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ORIGINAL ARTICLE

Surgical outcome and graded prognostic assessment of patients with brain metastasis from adult sarcoma: multi-institutional retrospective study in Japan

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Abstract

Background Brain metastasis (BM) is an uncommon complication of sarcomas with a poor prognosis. Little information is available about the feasibility and prognostic factors of surgical resection of BM from sarcomas.

Methods This study involved a retrospective analysis of 22 patients with BM from sarcomas who underwent resection at six institutes in Japan. Prognostic factors were analyzed to develop a graded prognostic assessment (GPA) using the log-rank test and Cox regression analysis. For validation of this GPA, we collected data on 100 surgical cases from 48 published reports.

Results Postoperative Karnofsky Performance Status (KPS) improved in 50% of our patients. Median overall survival (OS) was 21 months. Multivariate analysis showed age and alveolar soft part sarcoma (ASPS) were significant preoperative prognostic factors ($P < 0.05$). RTOG-RPA classification had no significant prognostic value. We developed a GPA system for OS after resection of BM. A score of 0 was assigned to patients aged 18–29 years with non-ASPS, 2 to patients aged 18–29 years with ASPS or 30–76 years with non-ASPS, and 4 to patients aged 30–76 years with ASPS. Median OS for patients with GPA scores of 0, 2, and 4 were 6.5, 16.0, and 44.0 months, respectively ($P = 0.002$). The results were validated by the data of 100 cases compiled ($P < 0.001$).

Conclusion Median OS of patients with BM from sarcomas was comparable to that from carcinomas after resection. A new sarcoma-specific GPA may help patients and clinicians to select resection as an option for treatment of BM from sarcomas.

Keywords Graded prognostic assessment · Karnofsky performance status · Metastatic brain tumor · Sarcoma · Surgical resection

Abbreviations

ASPS	Alveolar soft part sarcoma
BM	Brain metastasis
CI	Confidence interval
GPA	Graded prognostic assessment
GTR	Gross total resection
KPS	Karnofsky Performance Status
OS	Overall survival
RPA	Recursive partitioning analysis
RTOG	Radiation Therapy Oncology Group

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Introduction

Adult sarcomas are an uncommon, heterogeneous entity of solid tumors of mesenchymal origin with various distinct histological subtypes, accounting for 1% of all adult malignancies [1]. Brain metastasis (BM) from sarcomas is also rare, occurring in 1–8% of sarcoma patients [2, 3]. However, the incidence may increase due to advances in irradiation and systemic therapy effective for systemic disease but ineffective for BM [4, 5]. In fact, new systemic agents have shown encouraging activity in patients with advanced sarcomas of certain subtypes [6–9].

Survival outcomes in patients with BM are poor and treatment options are limited [10]. Surgical resection remains an important option for BM treatment. It aims at rapid mass reduction and improvement of neurological status, which may contribute to better performance status in patients with BM [11]. Surgical resection may locally control intracranial lesions, and may also provide opportunities for further systemic therapy and prolong the survival of selected patients with BM from sarcomas.

Surgical candidates should be selected carefully in consideration of the risks of craniotomy [11]. We need a system for assessing the prognosis of individual patients supporting decision-making regarding surgical resection. However, owing to the rarity of sarcomas, there are only a few reports about the feasibility or prognostic factors of surgical resection for BM from sarcomas [10, 12]

Here, we performed a nationwide multi-institutional study to evaluate recent clinical features and surgical outcomes, and constructed a preoperative graded prognostic assessment (GPA) of patients with BM from sarcomas.

Patients and methods

This study was a multi-institutional retrospective analysis of 22 patients over the age of 18 years with BM from sarcomas who underwent resection at six institutes in Japan between September 2002 and September 2018.

The indication for surgical removal of BM from sarcomas is similar to that for BM from carcinomas, depending on the judgment of neurosurgeons at each institute. We excluded sarcomas directly invading the skull base, hemangiopericytomas, chordomas, and gliosarcomas. The clinical data included date of birth, sex, date of the primary sarcoma diagnosis and presence of BM, histological type, number and maximum size of BMs, side/location of BM, symptoms due to BM, presence of intratumoral hemorrhage, date of surgical resection of BM, extent of resection, pre- and postoperative Karnofsky Performance Status (KPS), presence of lung metastases, whether the primary lesion was controlled at BM diagnosis, type of adjuvant therapy for BM, date of death or last follow-up visit, and cause of death. Overall survival (OS) was calculated from the date of diagnosis of BM to death from any cause or the last day of follow-up using Kaplan–Meier methods.

For validation study of GPA on surgical resection of brain metastases, we collected published literature about patients with BM from sarcomas who underwent surgical resection [3–5, 13–57]. The National Library of Medicine search engine, PubMed, was utilized for the literature search. For each of the sarcomas, the search terms "brain" and "intracranial" were combined with the tumor's name: "osteosarcoma," "Ewing's sarcoma," "malignant fibrous tumor," "malignant fibrous histiocytoma," "fibrosarcoma," "liposarcoma," "alveolar soft part sarcoma," "chondrosarcoma," "pleomorphic sarcoma," "leiomyosarcoma," "rhabdomyosarcoma," "malignant peripheral nerve sheath tumor," "MPNST," or "angiosarcoma." Relevant articles describing case reports or clinical studies were selected, and the reference lists from these articles were also inspected for other relevant articles [58]. The reports without survival data after craniotomy for BM were excluded. Only publications in English, peer-reviewed journals were included.

Prognostic factors were analyzed using the log-rank test for univariate analysis and Cox regression analysis for multivariate analysis. A P value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using EZR statistical software [59].

Results

Patient characteristics

The characteristics of our 22 patients with BM from sarcomas who underwent surgical resection are shown in Table 1 and summarized in Table 2. Eleven patients were male. The median age at the time of craniotomy was 45 years (range 18–76). In terms of the histological diagnoses of sarcoma, alveolar soft part sarcoma (ASPS) was the most common (27%). The median time from diagnosis of the primary sarcoma to the appearance of BM was 20 months (range 0–267), including two patients with BM prior to the diagnosis of primary sarcomas. Twenty patients (91%) were symptomatic. Eight patients (36%) had multiple BMs, and the laterality and location in the brain varied. Although lung metastases had already occurred in 19 patients (86%) at the time of craniotomy, the primary sarcomas were controlled in six patients (27%). Intra-tumoral hemorrhage of the BM was detected in seven patients (32%). Twenty-one patients (95%) underwent complete removal of the brain lesion. Postoperative mortality rate was 0% within 30 days.

Table 1 Characteristics of 22 patients with brain metastasis (BM) from sarcoma who underwent surgical resection

No	Age-ranges	Histology	Interval to BM (months)	Number of BMs	Laterality of BM	Locations of BM	Tumor size (mm)	Preoperative KPS	Symptoms	Systemic control	Lung metastasis	Intratumoral hemorrhage	EOR	Postoperative KPS	Adjuvant treatment	Survival time (months)	Cause of death
1	30–39	ASPS	114	S	Right	O	17	70	Headache	Unknown	Yes	No	GTR	100	TKI	56/alive	–
2	20–29	ASPS	93	M	Both	F, T, P	N/A	10	Disturbance of consciousness	No	Yes	No	GTR	10	None	3/dead	CNS
3	30–39	ASPS	85	M	Both	F, P, O	39	90	Writing disturbance	No	Yes	Yes	GTR	90	STI	44/dead	CNS
4	30–39	ASPS	5	M	Both	F, T, O	35	60	Headache	Yes	Yes	No	GTR	60	Maruyama vaccine, STI	65/unknown	–
5	30–39	ASPS	267	S	Right	O	37	70	None	Yes	Yes	No	GTR	70	TKI, WBRT	14/unknown	–
6	30–39	ASPS	52	M	Left	P, C	40	10	Disturbance of consciousness	No	Yes	Yes	GTR	50	Maruyama vaccine, STI	30/dead	CNS
7	30–39	Embryonal rhabdomyosarcoma	10	S	Left	O	56	80	Headache	Yes	Yes	Yes	GTR	80	Chemotherapy, STI	6/dead	Primary
8	50–59	Leiomyosarcoma	0	S	Left	O	59	40	Visual field abnormality, headache	No	Yes	No	GTR	60	Chemotherapy, STI	7/unknown	–
9	50–59	Leiomyosarcoma	89	S	Left	O	67	40	Visual field abnormality, headache	Unknown	Yes	Yes	GTR	70	STI	14/dead	CNS
10	50–59	Leiomyosarcoma	9	S	Right	P	34	70	Headache	No	Yes	No	GTR	50	WBRT	3/dead	Primary
11	40–49	Leiomyosarcoma	0	M	Both	F, T, P, O, C	64	50	Aphasia	No	Yes	No	GTR	90	TKI, WBRT, STI	21/dead	Primary
12	50–59	Leiomyosarcoma	66	S	Left	F	60	40	Aphasia, motor weakness	Yes	No	No	GTR	90	WBRT	9/alive	-
13	18–19	Malignant PNST	8	S	Left	C	50	40	Headache, Ataxia	Yes	Yes	No	GTR	10	WBRT	2/dead	Primary

Table 1 (continued)

No	Age-ranges	Histology	Interval to BM (months)	Number of BMs	Laterality of BM	Locations of BM	Tumor size (mm)	Preoperative KPS	Symptoms	Systemic control	Lung metastasis	Intratumoral hemorrhage	EOR	Postoperative KPS	Adjuvant treatment	Survival time (months)	Cause of death
14	20–29	Osteosarcoma	60	S	Right	F	42	50	Headache, motor weakness	Unknown	Yes	No	GTR	90	Maruyama vaccine, WBRT	11/dead	Primary
15	50–59	Perivascular epithelioid cell tumor	21	S	Right	P	31	50	Motor weakness	No	Yes	Yes	GTR	80	STI	29/dead	Primary
16	60–69	Pleomorphic sarcoma	13	S	Left	F	26	80	Motor weakness	No	Yes	No	GTR	100	STI	20/alive	-
17	70–79	Pleomorphic sarcoma	16	S	Left	O	28	90	Motor weakness	No	Yes	Yes	GTR	90	STI	6/alive	–
18	50–59	Synovial sarcoma	22	S	Left	P	30	20	Dizziness	No	No	Yes	GTR	70	Chemotherapy, WBRT	2/unknown	–
19	40–49	Synovial sarcoma	3	S	Right	P	5	100	None	Yes	No	No	GTR	100	TKI, WBRT, STI	16/dead	CNS
20	30–39	Undifferentiated sarcoma	14	M	Right	F, O	45	50	Motor weakness	No	Yes	No	STR	60	WBRT	2/dead	Primary
21	60–69	Undifferentiated pleomorphic sarcoma	19	M	Both	F, P, C	66	70	Aphasia	No	Yes	No	GTR	70	WBRT	6/unknown	–
22	60–69	Undifferentiated pleomorphic sarcoma	25	M	Both	F, I	30	80	Motor weakness	No	Yes	No	GTR	80	TKI, STI	7/dead	Primary

(Number of BMs) *S* single, *M* multiple; (locations of BM) *F* frontal lobe, *T* temporal lobe, *P* parietal lobe, *O* occipital lobe, *I* intraventricular, *C* cerebellum; (tumor size) *N/A* not available, *EOR* extent of resection, *GTR* gross total removal, *STR* subtotal removal; (adjuvant treatment) *TKI* tyrosine kinase inhibitor, *STI* stereotactic irradiation, *WBRT* whole-brain radiotherapy, *CNS* central nervous system

Table 2 Univariate analysis of overall survival in our cohort

	Number	Median OS	*P* value
Age			**0.003**
18–29 years old	3	3	
30–76 years old	19	29	
Sex			0.50
Male	11	21	
Female	11	14	
Number of BMs			0.94
Single	14	16	
Multiple	8	21	
Intratumoral hemorrhage			0.99
Present	7	29	
Absent	15	16	
Systemic control			0.86
Yes	6	16	
No	13	21	
Unknown	3	14	
Lung metastases			0.95
Present	19	21	
Absent	3	16	
Preoperative KPS			0.47
≥ 70	10	30	
≤ 60	12	14	
Postoperative KPS			0.43
≥ 70	15	21	
≤ 60	7	3	
Change of perioperative KPS			0.54
Increase	11	21	
No change or decrease	11	16	
RPA class			0.62
1	1	16	
2	9	44	
3	12	14	
Postoperative chemotherapy			0.74
Yes	8	16	
No	14	29	
Extent of resection			**0.002**
GTR	21	21	
STR	1	2	
Histology			**0.02**
ASPS	6	44	
Non-ASPS	16	14	

Bold values indicate statistical significance

OS overall survival, *KPS* Karnofsky Performance Status, *GTR* gross total resection, *STR* subtotal resection, *ASPS* alveolar soft part sarcoma

Changes of KPS in perioperative period in our cohort

Neither pre- nor postoperative KPS was a significant prognostic factor for OS. However, surgical removal markedly improved postoperative KPS in 50% (11/22) of the patients, especially in patients with lower preoperative KPS (Fig. 1).

Univariate and multivariate analyses of overall survival in our cohort

Figure 2 presents Kaplan–Meier survival curves for BM from sarcomas. Median OS was 21 months [95% confidence interval (CI) 7–30 months]. We set the age threshold to 30 years because the OS was significantly different between patients younger and older than this value by actual univariate analysis using 5-years steps from 25 to 65 years of age. *P* value was the minimum for a threshold of 30 years old. Univariate analysis of OS showed that age (≥ 30 years old), gross total resection (GTR), and histology of ASPS were significant positive prognostic factors ($P < 0.05$, Table 2; Fig. 3a, b). Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification [60–62] had no significant prognostic value in our cohort (RPA Class 2 vs. Class 3 $P = 0.38$, Fig. 3c). In non-ASPS patients, the RPA classification had no significant prognostic value (RPA Class 2 vs. Class 3, $P = 0.65$). Number of BMs, control of the primary sarcomas, and presence of pulmonary metastases also did not significantly correlate with the OS. To identify independent prognostic factors before surgery, we performed multivariate analysis on age (≥ 30 years old) and histology of ASPS. Multivariate analysis of OS showed that age (≥ 30 years old) and histological diagnosis of ASPS were significant preoperative prognostic factors ($P < 0.05$, Table 3). The hazard ratios of age (≥ 30 years old) and ASPS were 0.16 and 0.11.

Graded prognostic assessment (GPA) for patients with BM from sarcomas surgically treated

A new GPA index was introduced to predict individual survival after surgical resection of BM from sarcomas, as shown in Table 4. The GPA consisted of age and histology as independent prognostic factors. A score of 0 was assigned to patients aged 18–29 years with non-ASPS sarcomas, a score of 2 to patients aged 18–29 years with ASPS or aged 30–76 years with non-ASPS sarcomas, and finally a score of 4 to patients aged 30–76 years with ASPS. Since the hazard ratio of age and histology were equivalent, the weight of the assigned score was equally set among these factors. Kaplan–Meier survival curves showed that the median

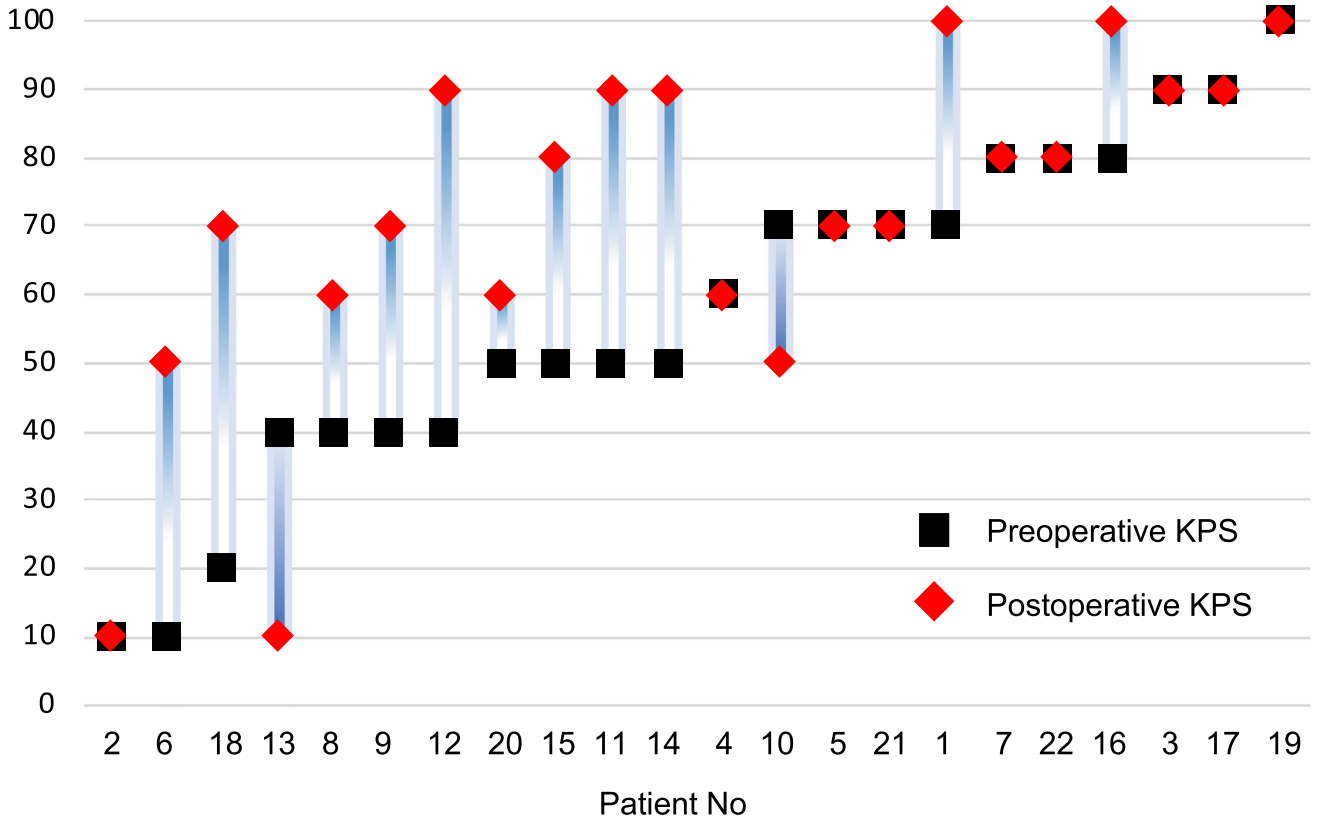

Fig. 1 Individual changes in pre- and postoperative KPS in our cohort. The *x*-axis represents patient number and the y-axis represents the post- and preoperative KPS. Black squares show preoperative KPS and red diamond shapes show postoperative KPS. Note that KPS improved in 11 patients after surgical resection

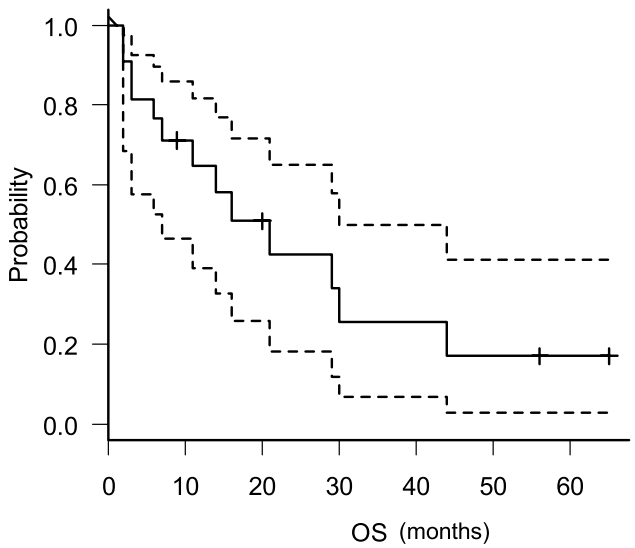

Fig. 2 Kaplan–Meier curves of overall survival after surgical resection of BM from sarcomas. Solid line and dotted lines illustrate survival curve and 95% confidence interval, respectively. Median OS was 21 months

durations of OS for our 22 patients with GPA scores of 0, 2, and 4 were 6.5, 16.0, and 44.0 months, respectively, which were significantly different ($P = 0.002$, Fig. 4a).

Validation of the GPA for cases in the literature

Data on 100 patients were collected from 48 published reports about patients with BM from sarcomas who underwent surgical resection [3–5, 13–57]. The characteristics are summarized in Supplemental Table. Median OS was 14 months [95% confidence interval (CI) 10.2–19.5 months]. Multivariate analysis of OS showed that histological diagnosis of ASPS was a significant preoperative prognostic factor ($P < 0.05$, Table 5) and age (≥ 30 years old) was a strong preoperative prognostic factor ($P = 0.11$, Table 5). We adapted our new GPA system to the 100 patients and found that Kaplan–Meier survival curves showed GPA score 4 (10 patients) median OS 97 months, GPA score 2 (67 patients) median OS 14.5 months, and GPA score 0 (23 patients) median OS 6.2 months, which were significantly different ($P < 0.001$, Fig. 4b).

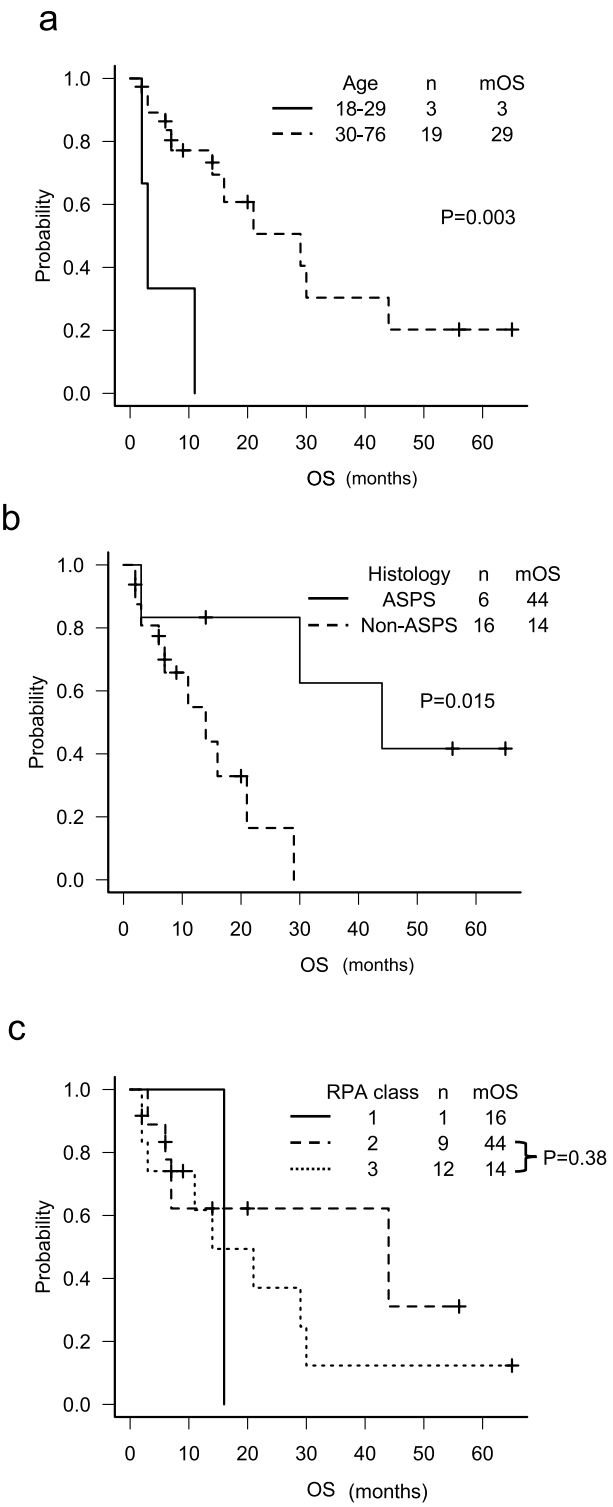

Fig. 3 Kaplan–Meier curves of overall survival. **a** Kaplan–Meier curves of overall survival after surgical resection of BM from sarcomas comparing younger patients aged 18–29 years old (solid line) with older patients aged 30–76 years old (dashed line). *P* value was the minimum for a threshold of 30 years old. **b** Kaplan–Meier curves of overall survival after surgical resection of BM from sarcomas comparing patients with ASPS (solid line) and with non-ASPS (dashed line). **c** Kaplan–Meier curves of overall survival after surgical resection of BM from sarcomas comparing patients with RPA class 1 (solid line), RPA class 2 (dashed line), and RPA class 3 (dotted line)

Discussion

In this study, we demonstrated that surgical resection was performed safely and may be a treatment option for the properly selected patients with BM from sarcomas. On the other hand, chemotherapy and radiation therapy have been remarkably developed in recent years. It was reported that stereotactic irradiation significantly prolonged survival time (median OS: 10.2 months, HR: 0.41, $P = 0.008$) [10] and provided a high local control rate (88%) [4]. It was also reported that chemotherapy including tyrosine kinase inhibitor significantly prolonged survival time (median OS: 7.7 months, HR: 0.38, $P < 0.001$) [10]. It is important to select an appropriate treatment for each patient.

We found that the median survival of patients with BM from sarcomas surgically treated was comparable to that from carcinomas. Median OS of our cohort and validation group was 21 and 14 months, respectively. A recent Japanese prospective study reported that median OS of 271 patients with carcinomatous BM was 15.6 months after removal [63]. Additionally, postoperative KPS was improved in 50% (11/22) of the patients and postoperative mortality was 0%. Surgical resection remarkably improved KPS in safety. Despite the large size of the BM, 95% of the patients underwent complete removal of the lesion, which is compatible with the data in previous reports [5, 12, 64]. These results suggest that BM from sarcomas may have features facilitating its safe and complete removal. When we select surgical removal as a treatment option for patients with BM, we ought to consider local control for not only the survival benefit but also for the immediate improvement of KPS.

Our cohort study revealed a few differences in clinical features between BM from sarcomas and that from carcinomas. Sarcomas occur in younger people than carcinomas do. The median age of the patients in this study was 45 years.

Table 3 Multivariate analysis of overall survival in our cohort

	Hazard ratio	95% CI	*P* value
Age: 30–76	0.16	0.03–0.71	**0.02**
Histology: ASPS	0.11	0.11–0.91	**0.046**

Bold values indicate statistical significance

ASPS alveolar soft part sarcoma

Given the risk of surgery, resection may be more suitable for BM from sarcomas than for BM from carcinomas, since young people have fewer systemic complications or frailty. Indeed, in our cohort, postoperative mortality rate was 0% within 30 days. However, older age (30–76 years old) was a

Table 4 Graded prognostic assessment on surgical resection of brain metastasis from sarcoma

	Score	
	0	2.0
Age	18–29 years old	30–76 years old
Histological type	Non-ASPS	ASPS

95% CI 95% confidence interval, *ASPS* alveolar soft part sarcoma

Table 5 Multivariate analysis of overall survival in validation group

	Hazard ratio	95% CI	*P* value
Age: 30–76	0.65	0.38–1.11	0.11
ASPS	0.14	0.050–0.39	**< 0.001**
Gender: men	1.05	0.64–1.75	0.84

Bold values indicate statistical significance

95% CI 95% confidence interval, *ASPS* alveolar soft part sarcoma

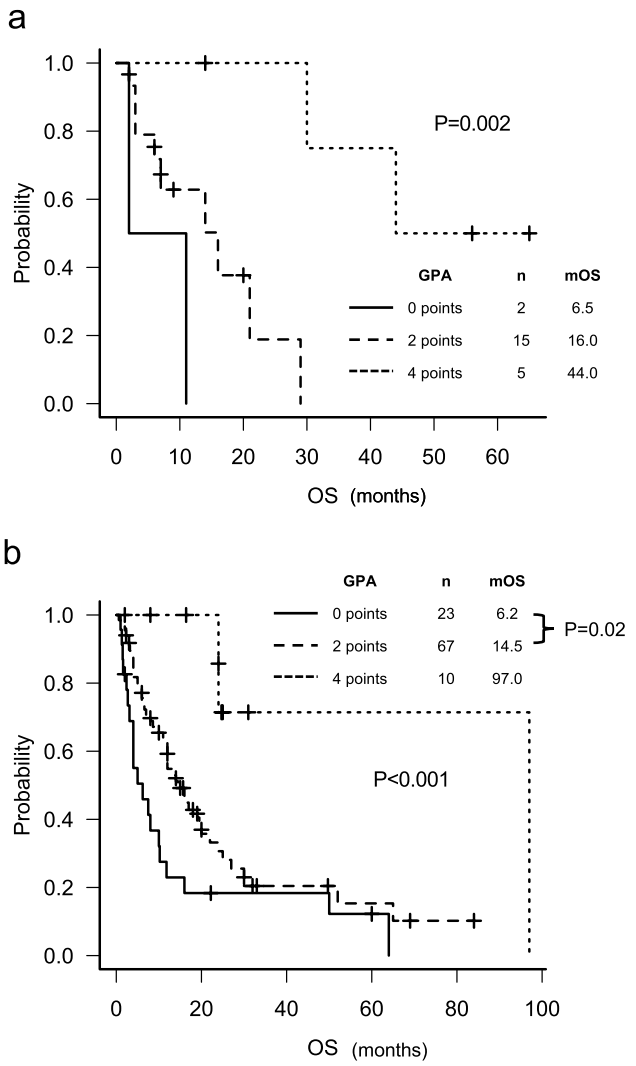

Fig. 4 Kaplan–Meier curves of overall survival after surgical resection of BM from sarcomas according to GPA. **a** Our cohort, **b** the validation group. 0 points (solid line), 2 points (dashed line), and 4 points (dotted line)

positive prognostic factor in both our cohorts and the validation group. This result contradicts that of the patients with BM from carcinomas [62]. We hypothesize on two possible reasons for this discrepancy. One is the selection bias for surgical removal in this retrospective study. Another is that adolescents and young adult patients had more aggressive sarcomas in this heterogeneous patient group.

We found that a histological diagnosis of ASPS is a significant positive prognostic factor for BM from sarcomas with surgical removal. Sarcomas include a variety of pathological diagnoses. ASPS is an extremely rare sarcoma, which accounts for about 0.5–1% of soft-tissue sarcomas [65]. However, ASPS is characterized by a high incidence (30%) of BM [66]. In this study, patients with BM from ASPS showed significantly longer OS than those with BM from other tissue types, which is consistent with previous reports [5, 64].

We developed a new GPA system from the data of multiple institutions in Japan, and validated it with 100 cases from 48 published reports [3–5, 13–57]. This GPA comprised patients' age and primary diagnosis because our study demonstrated only age (≥ 30 years old) and histological diagnosis of ASPS as significant preoperative prognostic factors. This GPA on surgical resection of BM from sarcomas enabled prediction of the postoperative survival. This result may help patients and clinicians to select resection as an option for treating BM from sarcomas.

Grossman et al. reported that the RTOG-RPA classification was applicable to patients who were operated on for BM from sarcomas [12]. However, we demonstrated that none of the constitutive factors of RTOG-RPA (age < 65 years old, preoperative KPS, control of primary lesion, and extracranial metastasis) presented significance as a positive prognostic factor in our cohort. Grossman's cohort did not contain patients with ASPS who have a high incidence of BM and significantly longer postoperative OS. The RTOG-RPA classification had no significant prognostic value even in our patients of non-ASPS. Regarding age, 86 and 88% of the patients were under 65 years of age in our cohort and the validation group, respectively. Preoperative KPS > 60 was reportedly associated with a good prognosis [3, 5, 17]. However, in our cohort, KPS was dramatically improved by surgical resection, especially in patients with worse preoperative KPS, because impaired KPS often depends on neurological deficits before surgery. In addition, patients usually had extracranial metastasis when BM was detected, as our data and previous reports showed [64, 66]. On the other

hand, control of the primary lesion was not significantly related to OS in our cohort. This discrepancy with previous reports may have resulted from the small size of the study, various degrees of malignancy, and heterogeneous postoperative treatments [11, 64]. Therefore, we concluded that the RTOG-RPA classification for cancerous BM is not appropriate for patients undergoing surgical removal of BM from sarcomas, and we need a new GPA specific for sarcomatous BM.

Our study has some limitations. The retrospective nature of this study is associated with potential bias of selection for surgical removal, and this study also has a small sample size because of the rarity of sarcomas with BM. Moreover, we analyzed the results in only sarcoma patients with BM surgically treated. Their pre- and postoperative treatments for BM and systemic sarcomas were heterogeneous and individualized. In addition, various subtypes of sarcomas were included in this study because of the rarity of this entity. These factors may have impacted on study outcomes and may limit the strength of the conclusions drawn here.

In conclusion, we reported that patients with BM from sarcomas surgically treated showed median survival comparable to that of patients with BM from carcinomas, and showed improvement in postoperative KPS. We developed a new GPA of patients with BM from sarcomas, which comprised age and histology. In addition, our cohort showed that surgical resection was performed safely and may be a treatment option for the appropriately selected patients with BM from sarcomas. Its clinical application may help patients and clinicians to predict survival time and select resection as an option for treating BM from sarcomas. We would like to encourage patients, surgeons, and oncologists to assess individualized surgical indications for BM from sarcomas.

Author contributions Study concept and design: SD and YN (Yoko Nakasu); Acquisition of data: TS, JA, KT, AN, MT, TO, HA, KM, NH, and YN (Yoshitaka Narita); Analysis and interpretation of data: SD and YN (Yoko Nakasu); Drafting of the manuscript: SD and YN (Yoko Nakasu); Statistical analysis: SD. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

Ethics approval and consent to participate This study was approved by the institutional research ethics board of Shizuoka Cancer Center (T29-36-29-2-3). Given the retrospective nature of this study, specific formal consent was not required.

Consent for publication Not applicable.

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