580		
Lung/breast	1.252 (0.821–1.910)	0.220		
TV (more than $20cm^3$/less than $20cm^{3)}$	0.154 (0.020–1.171)	0.071		
Prescribed dose (less than 13 Gy/more than 13 Gy)	0.294 (0.088–0.978)	0.046	0.401 (0.122–1.320)	0.130
Reduction rate (%) (less than 50%/more than 50%)	0.924 (0.320–2.671)	0.88		

KPS Karnofsky performance status, *GKS* Gamma Knife radiosurgery, *TV* tumor volume

Discussion

In this study, we assessed two-stage SRS as a strategy for treating large (> 10 cm^3) BMs by comparing its clinical outcomes among the different primary cancers. We compared the short-term tumor volume reduction rate and the long-term tumor control, as well as the relationship between tumor volume reduction and tumor control. We found that patients with GIC had a shorter OS than that in patients with BC and NSCLC. BMs from BC showed a higher tumor volume reduction rate than those from GIC. There was no correlation between the tumor reduction rate and tumor control. Additionally, patients under the age of 65 years showed a higher incidence of local recurrence than patients older than 65 years. A study by Serizawa et al. enrolled 1194 patients who had 2–10 BMs treated by SRS. They reported 4 clinical factors that affected local tumor progression based on the Fine-Gray proportional hazards model [26]. These poor prognostic factors were as follows: (1) patients under the age of 65 years, (2) patients with neurological symptoms, (3) patients with larger tumor volumes, and (4) a low prescription dose (< 22 Gy) [26]. In our study, we introduced a competing analysis method for evaluating local recurrence. We accounted for death as a competing risk for TR. The OS of the elderly was significantly shorter than that of younger patients, which might have contributed to the higher local recurrence among younger compared to that among older patients. The period from the date of primary cancer diagnosis to delivery of the first SRS fraction was 42.0 ± 64.5 months and 28.3 ± 29.1 months (p = 0.10) in patients aged above and below 65 years.

Consideration of the primary cancers affecting OS and tumor control

The MST was longest in patients with BC (7.0 months) and shortest (5.3 months) in patients with GIC. This is consistent with a previous study by Nieder et al. who conducted a diagnosis-specific graded prognostic assessment study of 412 patients with BMs. They found that many patients were treated with surgical resection or SRS and that the median OS was 3.6 months from the first treatment day [33]. The primary tumor type was associated with survival. Patients with BC had the most favorable MST (9.0 months) while those with GIC had the least favorable MST (5.3 months). Further, we found that the primary cancer type did not affect tumor control. Specifically, BMs from GIC with a short OS could be controlled to a similar extent as those from BC with a long OS. Even with control of intracranial metastases, patients with BMs from GIC have a short OS, which suggests that the survival prognosis is likely dependent on the progression of extracranial lesions in these patients.

Consideration of the tumor reduction rate according to the primary cancer type and the relationship between the tumor reduction rate and tumor control

Small cell lung cancer, lymphoma, and germ cell tumors are regarded as highly radiosensitive tumors; contrastingly, malignant melanoma, renal cell carcinoma, and sarcoma are regarded as radioresistant tumors [34, 35]. NSCLC, BC, and GIC are regarded as intermediate radiosensitive tumors. This study involved targeting these intermediate radiosensitive tumors. Differences in the reduction rate might have occurred due to differences in the radiosensitivity of the primary cancers and vascular effects. Ahmed et al. assessed radiosensitivity in patients with lung metastases [36]. They reported that lung metastases from BC showed higher radiosensitivity than those from GIC. It is unlikely that BMs and lung metastases have identical radiosensitivity; however, it is possible that BMs from BC have a higher radiosensitivity than BMs from GIC. Kocher et al. assessed and reported the vascular effects of radiosurgery with single fraction based on computer simulation [37]. We hypothesized that the vascular effect could differ among the primary cancer types. To the best of our knowledge, there has been no previous study comparing the tumor reduction rate and tumor control between different tumor groups with moderately radiosensitive tumors. Higuchi et al. reported the efficacy and safety of staged SRS for large BM treatment [18]. Their participants included 43 patients with large BMs (> 10 cm^3) treated using three-stage SRS without WBRT. The peripheral dose was 10 Gy and the interval between fractions was 2 weeks. They found that the mean tumor volume decreased by 18.8% after the second fraction. However, they did not report differences in the tumor volume reduction rate among the primary cancer types. In our study, the mean tumor volume decreased by 26.6% after the second fraction. We speculate that these differences in the reported tumor volume reduction rate could have resulted from differences in the treatment interval, prescribed dose, and patient characteristics. In our study, large BMs from BC showed significantly greater volume reduction than those from GIC and NSCLC.

A previous study reported a correlation between the tumor volume reduction rate and tumor control [20]. This previous study had longer treatment intervals and concomitantly longer reduction rate evaluation intervals. The treatment interval affects the tumor reduction rate, which could have contributed to the differences in our study and the aforementioned previous study. Contrastingly, some cancers show high radiosensitivity but poor tumor control, including SCLC [34, 35] Adenocarcinoma is known to have a slow radiation response [38]. Therefore, there is possibly no relationship between the reduction rate and tumor control. Staged SRS was developed to reduce the radiation prescription volume and toxicity by re-planning the irradiation range according to short-term tumor shrinkage for large BMs [18]. However, studies on the reduction rate and tumor control with staged SRS remain scares and future studies should assess more cases. In this study, as in other similar studies, we discussed the relationship between tumor control and OS. In contrast to our findings, a previous study reported that tumor reduction contributes to improved KPS scores [20]. Since improved KPS scores could expand treatment options, future studies should consider the relationship between tumor reduction, tumor control, and OS.

Consideration of treatment strategy for patients with large BMs by SRS

The tumor control rate at 1 year after treatment with other modalities, i.e., LINIAC, Cyber knife and staged Gamma Knife, were reported to be 81% [39], 87% [40], and 75.9–79.3% [18, 24], respectively. We found that the tumor control rate at 1 year after the first procedure was 88.5%. Comparisons with other findings are limited due to differences, including focusing on smaller tumor volume and differences in the percentage of the primary cancer types. The incidence of carcinomatous meningitis in our study was similar to that in a previous report [24]. Making a simple comparison is difficult; however, our results provide considerable evidence that staged SRS might be a treatment option for some cases. It is recommended that BMs with a diameter > 3 cm should be surgically excised and/or treated with WBRT or SRS [6, 7]. Surgery should be performed for any primary cancer type if the patient is young, has a tumor in a non-eloquent area, shows a good KPS score, and has no

active extracranial lesions. However, in some cases, choosing surgery might be difficult due to the patient's age, tumor localization in an eloquent area, poor general condition of the patient, presence of active extracranial lesions, and patient preference. In these cases, particularly for patients with large BMs from BC and NSCLC, staged SRS might be a treatment option that allows for short-term tumor reduction and KPS score improvement. Contrastingly, in patients with large BMs arising from GIC, it is difficult to expect significant tumor reduction; further, the progression of extracranial lesions could cause death within a relatively short period. In these cases, the adaptation of staged SRS should follow careful consideration.

Limitations and prospects

This study has several limitations. All our patients were treated with two-stage SRS as the initial therapy for large BMs. Despite advances in oncologic therapies, we could not analyze the effect of gene mutations or novel oncologic therapies, including molecular targeting drugs, since we could not obtain the relevant information. However, Yomo et al. reported that treatment with TKI affected survival; however, it did not affect tumor control. Therefore, we suggested that the effect of TKI on local control might be minimal [41].

There remains controversy regarding the maximum volume treatable by SRS, optimal interfraction interval, and optimal prescribed dose. We focused on patients with a tumor volume of less than 30 cc; therefore, we can tentatively consider that the therapeutic maximum volume for two-staged SRS is 30 cc. There is a need for further prospective studies that analyze more information on gene mutations and detailed oncologic therapies.

Conclusion

To the best of our knowledge, this is the first study to report the tumor reduction rate among primary cancer types after two-stage SRS using a large sample size. In this study, we found that the tumor reduction rate during both sessions was not a prognostic factor for tumor control. In patients with large BMs from BC, staged SRS could reduce the tumor size. In patients with large BMs from NSCLC, staged SRS could improve tumor control compared to single fraction, which is similar to BC. Therefore, clinical care in this regard could consider staged SRS. Careful consideration should be placed when adapting two-stage SRS for patients with large BMs from GIC since these patients show a lower tumor reduction rate and shorter OS.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Daisuke Ito, Kyoko Aoyagi, Osamu Nagano, Yoshinori Higuchi, and Toru Serizawa. The first draft of the manuscript was written by Daisuke Ito and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Research involving human participants The institutional review board of Chiba Cerebral and Cardiovascular Center IRB (IRB Number: #456) approved this retrospective study.

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