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ORIGINAL ARTICLE - TUMOR - OTHER

Safety and efficacy of upfront stereotactic radiosurgery for brain metastases with high cumulative intracranial tumor volume (> 7 ml): analysis of 233 consecutive patients

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Abstract

Background The cumulative intracranial tumor volume (CITV) has recently been suggested to be a more relevant predictive factor for patients with brain metastases (BM) treated with stereotactic radiosurgery (SRS). We aimed to investigate the feasibility of upfront SRS for patients with BM having a high CITV, i.e., exceeding 7 ml.

Methods Two hundred thirty-three consecutive patients with BM having a CITV > 7 ml who underwent SRS as first-line treatment from 2011 to 2019 were retrospectively identified. The overall survival (OS) and intracranial disease control rates were analyzed. Multivariate proportional hazards models were used to identify prognostic factors associated with treatment outcome. Toxicity and salvage therapy were also investigated.

Results The median OS was 8.7 months (95% confidence interval: 7.1–10.4), and 6-month and 1-year OS rates were 60 and 40%, respectively. Systemic anticancer therapy (hazard ratio (HR): 0.45, $p < 0.001$), female sex (HR: 0.61, $p = 0.001$), synchronous SRS (HR: 0.57, $p = 0.003$), number of BM (HR: 1.04, $p = 0.008$), controlled extracranial disease (HR: 0.56, $p = 0.009$), Karnofsky performance status (HR: 0.87, $p = 0.015$), and staged SRS (HR: 0.71, $p = 0.037$) were found to be factors independently associated with OS. Post-SRS toxicities of CTCAE grades 3, 4, and 5 were observed in 14, 5, and 1 patient, respectively. As salvage management, repeat SRS, whole brain radiotherapy, and surgical resection were required for 84, 16, and 10 patients, respectively,

Conclusions With vigilant surveillance and appropriate salvage management, upfront SRS alone can be considered as a relatively safe and effective treatment strategy even for BM with CITV > 7 ml.

Keywords Brain metastases · Stereotactic radiosurgery · Gamma Knife · Cumulative intracranial tumor volume · Staged radiosurgery

Introduction

The advancements in molecular targeted therapies including immunotherapies have paralleled remarkable progress in the technical precision of radiotherapy delivery in cancer treatment [8]. Although the survival of patients with brain metastases (BM) has been prolonged with these advances [4, 14, 16, 17, 34, 38], BM still represent an important cause of morbidity and mortality.

Stereotactic radiosurgery (SRS) has been established as a safe and effective treatment for patients with limited BM in both curative and palliative settings [3, 11, 13, 25, 39]. Recently, several investigators have suggested cumulative intracranial tumor volume (CITV) to be a more relevant predictive factor for patient survival than tumor size or number [2, 5–7, 15, 21–24, 27, 30, 31, 35] (Table 1). The Congress of Neurological Surgeons evidence-based guidelines launched in 2019, in fact, recommended the use of SRS alone even for patients with more than 4 metastases having CITV < 7 ml, based on level 3 evidence [20].

In the clinical scenario of high CITV BM, at present, an approach combining surgical resection for large metastases

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Table 1 Literature review of SRS for investigations of BM with high CITV

Author and year	No. of patients	Primary cancer	SRS modality	CITV cutoff	Prognostic factors for OS on MVA
Bhatnagar et al., 2006 [6]	205	Various	GK	NA	CITV, age, RTOG-RPA, SRS dose
Motta et al., 2011 [31]	373	NSCLC	GK	5 ml	CITV (only in patients dying of cerebral progression), RTOG-RPA, SRS dose
Likhacheva et al., 2013 [27]	251	Various	GK	2 ml	CITV, age, DS-GPA, extracranial disease
Baschnagel et al., 2013 [5]	250	Various	GK	2 ml	CITV, age, KPS, extracranial disease
Bowden et al., 2015 [7]	1004	NSCLC	GK	5 ml	CITV
Marcus et al., 2016 [30]	365	Lung cancer	GK	4 ml	CITV, KPS, No. of BM, extracranial disease
Emery et al., 2017 [15]	300	Various	GK	NA	CITV, age, primary cancer, extracranial disease, BM location
Kim et al., 2017 [24]	130	Various	CK	7 ml	CITV, No. of BM
Ali et al., 2017 [2]	360	Renal cell cancer	GK	4 ml	CITV, KPS, No. of BM
Routman et al., 2018 [35]	391	Various	GK	10 ml	CITV, KPS, primary cancer
Hirshman et al., 2018 [22]	344	Melanoma	GK	4 ml	CITV, KPS, No. of BM
Joshi et al., 2019 [23]	328	Gastrointestinal cancer	GK	12 ml	CITV, KPS
Hamel-Perreault et al., 2019 [21]	103	Various	GK	6 ml	CITV, RTOG-RPA, extracranial disease

SRS stereotactic radiosurgery, *BM* brain metastases, *CITV* cumulative intracranial tumor volume, *OS* overall survival, *MVA* multivariate analysis, *KPS* Karnofsky performance scale, *GK* Gamma Knife, *DS-GPA* disease-specific graded prognostic assessment, *NSCLC* non-small cell lung cancer, *CK* cyberknife, *NA* not available, *RTOG-RPA* Radiation Therapy Oncology Group-recursive partitioning analysis

followed by adjuvant radiotherapy is widely accepted [9, 25, 29, 32], while it is not yet fully understood whether upfront SRS is a safe and effective treatment for high CITV cases. We used our cohort dataset to investigate the therapeutic efficacy and toxicity of upfront SRS for BM with a CITV > 7 ml. Factors associated with patient survival and intracranial disease control were also investigated.

Materials and methods

Data source and study cohort

The present study was conducted in compliance with the Declaration of Helsinki (sixth revision, 2008), and the Aizawa Hospital Institutional Review Board approved this retrospective study protocol in January 2020.

We analyzed our institutional radiosurgical database to investigate radiological and clinical outcomes. Between January 2011 and July 2019, 1336 patients with BM underwent Gamma Knife SRS. Of these 1336, 363 patients had CITV > 7 ml at the time of SRS. One hundred and thirty patients who had undergone any form of prior local treatment for BM (surgical resection, cyst aspiration, and/or whole brain radiotherapy (WBRT)) were excluded. Thus, 233 patients were eligible for the present study (Fig. 1).

Clinical data were extracted, including sex; age; Karnofsky performance status (KPS) scores; primary cancer; extracranial disease control; neurological symptoms; concurrent systemic anticancer therapies, including therapies with small molecular targeted drugs; antiangiogenic agents such as bevacizumab; and immune checkpoint inhibitors. Treatment was considered to be concurrent if the time difference between SRS and drug administration was no more than 3 months. BM parameters, such as the number of BM and the CITV, were also collected.

Radiosurgical indications and techniques

SRS was performed using the Leksell G stereotactic frame (Elekta Instruments, Stockholm, Sweden). Prior to frame application, non-stereotactic three-dimensional volumetric gadolinium-enhanced T1-weighted and T2-weighted magnetic resonance (MR) images were routinely obtained. The frame was placed on the patient's head under local anesthesia supplemented with adequate sedation. Stereotactic computed tomographic images were used for dose calculation and as a reference for co-registration with MR images. An individual treatment plan was generated using Leksell Gamma Plan software (Elekta Instruments). All radiosurgical interventions were performed with the Leksell Gamma Knife Model C or Perfexion.

SRS was applied even for cases with more than 10 BM, when the patient's systemic condition was such that SRS was

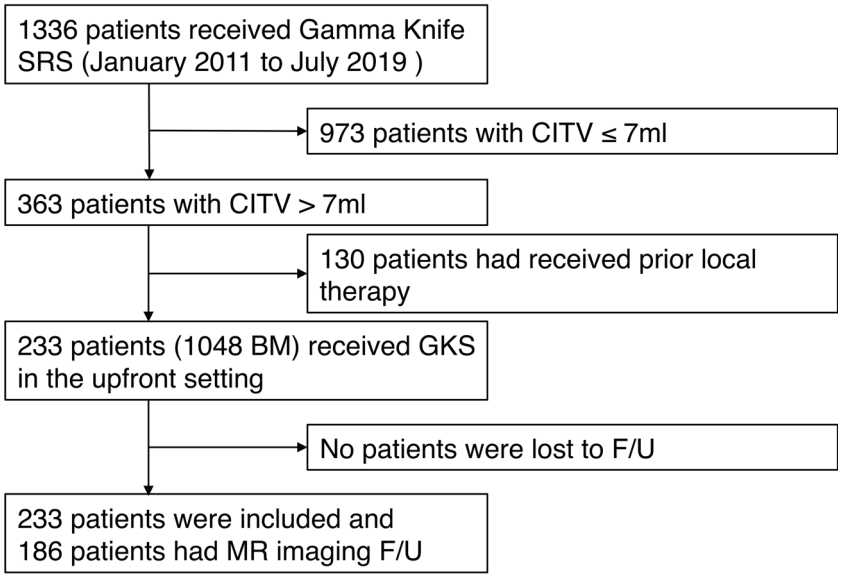

Fig. 1 Flow diagram showing the process of selecting the study participants

deemed to be tolerable. For large BM, our preference has been to adopt staged SRS over microsurgical resection with the aim of avoiding postsurgical leptomeningeal dissemination. After staged SRS for BM > 10 ml was proved to be a safe and effective treatment [41], these indications were expanded to include midsize symptomatic tumors—assumed to be high-risk for single-dose treatment [43]. The technical details of staged SRS were previously described in detail and thus are not repeated herein [41, 43].

Endpoints and post-SRS management

Clinical follow-up data as well as contrast-enhanced MR images were generally obtained every 2 to 4 months. At every follow-up visit, systemic anticancer therapy, neurological symptoms, and KPS scores were also recorded. For SRS treatment assessment, in principal, the response criteria for central nervous system metastases proposed by the RANO-BM working group [28] were applied. Neuroimaging worsening was defined as an increase in target lesion diameter of at least a 20% and an absolute value of 5 mm or more, taking as a reference the smallest documented diameter on MR images, regardless of whether the radiographic changes were due to a true progression or radiation necrosis. Salvage SRS was applied provided that the volume of the local recurrence was sufficiently small. Surgical removal was indicated when neurological signs became refractory to conservative management. When metachronous distant metastases were documented, they were also generally managed with repeat SRS. If leptomeningeal carcinomatosis or miliary parenchymal metastases were documented, WBRT was then considered. No further treatment was planned for patients with poor life expectancy and/or who were not expected to benefit from salvage treatment. Any adverse events attributable to SRS procedures were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; ver.4.0). Before closing the research database for analysis, we updated the follow-up data of patients who had not visited our outpatient department for more than 6 months. Inquiries about the date and mode of death were made by directly corresponding with the referring physician and/or the patient's family, with written permission obtained at the time of undertaking SRS from all patients and/or their relatives, allowing the use of personal data for clinical research.

Statistical analysis

Baseline characteristics and descriptive statistics were summarized using frequencies and proportions for categorical data and medians and ranges for continuous variables. The overall survival (OS) rate was calculated by the Kaplan-Meier product limit method. For the estimation of local and distant BM recurrence, Gray's test was applied, with subsequent WBRT for distant recurrence and the patient's death being regarded as competing events, respectively. All of the above analyses were based on the interval from the date of initial SRS until the date of each event. The Cox and Fine-Gray proportional hazards models were appropriately employed to investigate prognostic factors associated with OS and for local and distant intracranial disease control. Functional restoration was defined by a KPS score increase of ≥ 20 between the first treatment and the best follow-up and then the factors associated with functional restoration were explored employing multiple logistic regression analysis. Ten prognostic covariates were chosen for their potential associations with the outcome of interest based on clinical knowledge, sex, age (continuous), KPS (ordinal), extracranial disease status, concurrent systemic anticancer therapy, neurological symptoms, time difference

between primary diagnosis and SRS (SRS within 2 months after primary diagnosis was considered to be synchronous), number of BM (continuous), CITV (continuous), and staged SRS.

A statistical processing software package, the "R" version 3.0.1 (the R Foundation for Statistical Computing, Vienna, Austria), was used for all statistical analyses. A p value < 0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics, concurrent systemic anticancer therapy, and SRS dose prescription

During the study period, 233 consecutive patients with BM with high CITV (> 7 ml) underwent Gamma Knife SRS as upfront treatment. One hundred and thirty were male and 103 were female. The median age was 69 years (range: 36–93 years). The median KPS score at the time of SRS was 70 (range: 30–100). The median interval between primary diagnosis and SRS was 16.4 months (range: 0–230 months). The median interval between BM diagnosis and SRS was 0.5 months (range: 0–22.6 months). Fifty-eight patients (25%) had undergone SRS synchronously and the remaining patients had been diagnosed as having metachronous BM during their disease course. The primary cancers were of the lung in 126 patients (including 13 with small cell lung cancer), the colorectum in 38, the breast in 33, the kidney in 10, the stomach in 5, the esophagus in 3, the ovary in 3, melanoma in 2, and others in 10 and were of unknown origin in 3 patients. Thirty-seven patients (16%) had no evidence of progressive extracranial disease. One hundred and thirty-two (57%) were receiving systemic anticancer therapy at the time of the initial SRS and 88 of those were administered molecular targeted therapy (*targeted therapy agents are listed in Supplementary Table 1*). Sixty-eight (29%), 88 (38%), 55 (24%), and 22 (9%) patients had a single, 2 to 4, 5 to 10, and more than 10 BM, respectively. The median number of BM at the initial SRS was 3 (range: 1–28). The median CITV was 11.2 ml (range: 7.0–56.6 ml). The median tumor volume was 0.5 ml (range: 0.01–56.0 ml). The median prescribed dose for single-dose SRS was 20 Gy (range: 12–22 Gy). Staged SRS was indicated for 229 tumors in 129 patients (55%) and the median cumulative dose prescribed was 28 Gy (range: 20–30 Gy). Patient characteristics are summarized in Table 2.

Table 2 Clinical characteristics of 233 BM patients with high CITV (> 7 ml)

Characteristics	Overall ($n = 233$)
Sex (male/female)	130 (56%)/103 (44%)
Age (years), median (range)	69 (36–93)
< 65 years	72 (31%)
≥ 65 years	161 (69%)
KPS scores, median (range)	70 (30–100)
90–100	72 (31%)
70–80	83 (36%)
< 70	78 (34%)
Focal neurological symptoms	194 (83%)
Controlled extracranial disease	37 (16%)
Concurrent systemic anticancer therapy	132 (57%)
RTOG-RPA	
Class I	8 (3%)
Class II	147 (63%)
Class III	78 (34%)
Primary cancer	
Lung	126
Colorectum	38
Breast	33
Kidney	10
Stomach	5
Esophagus	3
Ovary	3
Melanoma	2
Others	10
Unknown	3
Time from primary diagnosis to initial SRS (months), median (range)	16.4 (0–230)
Time from BM diagnosis to initial SRS (months), median (range)	0.5 (0–22.6)
Synchronicity (SRS within 2 months after primary diagnosis)	
Synchronous	58 (25%)
Metachronous	175 (75%)
No. of BM at initial SRS, median (range)	3 (1–28)
Solitary	68 (29%)
2–4	88 (38%)
5–10	55 (24%)
> 10	22 (9%)
CITV at initial SRS (mL), median (range)	11.2 (7.0–56.6)
≤ 15 ml	162 (70%)
> 15 ml	71 (30%)
Two-staged SRS	129 (55%)
Prescription dose (Gy), median (range)	
Staged	28 (20–30)
Single	20 (12–22)

BM brain metastases, *CITV* cumulative intracranial tumor volume, *KPS* Karnofsky performance scale, *RTOG-RPA* Radiation Therapy Oncology Group-recursive partitioning analysis, *SRS* stereotactic radiosurgery

Survival outcomes

Full clinical results were available for all 233 patients, as follow-up data had been completely updated for the entire dataset. At the time of assessment, 32 patients (14%) were alive and 201 (86%) had died. The median clinical and imaging follow-up time for censored observations was 27.7 months (range: 9.5–100 months). The median OS time was 8.7 months (95% CI: 7.1–10.4). Six-month, 1-year, and 2-year OS rates after SRS were 60, 40, and 20%, respectively (Fig. 2a). The Cox proportional hazards model for OS identified concurrent systemic anticancer therapy (hazard ratio (HR): 0.45, 95% confidence interval (CI): 0.33–0.62, $p < 0.001$), female sex

(HR: 0.61, 95% CI: 0.45–0.83, $p = 0.001$), synchronous SRS (HR: 0.57, 95% CI: 0.39–0.82, $p = 0.003$), number of BM (HR: 1.04, 95% CI: 1.01–1.08, $p = 0.008$), controlled extracranial disease (HR: 0.56, 95% CI: 0.36–0.87, $p = 0.009$), KPS (HR: 0.87, 95% CI: 0.78–0.97, $p = 0.015$), and staged SRS (HR: 0.71, 95% CI: 0.51–0.98, $p = 0.037$), as factors independently predicting OS time (Table 3).

Intracranial disease control and functional restoration

In total, 186 patients (80%) with sufficient radiological follow-up data were analyzed herein. The data of the other patients were not available for this analysis because they died soon after SRS from systemic disease progression or were followed up by the referring hospitals. Distant metachronous BM were observed in 100 patients (54%) at a median time of 6.0 months (range: 1.0–76 months) after SRS. Six-month and 1-year cumulative incidence rates of distant BM recurrence after SRS were 27 and 41%, respectively (Fig. 2b). The proportional hazards model for distant BM recurrence identified KPS (HR: 1.24, 95% CI: 1.06–1.44, $p = 0.008$) as being associated with a probability of distant BM recurrence (Table 4). Sixty patients (33%) were eventually diagnosed as having local control failure at a median time of 5.9 months (range: 0–46 months) after SRS. Six-month and 1-year cumulative incidence rates of local BM recurrence (per patient) were 14 and 22%, respectively (Fig. 2c). No prognostic factors were identified as being statistically significantly associated with a likelihood of local BM recurrence (Table 4).

Seventy-two patients with KPS scores of 90 or higher at the time of SRS were excluded from this analysis because functional restoration required a KPS score improvement of at least 20. Of 161 eligible patients, 122 (76%) with post-SRS clinical evaluation at least once were analyzed herein. All of these patients had focal neurological symptoms due to BM at the time of SRS and 64 patients (52%) showed functional restoration. Multiple logistic regression analysis found staged SRS to be the sole factor associated with KPS improvement (odds ratio: 4.14, 95% CI: 1.95–8.8, $p < 0.001$) (Table 5).

Adverse events and salvage management

Regarding adverse radiation effects, we identified 20 patients (9%) with moderate to severe radiation-induced toxicity (CTCAE grade 3 or more). One male patient with multiple hemorrhagic metastasis from renal cell carcinoma died of re-bleeding from multiple metastases immediately after SRS (grade 5) [40]. One male patient experienced cerebellar tumor

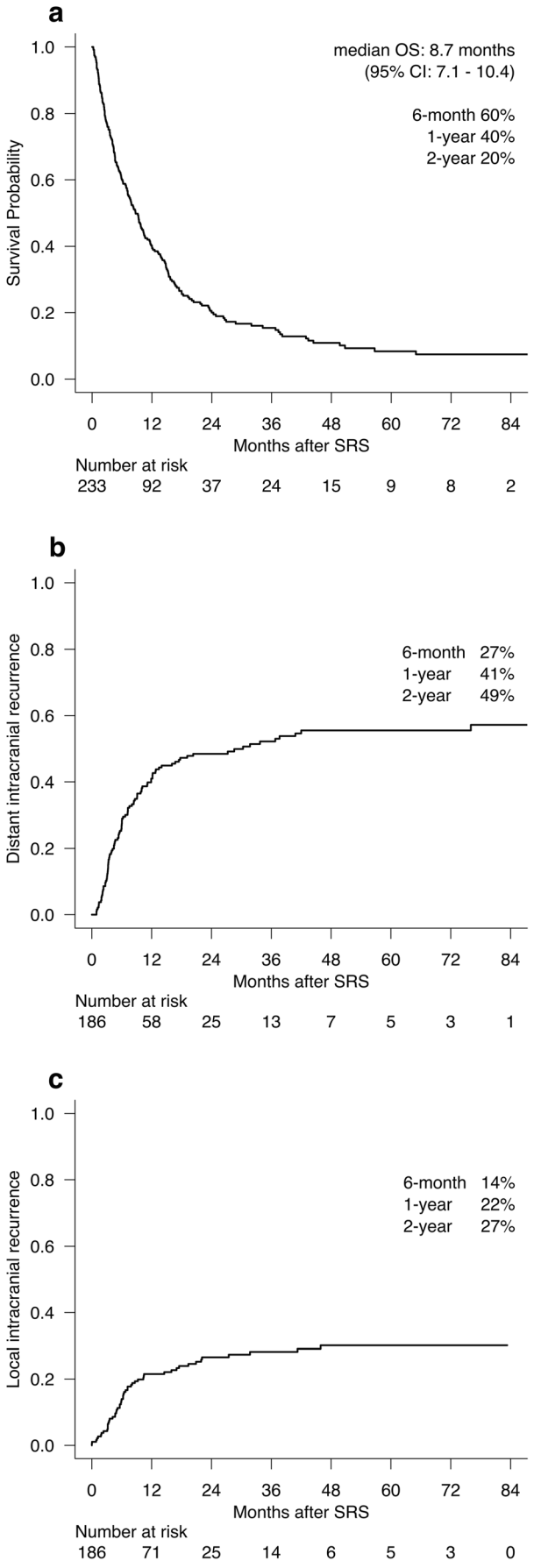

Fig. 2 Patient survival and intracranial disease control results after SRS. **a** Overall survival probability, **b** cumulative incidence of distant intracranial recurrence, and **c** cumulative incidence of local intracranial recurrence

Table 3 Analysis of factors predicting patient survival after SRS (Cox proportional hazards model)

Covariate	Overall survival	
	HR (95% CI)	*p* value
Age (continuous)	1.00 (0.99–1.02)	0.86
Female	0.61 (0.45–0.83)	0.001
KPS (ordinal)	0.87 (0.78–0.97)	0.015
Controlled extracranial disease	0.56 (0.36–0.87)	0.009
Focal neurological deficits	1.29 (0.82–2.03)	0.27
Systemic anticancer therapy	0.45 (0.33–0.62)	< 0.001
Synchronous SRS	057 (0.39–0.82)	0.003
Number of BM (continuous)	1.04 (1.01–1.08)	0.008
CITV (continuous)	1.01 (0.99–1.03)	0.49
Staged SRS	0.71 (0.51–0.98)	0.037

SRS stereotactic radiosurgery, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *KPS* Karnofsky performance scale, *BM* brain metastases, *CITV* cumulative intracranial tumor volume

hemorrhage 1 day after SRS and had to undergo emergency evacuation surgery, which achieved good functional recovery (grade 4). Three patients required urgent tumor removal within a month due to uncontrollable cerebral peritumoral edema (grade 4). One patient developed chronic encapsulated expanding hematoma in the left motor cortex, requiring surgical resection 91 months after staged SRS (grade 4). Ten patients were diagnosed as having symptomatic radiation necrosis refractory to oral steroids (grade 3) and required the following salvage treatments: bevacizumab rescue in 5, surgical resection in 4, and both in 1. Three patients experienced tumor-related status epilepticus necessitating brief hospitalizations (grade 3). One patient showed delayed cyst formation 48 months after staged SRS and required repeat cyst aspiration (grade 3).

Repeat SRS was applied for distant or local BM recurrence in 84 patients (36%). Sixteen patients (7%) underwent salvage WBRT, necessitated by the development of miliary BM and/or leptomeningeal metastases, at a median time of 6.8 months (range: 1.8–41 months) after SRS. The aforementioned 10 patients required surgical resection at a median time of 5.1 months (range: 0–91 months) after SRS, and the histopathological diagnoses were tumor hemorrhage in 1, tumor recurrence with various degrees of radiation necrosis in 6, pure radiation necrosis in 2, and chronic encapsulated expanding hematoma in 1.

Discussion

Clinical significance of high CITV BM and treatment options

The OS in the present study was relatively short, as compared to previous studies in our different BM cohorts [42, 43]. The proportion of patients with uncontrolled extracranial disease was quite high (84%) and one-third of cases were RTOG-RPA class III. The high CITV may directly reflect the severity of the total cancer burden. Several investigators have reported the CITV to offer a more reliable prognostic factor for BM patients treated with SRS than the number of BM and, furthermore, that patients with high CITV BM had short survival times [5–7, 21, 27]. Researchers at the University of California San Diego have conducted several rigorous studies, wherein they observed an inverse correlation between KPS and CITV and that CITV augmented the prognostic accuracy of diagnosis-specific graded prognostic assessment (DS-GPA) [37] for survival in patients with BM from various types of cancer [2, 22, 23, 30].

BM with high CITV often causes devastating neurological symptoms and thus can be regarded as an oncologic emergency, and it is critically important to choose the optimal treatment for each patient in such difficult situations, taking into account the patient's general condition, cancer gene mutations, and expected survival. The least desirable scenario is for BM progression to lead to neurocognitive and performance status decline, thereby hindering the chances for effective systemic treatment.

WBRT and surgery, both alone and in combinations including with SRS, are potential alternatives to SRS monotherapy. Several randomized clinical trials found WBRT to cause cognitive decline relatively early [9, 11, 13, 36], but various optimization efforts such as hippocampal avoidance WBRT and memantine use were recently suggested to be effective for decreasing neurocognitive toxicity [10, 12, 18]. Postoperative surgical cavity SRS and preoperative SRS followed by surgery have recently been emerging as a new treatment paradigm for relatively large BM [1, 33].

The therapeutic approach in our institution has consistently prioritized the use of SRS alone, even for cases with high CITV BM, because we consider upfront SRS strategy to be a minimally invasive and time-intensive treatment, avoiding the risk of leptomeningeal disease related to surgical resection and beneficial for the initiation or continuation of systemic anticancer therapy. On the other hand, we have also had concerns that the dose delivered by SRS for high CITV BM is necessarily limited by toxicity to adjacent tissues and may yield suboptimal treatment results.

Systemic prospective evaluation is warranted to elucidate which treatment options are the most efficient approach in overcoming the challenge of high CITV BM. The present retrospective analysis of a relatively large patient cohort aimed to provide data useful for generating the hypotheses warranting examination in future investigations.

Prognostic factors

The present study demonstrated that concurrent anticancer therapy had a strong impact on post-SRS OS. One of the main

reasons might be that the clinical use of molecular targeted agents has become mainstream in recent years. As many as 67% of patients on systemic anticancer therapy were actually using at least one molecular targeted agent. Small molecule compounds have been demonstrated to achieve a high response rate in patients with intracranial lesions [4, 14, 16, 34]. Immunotherapy can also be expected to obtain a certain response rate, though not as good as that of small molecule compounds [17, 38]. It has also been recognized that antiangiogenesis agents such as bevacizumab and ramucirumab exert mitigating effects on cerebral edema as well as late-onset radiation necrosis [19, 26]. Upfront SRS may be a reasonable option even for high CITV BM patients, when the use of molecular targeted therapy is anticipated. The synergy between these new agents and SRS represents a new therapeutic paradigm, and a multidisciplinary research is crucial for further improving treatment outcomes. We speculate that the major cause of female sex being a favorable prognostic factor was confounding with the use of molecular targeted agents. In fact, the use of molecular targeted agents was significantly higher in females than in males (49% vs. 28%) (p = 0.018, Fisher's exact test). In particular, epidermal growth factor receptor-tyrosine kinase inhibitors were used more frequently in female patients with lung adenocarcinoma. One of the reasons for better OS in the synchronous SRS subgroup might be that effective anticancer therapy was initiated after SRS and that more systemic treatment options remained available than those for BM treated metachronously during the disease course, while for patients treated metachronously, BM development might have been an early sign of systemic therapy failure.

High CITV may involve various pathological conditions, ranging from a single large BM to multiple midsize BM. The number of BM was found to be an independent poor prognostic factor for OS, although its threshold for SRS monotherapy could not be determined in the present study. In line with previous studies [37], more numerous metastases are still associated with a poor prognosis. A different approach such as combining SRS with WBRT to increase the treatment intensity may be necessary to improve the survival of patients with numerous BM.

Staged SRS was demonstrated to contribute more significantly to OS as well as functional restoration than single-dose SRS. The chief reason might be that local control of BM improves neurological symptoms (Table 5), in turn providing an opportunity to continue systemic treatment. Staged SRS also enabled us to broadly anticipate the post-SRS course at the time of the second treatment and thereby optimize the subsequent management, which might have indirectly contributed to better treatment outcomes.

KPS was identified as a risk factor for distant BM recurrence. This could possibly be due to a kind of detection bias. During post-SRS follow-up, patients with better KPS were more likely to be eager to receive regular post-SRS follow-up, while some patients continued to be followed by their referring oncologists, when they became very sick. It should be recognized that the real rates of intracranial disease control and functional restoration might be overestimated.

Toxicities and post-SRS management

First, post-SRS images were not available for 20% of patients, and we could not exclude the possibility that SRS-related neurotoxicity was not identified in this patient group. Second, both local and distant recurrences have been shown to affect a certain number of patients. CTCAE grade 4/5

Table 4 Analysis of factors predicting intracranial disease control after SRS (Fine-Gray proportional hazards model)

Covariate	Distant intracranial recurrence		Local intracranial recurrence	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (continuous)	0.99 (0.97–1.02)	0.62	0.99 (0.97–1.02)	0.57
Female	0.74 (0.49–1.14)	0.17	1.24 (0.67–2.30)	0.49
KPS (ordinal)	1.24 (1.06–1.44)	0.008	1.11 (0.92–1.34)	0.29
Controlled extracranial disease	0.81 (0.45–1.44)	0.47	1.23 (0.60–2.49)	0.58
Focal neurological deficits	1.68 (0.94–3.00)	0.08	1.04 (0.47–2.30)	0.92
Systemic anticancer therapy	1.19 (0.73–1.95)	0.49	1.54 (0.75–3.14)	0.24
Synchronous SRS	1.01 (0.62–1.65)	0.96	0.52 (0.23–1.20)	0.12
Number of BM (continuous)	1.03 (0.95–1.00)	0.23	0.97 (0.89–1.05)	0.42
CITV (continuous)	0.98 (0.98–2.17)	0.09	1.01 (0.98–1.04)	0.37
Staged SRS	1.33 (0.83–2.11)	0.24	0.95 (0.48–1.89)	0.89

SRS stereotactic radiosurgery, *HR* hazard ratio, *CI* confidence interval, *KPS* Karnofsky performance scale, *BM* brain metastases, *CITV* cumulative intracranial tumor volume

Table 5 Analysis of factors predicting [*] functional restoration after SRS (multiple logistic regression analysis)

Covariate	Patients with KPS scores of 80 or less ($n = 161$)	
	OR (95% CI)	p value
Age < 65 years	0.91 (0.45–1.87)	0.80
Female	0.70 (0.36–1.37)	0.30
[**] KPS	–	–
Controlled extracranial disease	1.17 (0.50–2.72)	0.72
[**] Neurological deficits	–	–
Systemic anticancer therapy	1.12 (0.55–2.30)	0.75
Synchronous SRS	0.95 (0.44–2.07)	0.90
Single BM	0.66 (0.32–1.38)	0.27
CITV ≤ 15 ml	1.90 (0.89–4.05)	0.095
Staged SRS	4.14 (1.95–8.80)	< 0.001

[*] Functional restoration was determined by KPS score improvement of ≥ 20 between the first treatment and the best follow-up. Seventy-two patients with KPS scores of 90–100 were excluded from this analysis. [**] KPS was the dependent variable and [**] neurological symptoms were observed in all cases. Thus, both covariates were excluded

SRS stereotactic radiosurgery, *KPS* Karnofsky performance scale, *OR* odds ratio, *CI* confidence interval, *BM* brain metastases, *CITV* cumulative intracranial tumor volume

complications were rare but this possibility cannot be ignored in terms of safety. We speculate that this is likely attributable to high CITV itself being a critical condition rendering patients susceptible to tumor bleeding and exacerbation of cerebral edema. Provided that post-SRS follow-up is vigilant and appropriate salvage treatment is administered when serious adverse events occur, SRS can be regarded as a rational and relatively safe procedure. Finally, another problem associated with SRS for high CITV BM is the increased rate of symptomatic radiation necrosis. Cerebral radiation necrosis, refractory to steroids and/or surgically inaccessible, remains a significant problem directly influencing quality of life for patients. Bevacizumab was first reported in 2007 to neutralize excessive release of vascular endothelial growth factor from perinecrotic tissues and has since revolutionized treatment for cerebral radiation necrosis [19, 26]. Although bevacizumab was indicated and obtained a distinct therapeutic effect for carefully selected patients in our cohort, we must be cautious about its use because in situations where it is difficult to differentiate between local recurrence and radiation necrosis, the injudicious use of this agent may make the clinical course even more complicated.

Limitations

The present study has several limitations. Given the retrospective design with a heterogeneous group of patients, all analyses were subject to confounding because of unmeasured variables. All treatments were administered at a single regional tertiary hospital, which may introduce various types of bias, including selection bias through regional referral patterns. There may have been eligible patients who were not sent to us and whose outcomes could have differed from what was observed in the present patient cohort. Caution is necessary when interpreting the efficacy of systemic anticancer therapy and staged SRS, because treatment decisions were made by comprehensively taking into account various clinical conditions and patient backgrounds may differ between subgroups. The present study was conducted exclusively in Japanese patients and the rate of using targeted agents in systemic treatment was relatively high (67%). Whether our findings are reproducible in other races/ethnicities or countries remains to be elucidated. A paucity of endpoints on intracranial recurrences may also have resulted in the dataset being unstable and underpowered to assess hypotheses and potential prognostic factors. Each of the targeted agents has a different molecular mechanism of action and therapeutic effects against BM. The limited number of cases, unfortunately, did not allow us to analyze each targeted agent separately. Similarly, analysis could not be performed by primary cancer type.

Conclusions

BM with high CITV (> 7 mL) accounted for a high proportion of patients with poor prognostic factors such as decreased KPS scores and uncontrolled extracranial disease. To date, the OS time after upfront SRS has reached almost 9 months, although intracranial recurrences were not uncommon. With vigilant surveillance and appropriate salvage management, upfront SRS alone can be regarded as a relatively safe and effective treatment for BM with high CITV. A prospective

study is warranted to elucidate the most efficient treatment for overcoming the challenge of high CITV BM.

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Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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