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Clinical Outcome of the Patients With Brain Metastasis from Soft Tissue Sarcomas

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Abstract. *Background/Aim: This study aimed to evaluate the association of clinical characteristics with treatment outcomes to ascertain the appropriate treatment options for soft tissue sarcomas (STS) patients with brain metastasis (BM). Patients and Methods: Medical records of STS patients with BM who were treated in our institutions were retrospectively reviewed, and analyzed to identify the factors associated with post-BM survival. Results: Among the 509 STS patients, BM occurred in five patients (0.98%). The median survival after BM was 1.5 months. Histological subtypes of the primary lesions in the five BM patients were: two synovial sarcomas, one myxoid liposarcoma, one alveolar soft part sarcoma, and one rhabdomyosarcoma. Among the five BM patients, the post-BM survival of two patients, who underwent surgery and postoperative radiotherapy, was longer than that of the other patients ($p<0.01$). Conclusion: Combined surgery and postoperative radiotherapy effectively managed symptoms and prolonged survival in STS patients with BM.*

Soft tissue sarcomas (STS) are uncommon and heterogeneous cancers of mesenchymal origin, representing approximately 1% of cancers in the adult population (1). Although adequate wide resection is the dominant curative therapy for primary STS (2), a multidisciplinary approach using chemotherapy and/or radiotherapy should be considered as pre- or post-operative adjuvant therapies (3). Half of patients with high-grade STS have been reported to die from metastatic disease, which may present as microscopic foci at the time of primary diagnosis (4). This is especially true in the lung, which is the most common site of distant metastasis (5). Brain metastasis (BM) in STS is rarely encountered, with a reported incidence of 1-8% (6-14). However, its incidence has been increasing due to advances in chemotherapeutic agents and diagnostic imaging technology (15). BM significantly affects the quality of life (QOL) and the prognosis of the patients. The mean overall survival after BM has been reported to be 1.8 to 11.8 months (6, 7, 9, 11-13, 15-18). Therefore, early diagnosis and effective treatment are crucial for BM patients. Valid treatment options for BM are surgery, radiotherapy, chemotherapy, and their combination. Previous reports have demonstrated that surgery and postoperative radiotherapy prolonged survival after BM, and it may be widely accepted as a standard treatment approach for BM from STS (19, 20). However, the appropriate treatment for each patient is still controversial due to the limited information available.

In the present study, we retrospectively reviewed BM in STS patients to clarify the prognostic factors that may affect post-BM survival in patients. We focused on the appropriate treatment for each patient.

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Key Words: Brain metastasis, sarcoma, prognosis, treatments.

Patients and Methods

Ethical considerations. This study was approved by the Ethics Review Board of our institutions (#B190213). Informed consent was obtained in the form of an opt-out system. Those who rejected were excluded.

Table I. *Histological subtypes of primary tumors.*

Histological subtypes	Number of patients (%)
UPS/MFH	108 (21.2)
Liposarcoma	100 (19.6)
Myxoid	55 (10.8)
Dedifferentiated	23 (4.5)
Pleomorphic	19 (3.7)
Mixed type	3 (0.6)
Myxofibrosarcoma	54 (10.6)
Leiomyosarcoma	48 (9.4)
Synovial sarcoma	45 (8.8)
MPNST	31 (6.1)
Rhabdomyosarcoma	13 (2.6)
Solitary fibrous tumor	12 (2.4)
EMC	11 (2.2)
Epithelioid sarcoma	5 (1.0)
ASPS	4 (0.8)
Others	79 (15.3)
Total	509 (100)

UPS/MFH: Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma; MPNST: malignant peripheral nerve sheath tumor; EMC: extraskeletal myxoid chondrosarcoma; ASPS: alveolar soft part sarcoma.

Table II. *Incidence of BM by sites of primary tumors.*

Sites	Number (%)	BM Incidence (%)
Thigh	197 (38.7)	2 (1.0)
Trunk	89 (17.5)	–
Lower leg	54 (10.6)	1 (1.8)
Upper arm	43 (8.4)	–
Buttocks	31 (6.1)	1 (3.2)
Forearm	23 (4.5)	–
Knee	18 (3.5)	–
Shoulder	14 (2.8)	–
Foot	12 (2.4)	1 (8.3)
Hand	9 (1.8)	–
Elbow	8 (1.5)	–
Neck	7 (1.4)	–
Ankle	4 (0.8)	–
Total	509 (100)	5 (0.98)

BM: Brain metastasis.

Table III. *Incidence of BM by histological subtypes of primary tumors.*

Histological subtypes	Number	BM Incidence (%)
Synovial sarcoma	45	2 (4.44)
Myxoid liposarcoma	55	1 (1.82)
Rhabdomyosarcoma	13	1 (7.69)
ASPS	4	1 (25.0)
Others	392	0 (0)
Total	509	5 (0.98)

BM: Brain metastasis; ASPS: alveolar soft part sarcoma.

Patients and study design. We retrospectively reviewed the records of 509 STS patients who were diagnosed and treated in our institutions between January 1998 and December 2016. The diagnosis of the primary tumor was confirmed by pathological examination. The following information was collected from the medical records: age at the primary tumor diagnosis, sex, primary tumor site, primary tumor size, histological type of the primary tumor, treatments for primary tumor, primary tumor grade, local recurrence, BM free period, signs/symptoms at the onset of BM, number of BM lesions, treatments for BM, presence of metastasis in organs other than the brain, and post-BM survival. BM was evaluated and confirmed by contrast-enhanced magnetic resonance imaging (MRI). The BM free period was defined as the time between primary tumor diagnosis and BM diagnosis by MRI. Cases with inadequate clinical records were excluded from this study.

Statistical analysis. Post-BM survival was defined as the time from the diagnosis of BM to death or last follow-up, and it was estimated using the Kaplan-Meier method (21). Significance of differences among groups was evaluated using the Mann-Whitney *U*-test. We performed a linear regression analysis of the correlations between post-BM survival and age at initial diagnosis, size of primary tumor, and BM free period. Differences and correlations were considered statistically significant at $p<0.05$. All statistical analyses were performed with EZR version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (22).

Results

Clinical characteristics of the patients and primary tumors. This study included 283 men and 226 women, with a median age of 63.0 years (range=0-94 years) at diagnosis of the primary tumor. The histologic results of the primary tumors are listed in Table I. The most common subtype was undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (UPS/MFH), which presented in 108 patients (21.2%). This was followed by liposarcoma (100 patients, 19.6%), myxofibrosarcoma (54 patients, 10.6%), and leiomyosarcoma (48 patients, 9.4%). The sites of primary STS are listed in Table II. The most common site of primary STS was the thigh, presenting in 197 patients (38.7%). This was followed by the trunk (89 patients, 17.5%), lower leg (54 patients, 10.6%), and upper arm (43 patients, 8.4%).

Compliance with ethical standards. Ethics approval for the retrospective data analyses was obtained from the Institutional Review Boards of the Kobe University Hospital and the Hyogo Cancer Center (IRB Number: B190213). Informed consent was obtained in the form of opt-out system. Those who rejected were excluded.

Brain metastasis. Among the 509 STS patients, five patients developed BM (0.98%). The numbers and incidence of BM

Table IV. *Clinical characteristics of 5 patients with BM from STS.*

	Age Gender	Histological subtype	Site	Primary tumor size (mm)	BM free period (month)	Number of BM lesions	Symptoms	Treatment for BM	Metastases in other sites	Post-BM survival (month)	Status at last follow-up
1	36M	Myxoid liposarcoma	Thigh	70	59	Solitary	Headache	Nothing	Bone	0.1	DOD
2	77M	Rhabdo-myosarcoma	Buttock	110	8	Solitary	Wobble	WBRT	Lymph node, Soft tissue	1	DOD
3	36M	Synovial sarcoma	Thigh	157	24.5	Solitary	Convulsion	Surgery	Lung	1.5	DOD
4	58M	ASPS	Lower leg	80	38	Solitary	Level lowering	Surgery+ WBRT	Lung	14	DOD
5	41F	Synovial sarcoma	Foot	98	37	Solitary	Numbness of extremities	Surgery+ SRS+ Chemotherapy	Lung	21	AWD

BM: Brain metastasis; ASPS: alveolar soft part sarcoma; WBRT: whole-brain radiotherapy; SRS: stereotactic radiotherapy; DOD: died of disease; AWD: alive with disease.

from STS according to site and histological subtypes of primary tumors are shown in Tables II and III, respectively. BM developed in two patients with primary STS in the thigh. The remaining three STS patients who developed BM had primary lesions in the buttock, lower leg, and foot. The patients with primary STS in the foot had the highest incidence rate of BM (1 patient out of 12 patients, 8.33%). The histopathological subtypes of the primary tumors were synovial sarcoma (2 patients out of 45 patients, 4.44%), myxoid liposarcoma (1 patient out of 55 patients, 1.82%), rhabdomyosarcoma (1 patient out of 13 patients, 7.69%), and ASPS (1 patient out of 4 patients, 25.0%). In terms of histological subtypes, only four patients had ASPS, but BM occurred in one of these patients. The incidence rate of BM in ASPS was relatively high compared to the other subtypes. Regarding the treatment for the primary tumor of the five patients, all patients underwent radical resection with an adequate wide margin, including two amputations. In addition to the surgery, two patients received preoperative chemotherapy, one received preoperative and postoperative chemotherapy, one received postoperative radiotherapy, and one received chemotherapy (pre- and post-operative) and pre-operative radiotherapy. Local recurrence of the primary lesion occurred in two of the five patients (40.0%) before the diagnosis of BM.

The detailed clinical characteristics of the five patients with BM are summarized in Table IV. There were four men and one woman, with a median age of 41.0 years (range=36-77 years) at diagnosis of the primary lesion. The median maximum size of the primary lesion was 98.0 mm (range=70-157 mm), and the lesions were located in the thigh (2 patients), buttock (1 patient), lower leg (1 patient), and foot (1 patient). The American Joint Committee on Cancer staging of the primary tumor was III in four patients (80.0%) and IV in one patient (20.0%). Among the five patients, the median BM free period was 37.0 months (range=8-59 months), and the median time from the diagnosis of primary tumor to death or last follow-up was 52.0 months (range=9-59.1 months). In all five patients, the BM was a solitary lesion, and the clinical symptoms, such as aphasia, convulsions, numbness, headache, wobble, and level lowering, appeared prior to a radiological confirmation by contrast-enhanced MRI. Treatments performed for the BM lesion were: surgery alone (1 patient), radiotherapy alone (1 patient), surgery and post-operative radiotherapy (1 patient), and surgery and postoperative radiotherapy and chemotherapy (1 patient). One patient did not receive treatment for BM. All patients had metastases in organs other than the brain before the BM diagnosis, and the most common site was the lung (3 patients, 60.0%). Lung metastasis was present during the primary tumor diagnosis in an ASPS patient (Patient #4). Treatments performed for lung metastasis were chemotherapy alone (1 patient), surgery and chemotherapy (1 patient), and none (1 patient).

Post-BM survival. Post-BM survival of the five patients ranged from 0.1 to 21 months, and the median survival was 1.5 months (Table IV and Figure 1). At the time of the final analyses, four patients (80.0%) died of disease (DOD), and one patient (20.0%) was alive with disease (AWD). The median survival of the four DOD patients was 1.25 months (range=0.1-14 months). During the last follow-up, the one AWD patient survived for 21 months after BM diagnosis (Patient #5). The estimated 3-, 6-, and 12-month survival rates of the five patients were 60.0%, 40.0%, and 40.0%, respectively (Figure 1). Two patients (Patient #4 and #5) who underwent a combination of surgery and postoperative radiotherapy survived over 12 months after the BM

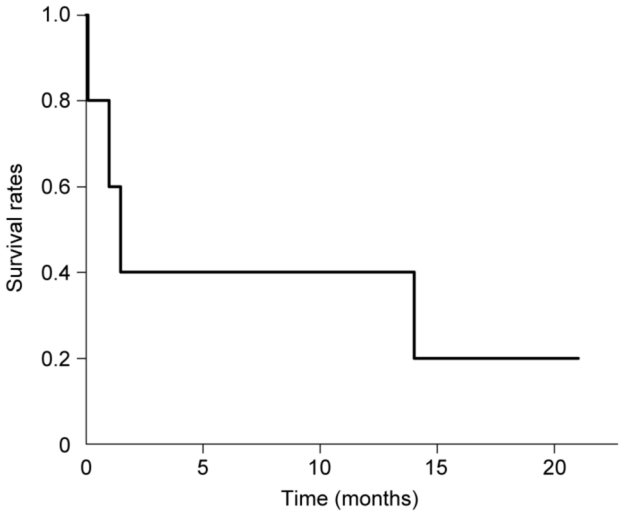

Figure 1. *Survival after BM in all of the five patients with STS.*

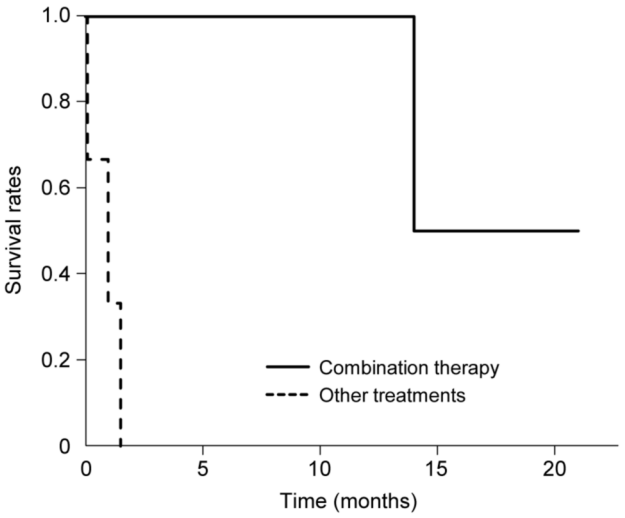

Figure 2. *Kaplan-Meier survival curves according to treatments for BM (p<0.01).*

diagnosis, and they had significantly longer median post-BM survival (17.5 months *vs*. 0.87 months, $p<0.01$) than the other three patients (Figure 2). In one patient (Patient #5) who underwent surgery, postoperative stereotactic radiotherapy (SRS), and chemotherapy, BM recurred twice at 12 months and 20 months after the initial diagnosis of BM. Both recurrent lesions were treated with SRS alone, and the patient survived for 59 months after the time of initial diagnosis of BM. Post-BM survival was not correlated with age at initial diagnosis ($p=0.93$), maximum size of primary tumor ($p=0.86$), and BM free period ($p=0.71$).

Discussion

In the current study, we retrospectively reviewed the records of STS patients with BM and analyzed factors associated with post-BM survival to determine the appropriate treatment for each patient to achieve long-term survival. Patients who underwent a combination of surgery and post-operative radiotherapy showed significantly longer post-BM survival than those who received other treatment options. Our results strongly indicated that combination therapy prolonged the survival of STS patients with BM.

The number of cancer patients has been increasing, and there are approximately one million newly diagnosed patients in Japan every year. Despite significant advances in diagnosis and treatment, the disease remains the leading cause of death; 370,000 patients die annually (23). BM is reported to occur in approximately 10 to 30% of all cancer patients. It commonly develops in carcinomas, particularly in lung, breast, and colorectal cancer (24). While BM develops in up to 30% of all cancer patients, its incidence in STS patients is extremely rare, ranging from 1 to 8% (6-14). In line with previous reports, our study detected BM in only five (0.98%) of 509 STS patients. Although BM in STS patients is rare, the number of cases has been increasing due to the development of diagnostic imaging technology and systemic chemotherapy regimens. These may be effective for systemic disease control but are ineffective on BM (15).

Previous reports have suggested that various histological subtypes of STS can spread to the brain. Sawaya *et al*. have reported that the most common subtype was UPS/MFH, which progressed to BM in adults. The other type was rhabdomyosarcoma, which develops in children (25). Another report has noted that the most frequent histological subtype was leiomyosarcoma, followed by UPS/MFH (26). In the current study, there were four different histological subtypes of STS. The incidence rate of BM in ASPS was the highest at 25% (one of 4 patients) while BM did not develop in UPS/MFH patients, which was the most common subtype in this study. ASPS, a rare type of sarcoma accounting for less than 1% of all STS (8, 27), has been reported to show a high incidence rate of BM, approaching 30% (14, 28), and the post-BM survival of ASPS patients was relatively good (6, 8). An ASPS patient with BM (Patient #4) in our series survived over 14 months after being diagnosed with BM, despite having lung metastases at the time of the primary tumor diagnosis.

All five STS patients with BM in this study showed signs and/or symptoms prior to MRI confirmation. Previous studies have also demonstrated that most patients with BM were symptomatic at diagnosis (12, 15). In STS patients, surveillance for BM, such as a brain CT and/or MRI, is not cost-effective and is, therefore, not routinely performed as a

regular follow-up examination due to the rarity of BM (29). Therefore, brain imaging should depend on the patients' symptoms, and the detection of BM lesions may be delayed. FDG-PET can be performed for systemic screening in STS patients and may be useful for the early detection of metastatic brain lesions. However, the sensitivity of FDG-PET for BM lesions in lung cancer patients has been reportedly low, with an incidence of 24-27%. Therefore, enhanced MRI should be combined with this examination for the early detection of BM (30, 31). Based on these reports, FDG-PET and enhanced brain MRI may be considered part of BM surveillance during regular follow-up in STS patients. This is especially applicable in patients with ASPS, which have a relatively high incidence of BM.

Post-metastasis survival of STS patients with BM has been reported to be shorter than that in other cancers because standard treatment has not been established for these cases. The median survival after BM of STS patients has been reported to be between 1.8 and 11.8 months (6, 7, 9, 11-13, 15-18) while the survival of patients with BM in other cancer types has been reported to be 18 months (32). In this study, the post-BM survival of the five patients was 7.5 months, which is similar to previous reports. Early initiation is required to prevent metastasis of STS (33) and the treatment approach for BM is crucial for the prognosis of the patients. However, multimodal therapies including surgery, radiotherapy, and chemotherapy have not proven to be beneficial to patients' survival, and there is no established treatment for BM. Surgery and/or radiotherapy for metastatic lesions in the brain could improve the outcome of STS patients (7, 8, 10, 34), and these treatments have become the mainstay for BM. Although surgery is invasive, removing the BM lesion improves performance status, and a pathological diagnosis is obtained. Moreover, Tsuchie *et al*. reported that removing distant metastatic lesions surgically is important to improve the patient's prognosis (35). However, surgery alone may not be enough to prolong the patient's survival and is likely to cause recurrence of BM lesions. For these reasons, radiotherapy has been commonly utilized in conjunction with surgical resection for BM lesions (19, 20). Whole-brain radiotherapy (WBRT) is effective for patients with multiple BM lesions. WBRT has been a standard treatment option in BM patients for several decades (20, 36-41). However, therapy frequently causes cognitive dysfunction. Recently, SRS has been preferred to avoid adverse effects. SRS is a method of delivering high doses of focal radiation to a tumor while minimizing irradiation of the adjacent normal tissues. The advantages of SRS include the noninvasive approach and the possibility of treating multiple lesions on an outpatient basis (42). It has been reported that administering SRS to the post-operative cavity of BM lesions effectively achieved local control one year after treatment (43-48). Moreover, compared to SRS alone, the use of WBRT in addition to SRS was not proven to influence the survival of patients with few BM lesions (38, 49, 50). In addition, the survival of SRS-treated patients with five to ten BM lesions was not inferior to that of patients with two to four BM lesions (51). In this study, two patients who underwent a combination of surgery and post-operative radiotherapy achieved long-term survival over 12 months after BM diagnosis. Therefore, combination therapy is a viable treatment for STS patients with BM. The role of chemotherapy in treating metastatic sarcoma remains controversial. Cytotoxic chemotherapy with anthracycline-containing regimens has been the mainstay treatment for unresectable and/or metastatic sarcomas. However, previous studies have not proven its effectiveness in patients with metastasis, particularly BM, due to its poor blood-brain barrier penetration (52-56). Therefore, systemic chemotherapy has been used in palliation to improve QOL by reducing symptoms. In recent years, recently approved agents for sarcoma, such as trabectedin and eribulin, have effectively treated specific sarcoma subtypes (57). In the current study, the patient with synovial sarcoma (Patient #5), who was treated with the combination of surgery and postoperative SRS as well as chemotherapy with second-line agents, showed the longest survival of 21 months after BM diagnosis. Further investigations are required to clarify the effects of chemotherapy on BM in STS patients.

This study has several limitations. First, due to its retrospective design, we cannot exclude the possibility of selection bias. Second, since STS is a rare cancer, the sample size was small. Therefore, multicenter studies with larger samples, meta-analyses, or systemic reviews will be helpful in elucidating the factors associated with the prognosis of sarcoma patients with BM.

Conclusion

In the current study, the combination of surgery and postoperative radiotherapy prolonged the survival of STS patients with BM. With proper consideration of the risks and benefits, early diagnosis and appropriate treatment may positively affect the survival of patients with BM. Surgeons treating patients with STS must be aware that the brain is a potential metastatic site of STS.

Conflicts of Interest

The Authors have no conflicts of interest to declare that are relevant to the content of the article.

Authors' Contributions

TT and TK were responsible for the study conception and design, and drafted the manuscript. TK, MM, HH, NF, YK, SF, KaK, SY, TomohiroM, TF, and IF were responsible for data acquisition. YM,

YH, KeK, TomoyukiM, and TakehikoM were responsible for data analyses. TN, RK, and TA helped in the editing of the manuscript. All Authors contributed to and approved the final version of the manuscript.

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