Staged stereotactic radiosurgery for brain metastases

(転移性脳腫瘍に対する段階的定位放射線治療)

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Abstract

Purpose: Stereotactic radiosurgery (SRS) is typically considered for patients who are unable to undergo surgical resection for large (> 10 cm^3) brain metastases (BMs). While staged SRS requires adaptive planning during each stage of the irradiation period to improve tumor control and reduce radiation damage, no studies have previously evaluated tumor reduction rates using this method. We evaluated the outcomes of 2-stage SRS according to primary cancer type.

Methods: We analyzed 178 patients with 182 large BMs initially treated with 2-stage SRS. Primary cancers included breast (BC), non-small cell lung (NSCLC), and gastrointestinal tract cancers (GIC). We analyzed overall survival (OS), neurological death, systemic death (SD), tumor progression (TP), tumor recurrence (TR), radiation necrosis (RN), and the tumor reduction rate during both sessions.

Results: Median survival time after the first Gamma Knife surgery (GKS) procedure was 6.6 months. OS was shorter, and SD incidences were higher in patients with GIC than those with BC and NSCLC. Tumor reduction rate was significantly higher in patients with BC than in those with NSCLC and GIC. TP rates were similar among primary cancer types. Tumor reduction rate was not associated with tumor control. The overall cumulative incidence of RN was 4.2% and 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 might be carefully considered and adapted depending on the case, considering

the lower tumor reduction rate and shorter OS.

Keywords 2-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, and molecular targeting drugs, immune checkpoint inhibitors, and radiotherapy have improved the life expectancy of cancer patients. Large BMs (> 10 cm^3) can typically be treated with surgery and/or whole brain radiation therapy (WBRT) [2-7]. However, the selection of patients 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 [31] and positively correlated with the risk of neurotoxicity. The prescribed dose should decrease for larger BMs; however, low prescribed doses (< 15Gy) are associated with poor outcomes [16]. In patients with large BMs who cannot undergo craniotomy or WBRT, tumor control and radiation damage are challenging. In these cases, stereotactic radiosurgery (SRS) is an effective option [5, 9-13]. Meanwhile, SRS by Gamma Knife limits the indication for treatment according to the volume of the metastatic tumors [14-16].

Recently, staged SRS has been developed to deliver a sufficient prescribed radiation dose while reducing the risk of neurotoxicity, and its effectiveness has been reported [17-24]. Both 3-stage and 2-stage SRS have been reported, and there was no difference in the outcomes [23]. In staged SRS, tumor volume is calculated for adaptive planning at the time of second fractions. This leads to a reduction of prescription volume, and reduced neurotoxicity.

To the best of our knowledge, tumor reduction rates achieved with staged SRS have not yet been reported according to the primary cancer type. In this study, we aimed to clarify the role of staged SRS in cancer treatment, focusing on tumor volume reduction rate and tumor control, and compared the effectiveness according to primary cancer type, with a view to suggesting 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 major eligibility criteria were as follows: 1) newly diagnosed BMs, 2) tumor volume > 10 cm^3, 3) primary cancer was BC, non-small cell lung cancer (NSCLC), or GIC. We enrolled 178 patients with 182 lesions treated with 2-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 necessary. For each dose planning, gadolinium (Gd)-enhanced T1-weighted magnetic resonance (MR) images were obtained. Neither the Extend system with Perfexion nor the mask system with ICON was used in this series. No margins were set for the gross, clinical, or planning target volumes. All patients underwent staged SRS alone, 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 [23, 30]. Neurologic death (ND) was defined as death by intracranial disease progression, such as tumor recurrence, or leptomeningeal and cerebral dissemination. Systemic death was defined as death due to primary lesion progression. Tumor recurrence (TR) and radiation necrosis (RN) were judged by various imaging findings on MR imaging, MR spectroscopy, single-photon emission computed tomography, positron emission tomography, and clinical course. The reduction rate was calculated from the difference in the tumor volume, measured by Gamma Plan^{TM}, at the first and second SRS.

Statistical analysis

Patient characteristics related to sex, age at diagnosis, primary cancer, KPS score, tumor volume, prescribed dose, duration between first and second SRS were obtained, using median values for continuous factors and percentages for categorical factors. OS was estimated by the Kaplan–Meier method. Tumor control, including TP and TR, was calculated by Gray analysis taking competing risk into consideration. We accounted

for death as a competing risk for TP, death or RN as a risk for TR, and death or TR as a risk for RN. The reduction rate was analyzed by 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

Clinical characteristics were compared among primary cancer types, and are shown in Table 1. In patients with GIC, KPS scores were significantly worse ($p = 0.001$), neurological symptoms more frequent ($p = 0.022$), and modified recursive partitioning analysis classes [25] worse ($p = 0.0001$) than in patients with BC and NSCLC. 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 were not significantly different among three primary cancer types.

Clinical outcomes

Comparison of clinical outcomes among primary cancer types is shown in Table 2. 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 MST after the first GKS procedure was 6.6 months. The OS since the first GKS differed among the primary cancer types (Fig. 1A, p = 0.002). Patients with GIC showed a significantly higher rate of systemic death compared with those with BC and NSCLC (p = 0.002). A total of 141 patients (79.8%) had died by the time of the final data analysis; among these, 20 were associated with ND, 8 with BC, 3 with GIC, and 9 with lung cancer. The cumulative incidence of ND was 11.2% in patients overall. The causes of ND were classified as carcinomatous meningitis in 10 (50.0%), recurrence of the GKS-treated lesion in 8 (40.0%), and progression of the untreated lesion in 2 (10.0%).

Tumor control

Thirty-three patients (18.5%) were associated with TP, 8 with BC, 10 with GIC, and 15 with lung cancer. Among the 33 patients with TP, 19, 11, 2, and 1 underwent repeated SRS, observation, surgical removal, and WBRT, respectively. The cumulative incidence of TP was 6.8% in patients overall, 0.0% in BC, 14.3% in GIC, and 6.0% in NSCLC patients at 6 months after the first GKS procedure. The rate of TP was not significantly different among the three primary cancer types. No cases were diagnosed as mixed/undetermined lesions. Twenty-two patients (12.4%) were associated with TR, 7 with BC, 6 with GIC, and 9 with lung cancer. The cumulative incidence of TR was 2.5% in patients overall 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 was 4.2% in patients overall. The RN rate was not significantly different among the three primary cancers. RN occurred in 11 patients (6.2%): 1 patient with BC, 4 patients with GIC, and 6 patients with lung cancer. 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 RN rate.

Tumor volume reduction during the treatment protocol

The median tumor volume reduction rate with the second GKS procedure was 26.6% (interquartile range; IQR: 7.4–44.8%) in patients overall, 46.1% (IQR: 14.1–68.8%) in BC, 18.2% (IQR: 3.4–37.0%) in GIC, and 26.6% (IQR: 7.2–38.3%) in NSCLC. The tumor volume reduction rate differed significantly among the primary cancer types ($p = 0.002$) (Fig1-B). Tumor reduction rate was significantly higher in patients with BC than in those with NSCLC and GIC. Forty lesions showed volume decreases of < 5% with 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%); these rates differed significantly ($p = 0.011$). In the low-responders, we observed TP in 7 lesions, TR in 4 lesions and RN in 3 lesions. ND occurred due to carcinomatous meningitis in 1 and recurrence of the GKS-treated lesion in 2 patients.

Prognostic factors for clinical outcomes

The proportion hazards model for OS is shown in Table 3. 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 OS rates. The proportion hazards model for TR is shown in Table 4. Older age (> 65-years old) was identified as a favorable prognostic factor independently predicting TR rate. Therapeutic factors, such as the duration between the first and second GKS or the prescribed dose were not identified as prognostic factors predicting either tumor progression or TR.

Discussion

In this study, we assessed 2-stage SRS as a strategy for treating large (> 10 cm^3) BMs by comparing the clinical outcomes among different primary cancers; we compared tumor volume reduction rate in the short term, tumor control in the long term, as well as the relationship between tumor volume reduction and tumor control. We found that patients with GIC had a shorter OS than patients with BC and NSCLC. BMs from BC showed a higher tumor volume reduction rate than those arising from GIC. There was no correlation between tumor reduction rate and tumor control. Additionally, patients under 65-years old showed a higher incidence in local recurrence than older patients. A study by Serizawa et al. included 1194 patients who had 2–10 BMs treated by SRS. They reported 4 clinical factors that impacted local tumor progression using the Fine-Gray

proportional hazards model [30]. These poor prognostic factors were 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 (< 22Gy) [30]. In our study, we introduced a competing analysis method to evaluate local recurrence. We accounted for death as a competing risk for TR. The OS of the elderly was significantly shorter than that in younger patients, which may affect the finding that younger patients showed higher local recurrence than older patients. The period from the date of primary cancers diagnosis to delivery of the first SRS fraction was 78.2 months ± 220.7 months in patients over 65-years old, and 28.3 ± 29.1 months ($p = 0.07$) in patients under 65-years old. This showed a trend for a shorter period in patients under 65-years old.

Consideration of the primary cancers affecting OS and tumor control

The median survival time (MST) was the longest in patients with BC (7.0 months), and was the shortest (5.3 months) in patients with GIC. This result was consistent with a previous study by Nieder et al. In their diagnosis-specific graded prognostic assessment study of 412 patients with brain metastases, many patients were treated with surgical resection or SRS, and the overall median survival was 3.6 months from the first day of treatment [26]. The primary tumor type was associated with survival. The MST of patients with BC was most favorable (9.0 months), and that of patients with GIC was least favorable (5.3 months). Furthermore, in our

study, the primary cancer type did not affect tumor control. In other words, in patients with BMs from GIC, with a short OS, intracranial metastases were controlled to the same extent as those in patients with BMs from BC, with a long OS. Despite control of intracranial metastases, the OS is short in patients with BMs arising from GIC, suggesting that the survival prognosis is likely dependent on the progression of extracranial lesions in these patients.

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

Small cell lung cancer, lymphoma, and germ cell tumors are regarded as highly radiosensitive tumors, while malignant melanoma, renal cell carcinoma, and sarcoma are regarded as radioresistant tumors [27 28]. NSCLC, BC, and GIC are regarded as intermediate radiosensitive tumors. In our study, we targeted these intermediate radiosensitive tumors. To the best of our knowledge, no previous study compared the tumor reduction rate and tumor control between different tumor groups involving moderately radiosensitive tumors. Higuchi et al. have reported the efficacy and safety of staged SRS for the treatment of large BMs [17]. Their subjects included 43 patients who had large BMs (> 10 cm^3) treated by 3-stage SRS without WBRT. The peripheral dose was 10 Gy and the interval between fractions was 2 weeks. According to their study, the mean tumor volume decreased by 18.8% with the second fraction. However, they did not report a difference in the

tumor volume reduction rate among primary cancer types. In our study, the mean tumor volume decreased by 26.6% with the second fraction. We speculate that the difference in tumor volume reduction rate between our study and that of Higuchi et al. could be due to the difference 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 demonstrated that the tumor volume reduction rate was related to tumor control [19]. Their treatment interval was longer than that in our study, and the reduction rate evaluation interval was longer accordingly. The treatment interval is a factor that affects tumor reduction rate; this may underlie the difference between the findings of the previous and our present study. On the other hand, some cancers show high radiosensitivity, but poor tumor control, such as small cell lung cancer [27, 28] Adenocarcinoma is known to show a slow radiation response [29]. Thus, it is possible that there is no relationship between the reduction rate and tumor control. Staged SRS was developed to reduce the radiation prescription volume and radiation toxicity by re-planning the irradiation range according to short-term tumor shrinkage for large BMs [17]. However, there are still few reports on the reduction rate and tumor control with staged SRS, and additional cases should be accumulated in future studies. We have discussed the relationship between tumor control and OS, as is the convention in such studies. However, a previous study has reported that tumor reduction

contributes to improved KPS [19]. Because the improvement of KPS may expand treatment options, the relationship between tumor reduction, tumor control, and OS should also be considered in future studies.

Consideration of treatment strategy for patients with large BMs by SRS

It is recommended that BMs with a diameter exceeding 3 cm be surgically excised and/or treated with WBRT or SRS [6,7]. Surgery should be performed if the patient is young, has a tumor in a non-eloquent area, shows a good KPS, and has no active extracranial lesions, for any primary cancer type. However, in some cases, it is challenging to select surgery, due to the patient's age, localization of the tumor in an eloquent area, the patient's poor general condition, presence of active extracranial lesions, and patient preference. In these cases, particularly for patients who have large BMs arising from BC and NSCLC, staged SRS may be a treatment option and provide short-term tumor reduction and improvement of the KPS. On the other hand, for patients who have large BMs arising from GIC, it is difficult to expect a significant tumor reduction, and the progression of extracranial lesions is likely to cause death within a relatively short period. In these cases, we may have to carefully consider the adaptation of staged SRS.

Limitations and prospects

This study had some limitations. All patients in this study were treated with 2-stage SRS as the initial therapy for large BMs. Despite advances in oncologic therapies, we could not analyze the effect of gene mutation or novel oncologic therapies, including molecular targeting drugs, as such information was not available for the patients involved in this study. The maximum volume treatable by SRS, optimal interfraction interval and prescribed dose are still controversial. Further prospective study with more information on gene mutation and detailed oncologic therapies will be required.

Conclusion

To the best of our knowledge, this is the first study to report the tumor reduction rate among primary cancers after 2-stage SRS in a large number of patients. In this study, tumor reduction rate was not a prognostic factor for tumor control. In patients with large BMs due to BC, staged SRS can be expected to reduce tumor size. In patients with large BMs from NSCLC, staged SRS can be expected to improve OS and tumor control, similar to BC; therefore, staged SRS can be considered. In patients with large BMs from GIC, 2-stage SRS might be carefully considered, as these patients show a lower tumor reduction rate and shorter OS.

Figure Captions

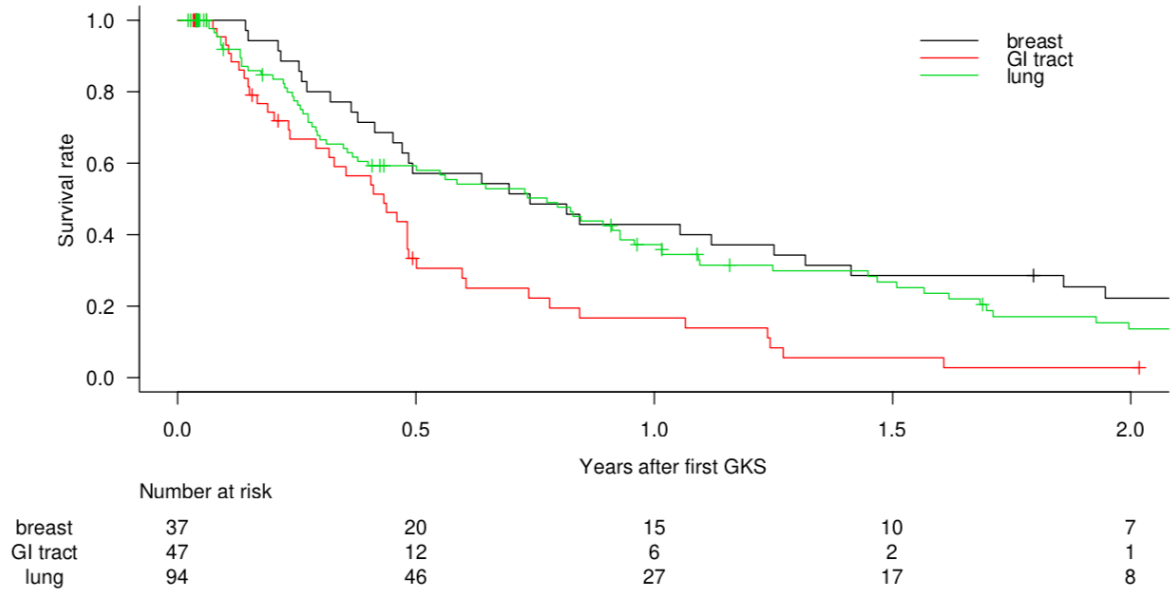

Fig. 1A Kaplan–Meier curves showing overall survival of patients with different primary cancers

The median survival time of all patients was 6.6 months (95% CI: 5.3–9.3). The median survival time of 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 were 52% and 33%, respectively, and 57.1% and 42.9%, 59.3% and 36.8%, and 33.4% and 15.9%, respectively, in patients with BC, NSCLC, and GIC

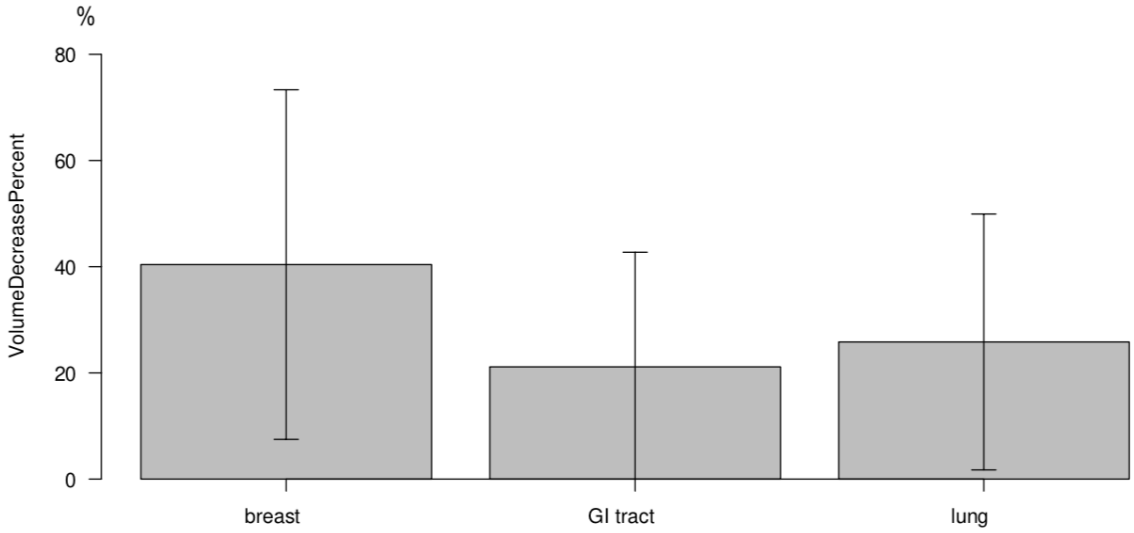

Fig. 1B The reduction rate was analyzed by one-way analysis of variance

The median tumor volume reduction rate was 46.1% in BC, 18.2% in GIC, and 26.6% in NSCLC. BMs from BC showed significantly higher rate of reduction compared with those with GIC (p=0.001) and NSCLC (p=0.007).

Tables

Table 1 Comparison on clinical characteristics among 3 primary cancers

Categories		Breast	GI tract	Lung	P value*
No. of patients		37	47	94	
Age (years)	median range IQR	63 29–90 57–72	69 35–90 63–76	69 40–86 63–72	0.070
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 IQR	12.9 10.0–30.1 11.7–17.5	15.5 10.0–35.8 12.9–20.4	14.4 10.0–69.0 11.6–19.6	0.416
Neurological symptoms	Yes (%)	32 (86.5)	41 (87.2)	71 (75.5)	0.022
MRPA	I+IIa (%) IIb (%) IIc+III (%)	7 (18.9) 9 (24.3) 21 (56.8)	4 (8.5) 14 (29.8) 29 (61.7)	29 (30.9) 40 (42.6) 25 (26.6)	0.0001
Prescribed Dose (Gy)	median range IQR	13.0 12.5–14.0 12.5–13.0	13.0 10.0–14.0 12.5–13.0	13.0 10.0–14.0 12.5–13.0	0.324
First–second GKS duration (day)	Median range IQR	22 7–38 14–30	21 11–32 14–28	15 7–38 14–27	0.110

Values represent numbers 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.

Table 2 Comparison on 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)	Median (95% CI)	9.0 (5.5–13.6)	5.3 (3.5–5.9)	9.4 (4.6–11.1)	0.002
Survival rate (%)	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	0.0	13.7	5.9	0.615
	1 year	2.9	21.5	9.7	
Tumor recurrence (%)	6 months	0.0	4.7	2.5	0.439
	1 year	2.9	12.5	6.3	
Radiation necrosis (%)	6 months	0.0	9.0	3.4	0.452
	1 year	0.0	9.0	3.4	

Reduction rate was analyzed by one-way ANOVA. OS was analyzed by Log rank test. Neurological death, Tumor progression, Tumor recurrence and Radiation necrosis were analyzed by Gray test.

Table 3 Analysis of clinical factors predicting survival after 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 Breast/Lung Lung/GI tract	 0.441 (0.270–0.722) 0.799 (0.524–1.218) 0.553 (0.369–0.828)	 0.001 0.297 0.004	 0.541 (0.330–0.886) 0.686 (0.447–1.053)	 0.015 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 first to second GKS (more than 21days/less than 21days)	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 Lung/Breast	0.737 (0.252–2.156) 1.252 (0.821–1.910)	0.580 0.220		
TV (more than 20cm^{3}/less than 20cm$^{3)}$	0.154 (0.020–1.171)	0.071		
Prescribed dose (less than 13Gy/more than 13Gy)	0.294 (0.088–0.978)	0.046	0.401 (0.122–1.320)	0.130

KPS; Karnofsky Performance Status, GKS; Gamma Knife radiosurgery, TV; tumor volume

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