Brain, the Last Fortress of Sarcoma: Similar Dismal Outcome But Discrepancy of Timing of Brain Metastasis in Bone and Soft Tissue Sarcoma

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Background and Objective: Brain metastasis is a rare but dismal event in sarcomas. However, the pattern of occurrence and the prognostic factors associated with post-brain metastasis survival (PBMS) are not yet well-characterized.
Methods: Sarcoma patients treated at one institute within 10-year period were retrospectively reviewed and those with brain metastasis were identified. The incidence of brain metastasis was demonstrated by case per person-years and cumulative incidence curves. Univariate factors associated with PBMS were analyzed.
Results: Among 611 sarcoma patients, 20 (3.3%) developed brain metastasis. Alveolar soft part sarcoma (ASPS) and osteosarcoma were the most common subtypes. Overall, the cumulative incidence was 3.9% at 5 years and 8.4% at 10 years. However, the incidence in STS patients continued to rise up to 10 years after primary diagnosis, whereas it reached a plateau in bone sarcoma patients at 3 years. Median PBMS was 1.67 months. Univariate factors associated with better PBMS included ASPS histology, initial surgical treatment, and brain irradiation for non-surgically treated patients.
Conclusion: Our study revealed a discrepancy in the timing of occurrence of brain metastasis between STS and bone sarcoma. However, patients with brain metastasis had a poor prognosis, implicating the brain as the last fortress of sarcoma.
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KEY WORDS: alveolar soft part sarcoma; brain metastasis; osteosarcoma; soft tissue sarcoma

INTRODUCTION

Approximately 10,000 soft tissue sarcoma (STS) and 2,650 bone sarcoma cases are diagnosed annually in the United States, accounting for 0.8% of all adult cancers [1]. For localized STS, conservative, function-preserving and margin-free surgery is the mainstay of treatment, and a 5-year distant metastasis-free survival of over 60% can be achieved [2–6]. While adjuvant chemotherapy are still controversial, adjuvant radiotherapy has been considered the standard of post-operative management for high-grade tumors [7]. On the contrary, osteosarcoma (OS), the major histological type of bone tumor, is a chemo-sensitive disease. By using sequential neoadjuvant chemotherapy, surgery and adjuvant chemotherapy, a 50–70% 5-year overall survival can be achieved in patients with localized disease [8]. For both STS and OS, the lung is the most common metastatic site. However, even in cases of advanced disease, long-term survival could be achieved in 20–30% of patients using a combination of pulmonary metastatectomy and aggressive chemotherapy [8–10].

On the other hand, brain metastasis, albeit commonly seen in breast cancer (28–43% of stage IV disease with recurrence) [11], non-small cell lung cancer (30–40% of locally advanced cases) [12,13], or melanoma (up to 73% in autopsy series) [14], appears to be a rare event in sarcomas (<6%) [15–17], with the exception of alveolar soft part sarcoma (ASPS; up to 30%) [18–20]. In general, brain metastasis often occurs after local recurrence or lung metastasis [15,16], and the outcome of these patients is often dismal [17,21,22] due to its "sanctuary site" nature against chemotherapy [23]. Moreover, metastatic brain sarcomas are relatively radioresistant [24], and surgery is only beneficial in selected cases [15–17,25]. However, the difference in the pattern of occurrence of brain metastasis between STS and OS and the prognostic factors associated with post-brain metastasis survival (PBMS) are not yet well-characterized. In this study, we aimed to explore these questions by analyzing an

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ethnic Chinese sarcoma patient population from a single center over a 10-year period.

PATIENTS AND METHODS

Study Design, Patient Population, and Data Collection

This study, approved by the Institutional Review Board of Taipei Veterans General Hospital, was a retrospective cohort analysis of consecutive adult patients (≥16 years old) with sarcomas who received therapy at Taipei Veteran General Hospital from January 1999 to January 2009. Patients with brain metastasis were identified, diagnosis being based on either histology if patients were surgically treated or on imaging studies such as magnetic resonance imaging (MRI) or computed tomography (CT). The demographic data and clinical characteristics of the study population were obtained from clinical chart review, tumor registry information, and physician's records.

Statistical and Survival Analysis

The incidence of brain metastasis was described by crude incidence and by cases per person-years. The cumulative incidence of brain metastasis during the 10-year period was also depicted. PBMS was determined from the date of brain metastasis to the date of death due to cancer or the date of last contact. Survival was estimated using the Kaplan–Meier method, and the log-rank test was used for comparison of survival curves. The Cox proportional hazards model was applied for univariate analyses to determine the prognostic influence of clinicopathological factors on survival endpoints. A P-value < 0.05 was regarded as statistically significant in two-sided tests. SPSS software (version 13.00, SPSS, Chicago, IL) was used for all statistical analyses.

TABLE I. Histological Classification and Incidence of Brain Metastasis Among 611 Patients With Sarcoma

Tumor type	Total case no.	No.(%) with brain metastasis
Soft tissue sarcoma		
Malignant fibrous histiocytoma (MFH)	49	1 (2.04)
Liposarcoma (LPS)	70	2 (2.86)
Leiomyosarcoma (LMS)	49	1 (2.04)
Malignant schwannoma (MS)	23	1 (4.34)
Synovial sarcoma (SS)	25	2 (8.00)
Rhabdomyosarcoma	6	
Angiosarcoma	17	
Fibrosarcoma	22	
Hemangiopericytoma	5	
Alveolar soft part sarcoma (ASPS)	13	4 (30.77)
Clear cell sarcoma	2	
Kaposi's sarcoma	4	
Epitheloid sarcoma	2	
Spindle cell sarcoma	11	
Gastrointestinal stromal tumor(GIST)	6	
Giant cell tumor (GCT)	16	1 (6.25)
Unclassified (UC)	50	1 (2.00)
Sum	370	13 (3.51)
Bone sarcoma		
Osteosarcoma (OS)	156	5 (3.21)
Chondrosarcoma	66	
Ewing's sarcoma (EWS)	14	2 (14.29)
Extraskeletal Ewing's sarcoma	3	
Osteoblastoma	2	
Sum	241	7 (2.90)

RESULTS

Clinicopathological Characteristics of Sarcoma Patients With Brain Metastasis

A total of 611 patients, consist of 370 STS and 241 bone sarcomas, were retrospectively evaluated over the 10-year study period (Table I). A total of 20 patients (3.27%) developed brain metastasis during the study period, including 13 STS (3.50%) and 7 bone sarcoma patients (2.90%). Brain metastasis was most common in the ASPS subtype of STS; on the other hand, among 7 patients with bone sarcoma who developed brain metastasis, 5 were cases of OS (Table I). As shown in Figure 1, sarcoma patients who developed brain metastasis had a poorer overall survival than those who did not ($P < 0.001$). The 1-/3-year actuarial survival rates in sarcoma patients with or without brain metastasis were 80% (95% CI: 97.8–62.2%)/30% (95% CI: 56.4–13.6%) and 91.9% (95% CI: 94.3–89.5%)/81.1% (95% CI: 84.9–77.3%), respectively.

Table II summarizes the characteristics of brain metastasis in the sarcoma patients. Thirteen males and 7 females developed brain metastasis. Thirteen patients had their primary tumors located over the lower extremities, 2 over the upper extremities, and 5 over the trunk. The number of brain metastases at diagnosis was solitary in 10 (50%) and multiple in 10 cases (50%). The cerebrum was the most frequent metastatic site (15 cases). Of all metastases of the cerebrum, the frontal lobe was most commonly involved (10 cases), followed by the parietal lobe (8 cases), the occipital lobes (7 cases), and the temporal lobes (4 cases).

Common symptoms of brain metastasis included headache (45%), disturbed consciousness (25%), nausea/vomiting (22%), and vertigo or dizziness (30%). Five patients (25%) presented with symptoms of motor deficit, such as bilateral lower leg weakness, hemiplegia, episodic jerking of the left or hemilimbs, and 5 patients (25%) presenting with ocular symptoms such as blurred vision, double vision, protrusion of the eye, and homonymous quadrianopsia.

Prior to or at the time of brain metastasis, 18 (90%) patients had distant non-brain metastasis, including 17 with pulmonary metastasis and 12 with bone metastasis. One patient developed pulmonary metastasis 6.3 months after diagnosis of brain metastasis (case 10). Surgical resection of pulmonary metastasis was performed in 10 of the 18 patients with pulmonary metastasis (55.6%).

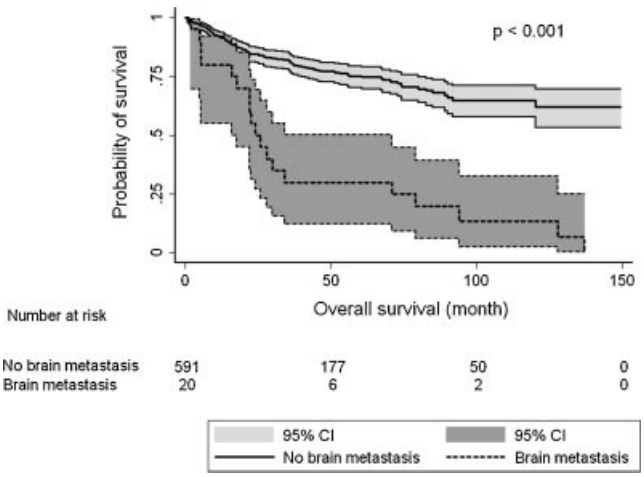

Fig. 1. Kaplan–Meier curve for overall survival of 611 sarcoma patients with or without brain metastasis.

TABLE II. Characteristics of 20 Patients With Brain Metastasis of Sarcoma

No.	Type	Age/sex	Symptoms and Signs	TNM[a]	ECOG	Lung/bone mets	No./location	Treatment	Outcome
1	ASPS	17/M	Double vision, headache, right homonymous quadrianopsia	N/A	1	Yes/no	Single/cerebrum	Preoperative embolization + surgery + GKRS	Dead
2	ASPS	33/F	Dizziness	N/A	2	Yes/yes	Single/cerebrum	Surgery	Alive
3	ASPS	29/F	Dizziness, headache, seizure, consciousness change, blurred vision	N/A	1	Yes/no	Single/cerebrum	GKRS	Dead
4	ASPS	22/M	Nausea, vomiting, headache	IV	1	Yes/no	Multiple/cerebellum	Radiotherapy	Dead
5	OS	15/F	Headache	Ib	3	Yes/no	Single/cerebrum	Surgery	Dead
6	OS	58/M	Left leg weakness	IVa	2	Yes/no	Multiple/pons, brain stem	Radiotherapy	Dead
7	OS	21/M	Bilateral lower leg weakness	Ib	3	Yes/yes	Multiple/cerebrum	Radiotherapy	Dead
8	OS	17/M	Diplegia	IVb	4	Yes/yes	Single/cerebrum	Radiotherapy	Dead
9	OS	55/M	Disturbed consciousness, slurred speech	Ib	3	No/no	Single/cerebrum	Surgery	Dead
10	LMS	36/M	Headache, lethargy	IIb	N/A	Yes[b]/no	Single/cerebrum	Surgery + adjuvant radiotherapy	Dead
11	EWS	33/F	Double vision, ptosis, EOM limitation	III	2	Yes/yes	Multiple/pons, brain stem	Conservative	Dead
12	EWS	17/M	Left facial palsy, vertigo	IV	1	No/yes	Multiple/cerebrum	Conservative	Dead
13	GTC	77/M	Nausea, vomiting, left-side limb weakness	IV	3	Yes/yes	Multiple/cerebrum	Radiotherapy	Dead
14	LPS	29/M	Diplopia	III	2	Yes/yes	Single/cerebrum	Conservative	Dead
15	LPS	61/M	Headache, consciousness disturbance	IIb	4	Yes/yes	Multiple/cerebrum	Conservative	Dead
16	MFH	26/M	Headache	III	1	Yes/yes	Multiple/cerebrum	Radiotherapy	Dead
17	MFH	48/F	Stupor consciousness	II	2	Yes/yes	Multiple/cerebrum, brain stem	Conservative	Dead
18	SS	55/M	Vertigo, vomiting, headache	IIa	2	Yes/yes	Single/cerebellum	Radiotherapy	Dead
19	SS	20/F	Double vision	Ia	1	Yes/yes	Multiple/pons, brain stem	Radiotherapy	Dead
20	UC	33/F	Headache, left limbs weakness	IIa	3	Yes/no	Single/cerebrum	GKRS	Dead

ASPS, alveolar soft part sarcoma; OS, osteosarcoma; LMS, leiomyosarcoma; EWS, Ewing's sarcoma; GCT, giant cell tumor; LPS, liposarcoma; MFH, malignant fibrous histiocytoma; SS, synovial sarcoma; UC, unclassified; ECOG, Eastern Cooperative Oncology Group; M, male; F, female; EOM, extraocular movement; N/A, not available; GKRS, Gamma knife radiosurgery.

[a]According to the American Joint Committee on Cancer's *AJCC Cancer Staging Manual*, 7th edition (2010).

[b]Pulmonary metastasis developed after brain metastasis.

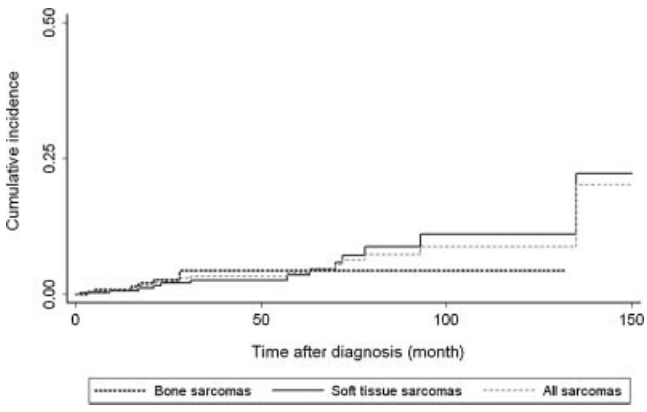

Fig. 2. Cumulative incidence of brain metastasis among the general sarcoma population, bone sarcoma, and soft tissue sarcoma.

Timing of Occurrence of Brain Metastasis

Overall, the incidence of brain metastasis was 10.2 cases per 1,000 person-years, and the median time to brain metastasis was 25.2 months (range: 0–135.3 months). As shown in Figure 2, the cumulative incidence of brain metastasis was 3.9% at 5 years and 8.4% at 10 years. However, distinct patterns of occurrence of brain metastasis were found in bone sarcoma and STS. The cumulative incidence curve of brain metastasis in the STS patients continued to rise steadily and slowly up to 10 years after primary diagnosis, whereas the curve in the bone sarcoma patients reached a plateau at approximately 3 years (Fig. 2).

Treatment of Brain Metastasis

Initial treatment modalities included surgical removal (n = 5), whole brain irradiation consisting of 30 Gy delivered in 12 fractions (n = 8), gamma-knife stereotactic radiosurgery (GKRS; n = 2), and conservative medical treatment alone (n = 5). Of the 5 patients receiving surgery, 2 were treated with sequential modalities, including preoperative embolization, surgery plus GKRS for case 1 and

surgery plus adjuvant radiotherapy for case 10. In 8 patients receiving whole brain irradiation, one (12.5%) developed post-irradiation hemorrhage in the previously irradiated brain metastasis area.

Five patients received conservative treatment only due to rapid progression of systemic disease or complications. Case 11 have concomitant multiple lung metastases which progressed rapidly and resulted in respiratory failure. Case 12 was found to have small brain metastatic lesions in together with multiple bone metastases, and chemotherapy was given first for systemic control. Unfortunately, he succumbed to aspiration pneumonia due to neutropenia. Case 14 died of rupture of intra-abdominal tumor with subsequent shock. Case 15 had bilateral frontal hemorrhagic metastases with uncontrollable increased intracranial pressure. Case 17 declined further aggressive therapies due to personal reasons and died 1 month later.

Analysis of Post-Brain Metastasis Survival

Nineteen patients eventually died. The median PBMS in the 20 patients was 1.67 months (range: 0.43–64.1 months; Fig. 3). Univariate factors associated with better PBMS included ASPS histology, initial surgical treatment, and brain irradiation for non-surgically treated patients (Table III). Due to the limited case numbers, multivariate analysis was not performed.

TABLE III. Univariate Analysis of Factors Associated With Post-Brain Metastasis Survival

Characteristics	HR	95% CI	*P*-value
Initial treatment			
Surgery versus irradiation or BSC	0.26	0.07–0.91	0.036*
Irradiation versus BSC	0.21	0.06–0.75	0.016*
Alveolar soft part sarcoma			
Yes versus no	0.08	0.01–0.62	0.016*
ECOG performance status			
0–2 versus 3–4	0.58	0.21–1.61	0.297
Lung wedge resection			
Yes versus no	0.89	0.35–2.27	0.809
Initial stage			
Stage I or II versus III or IV	0.76	0.28–2.06	0.585
Primary site			
Limbs versus non-limbs	1.22	0.39–3.77	0.732
Sarcoma type			
Soft tissue versus bone	0.53	0.20–1.43	0.209
Bone to bone metastasis			
Yes versus no	2.16	0.78–5.96	0.139
Local recurrence			
Yes versus no	1.04	0.39–2.73	0.942
Number of concurrent metastasis			
>1 versus =1	1.43	0.55–3.70	0.465

HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; CI, confidence interval; BSC, best supportive care.
*$P < 0.05$.

DISCUSSION

In this study, we confirmed the poor prognosis of sarcoma patients with brain metastasis. In addition, we found that patients with ASPS tumors and those who received either surgery or radiotherapy may have a better PBMS, which is similar to other reports [15–17,21,22,25,26]. Most interestingly, we found that most brain metastases in bone sarcoma patients occurred within 3 years of diagnosis, while in STS, recurrence in the brain could be found up to 10 years after primary diagnosis.

The incidence of brain metastasis in sarcoma patients at our institute was 3.27%, which is compatible with other reports [15–17]. Previous studies have shown that, in terms of case numbers, the histological subtypes of STS that most commonly develop brain metastasis are either leiomyosarcoma [17,25,26] or malignant fibrous histiocytoma (MFH) [15,16]. These results may just reflect the prevalence of both tumor types within the total sarcoma population [6]. However, the subtype with the highest proportion of patients developing brain metastasis is ASPS [15,16]. In this study, we also found that 30.8% of ASPS patients developed brain metastasis. For bone tumors, we found that OS is the most common subtype that metastasized to the brain, as reported by others [15,16,21,25,26], indicating its aggressive nature. On the other hand, none of the chondrosarcoma patients, in spite of its metastatic rate of over 70% for high-grade disease [27], developed brain metastasis. In fact, only a small number of case reports of chondrosarcoma with brain metastasis could be found in the literature [28,29]. The underlying mechanism of this discrepancy deserves further exploration.

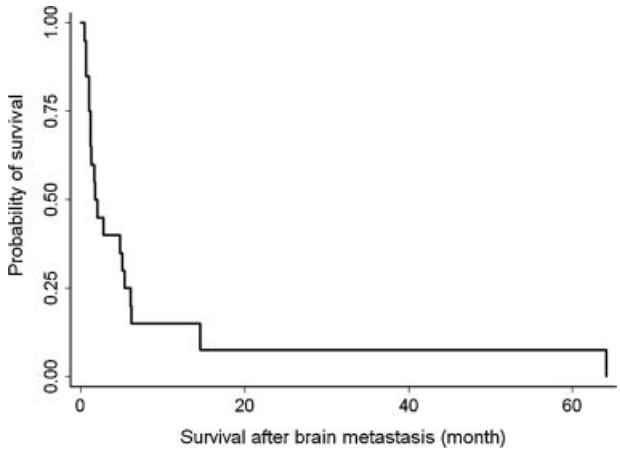

Fig. 3. Kaplan–Meier curve of post-brain metastasis survival for all sarcoma patients with brain metastasis.

In sarcoma, brain metastasis usually occurs as part of the systemic disease. In this study, we found that 17 patients (85%) had concurrent lung metastatic tumors. In the study by Yoshida et al., 16 (59.3%) of 27 cases had lung metastasis [16]. Ogose et al. [15] disclosed that 80% (16 out of 20) of cases had concomitant lung metastasis. Patients also frequently had local recurrence and non-pulmonary (mostly bone) metastasis [15,16,21,26]. As stated previously, patients with lung metastasis still had a 20–30% chance of long-term survival; however, PBMS is usually poor. These observations supported the notion that the brain may serve as the last sanctuary site of sarcoma.

The most interesting finding of our study was that we found different timings of occurrence of brain metastasis in bone sarcoma and STS. The cumulative incidence of bone sarcoma reached a plateau at approximately 3 years, while in STS, brain metastasis could occur even 10 years after the initial diagnosis. As mentioned earlier, the overall survival in cases of both localized and metastatic OS was greatly improved by a combination of aggressive surgery and chemotherapy [8–10]. However, once it becomes refractory, the disease will spread rapidly and kill patients. On the other hand, STS is a group of heterogeneous diseases. Some STS, such as ASPS, ran an incurable, yet indolent, course of disease. In fact, three of our patients with ASPS developed brain metastasis at around 5–6 years after initial diagnosis. Therefore, the difference in underlying aggressiveness of bone sarcoma and STS may contribute to the difference in the time of occurrence of brain metastasis between the diseases.

Chemotherapy is usually considered ineffective in brain metastasis, which leaves surgery and radiotherapy as the remaining options.

In our study, we found that surgery conferred a significantly better PBMS (median 6.17 months, range: 1.63–64.07) in comparison with non-surgical treatment (median 1.23 months, range: 0.43–14.53). Importantly, 2 of the surgically treated patients had long survival time (11.2 and 64.07 months, respectively) after surgical removal of brain metastasis. Our result was comparable with previous studies [15–17,21,22,25,26]. Among patients who did not receive surgery, radiotherapy, either whole brain irradiation or GKRS, also provided a significant survival benefit for patients (Table III).

Previous studies have shown that ASPS histology is a good prognostic factor for patients receiving surgical therapy [25]. In this study, we also found that ASPS histology was an important determinant of PBMS (PBMS of ASPS vs. non-ASPS, 14.53 months vs. 1.23 months, $P = 0.003$). However, there is no difference in treatment modality between ASPS and non-ASPS tumors (surgery or whole brain irradiation, $P = 0.197$ between ASPS and non-ASPS patients). On the other hand, as mentioned previously, 3 out of 4 patients with ASPS with brain metastasis developed brain recurrence 5 years after initial diagnosis. These observations indicated that the indolent nature of ASPS, rather than treatment, may contribute to the greater PBMS of the disease. Recently, tyrosine kinase inhibitors (TKIs) such as sunitinib have exhibited promising results for the treatment of ASPS [30,31]. These TKIs could enter the ''sanctuary site'' through the blood–brain barrier and may further enhance disease control in cases of brain metastasis.

One issue raised here is the necessity of routine brain surveillance. Reviewing current literatures, there is little evidence supporting surveillance with routine intracranial imaging with brain MRI or PET in sarcoma patients, even for those with high risk of brain metastasis, such as patients with ASPS [20]. However, based on current study and previous reports, brain metastasis of sarcoma often occurs as late sequelae of local relapse or systemic metastasis [15,16,20,21,26]. In addition, as mentioned earlier, patients with limited brain lesions who can be surgically treated had better survival than those who cannot [15–17]. Therefore, it is reasonable to consider brain image study for patients with local or distant recurrence, especially for patients with ASPS. This strategy may help detect brain metastasis earlier and make surgery possible. However, further prospective studies are necessary to explore this issue.

In conclusion, our study revealed different timings of occurrence of brain metastasis in STS and bone sarcoma. However, a poor outcome of brain metastasis remained for both types of tumors, implicating the brain as the last fortress for sarcoma. Palliative surgical treatment in selected patient and radiotherapy should be given to patients to improve survival.

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