Ann Surg Oncol (2016) 23:S962–S967
DOI 10.1245/s10434-016-5559-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – NEURO-ONCOLOGY

Sarcoma Brain Metastases: 28 Years of Experience at a Single Institution

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ABSTRACT

Background. Brain metastasis from sarcoma is rare, thus limited information is available. We examined sarcoma brain metastases diagnosed at our institution over a period of 28 years.

Methods. This is a retrospective study of 112 cases. Clinical records were reviewed and clinical, pathological, and survival data were tabulated.

Results. Undifferentiated sarcoma was the most common source. In 50 % of cases, the primary sarcoma was in the extremities. Most patients were adults at the time of first brain metastasis, and median age was 34.8 years. Although most patients evidenced metastatic disease to other sites prior to developing brain metastasis, in almost one quarter, brain was the initial site. Most of the metastatic foci were parenchymal, nonhemorrhagic, and solitary. Forty percent of the brain metastatic deposits were located in the frontal lobes. Thirty-one percent recurred—all within 5.3 years. Seventy-six percent of patients succumbed to the disease, with a median survival time of only 0.6 years. Hemorrhagic metastatic foci were found to be associated with significantly lower recurrence-free, as well as disease-specific survivals. No difference in survival was noted between single versus multiple deposits or primary soft tissue versus bone sarcomas. No statistically significant effect on survival was found when neurosurgical resection was combined with radiotherapy. Chemotherapy, on the other hand, was found to significantly improve disease-specific survival when combined with metastasectomy.

Conclusions. Undifferentiated sarcoma was the most common source of brain metastasis. Most cases showed evidence of prior metastatic disease. Surgical resection is employed to manage symptoms, but prognosis remains dismal.

Sarcoma is a heterogeneous group of more than 50 clinicopathological subtypes of malignant neoplasms showing various types of mesenchymal differentiation. Sarcomas are rare and comprise merely 1 % of all forms of cancer in the adult population.[1] The most common histological subtypes of sarcoma in adults are liposarcoma, undifferentiated pleomorphic sarcoma, and leiomyosarcoma.[2] Local recurrences (sometimes multiple) and distant metastases are commonly seen throughout the course of many sarcomas. The lung is the most common site for distant metastases for most sarcomas, followed by liver and bone. Brain is an unusual metastatic site for sarcoma and usually occurs late in disease progression, often following other distant metastasis, particularly to the lung. The incidence of sarcoma brain metastases, however, is thought to have increased during the past decade.[3,4] This increase could be due to the increased sensitivity and specificity of imaging technology as well as new radiotherapeutic and chemotherapeutic regimens, which can be beneficial in systemic disease control (and thus prolong life) but are relatively ineffective on brain metastases.[3,4]

Brain metastasis, commonly seen in carcinomas, particularly those of breast and lung, as well as melanoma, is encountered in only 1–8 % of sarcomas in aggregate.[3] Due to the rarity of sarcoma brain metastasis, available literature is limited to isolated case reports and small, retrospective studies. We examined our institutional

First Received: 12 May 2015;
Published Online: 19 September 2016

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experience with sarcomas metastatic to the brain, including histological subtypes, clinical presentation, pathological features, and clinical outcomes.

MATERIALS AND METHODS

With institutional review board approval, the records of patients with soft tissue and bone sarcomas treated at The University of Texas M D Anderson Cancer Center were reviewed. We identified 112 cases of sarcomas with brain metastases presented during a period of 28 years (1985–2013). A subset of these cases diagnosed between 1993 and 2005 were previously reported.[5] The diagnosis was confirmed by tissue pathological examination in the majority of patients ($n = 108$; 96 %). Three patients had cytological examination (3 %), and one patient was diagnosed based on imaging study only (1 %). Cases with spinal cord metastasis, cranium metastasis, primary brain sarcoma, and gliosarcoma were excluded from the study. Clinical and imaging records, when available, were examined for demographic, clinical, pathological, and survival data. Continuous variables were summarized using descriptive statistics, including median and range values, and were compared by the Mann–Whitney *U* test where appropriate. Categorical variables were summarized using descriptive statistics, including counts and percentages, and were compared by the Fisher's exact test where appropriate. Survival outcomes were evaluated by univariate Kaplan–Meier and Cox regression methods. Two-sided p values <0.05 were considered statistically significant. Statistical analyses were computed using SPSS 22 (IBM Corp., Armonk, NY).

RESULTS

Clinical and Demographic Findings

The clinical and demographic findings are tabulated in Table 1 and discussed in detail below.

Age and Gender The majority of patients ($n = 88$; 83 %) with known age at primary tumor diagnosis were adults over the age of 18 years, but 18 (17 %) patients were children. The age range at primary presentation was 1.0–79.6 (median, 31.0) years. At the time of diagnosis of first brain metastasis, 89 % ($n = 100$) were adults and 11 % ($n = 12$) were children (median age, 34.8 years; range, 1.9–80.3 years). A slight male predilection was noted; 55 % ($n = 62$) of patients were male and 45 % ($n = 50$) were female (ratio, 1.2:1).

Clinical Findings The anatomic location of the primary tumor was available in 106 patients. Sarcomas affecting the extremities were the most common source of brain metastases ($n = 53$; 50 %), followed by visceral sarcomas ($n = 28$; 27 %). Headache was the most common presenting symptom, found in 39 % of cases and followed by seizure (14 %). Some patients (12 %) did not demonstrate any neurological symptoms, and metastatic brain deposits were only revealed during radiological screening. Most cases ($n = 82$; 77 %) showed evidence of nonintracranial metastatic disease before development of brain metastasis. Brain was the only initial site of metastasis in 22 cases (20 %). These cases included six undifferentiated sarcomas and one to two cases each of various other sarcoma types. The lung was the most common site of initial metastasis ($n = 65$; 61 %), followed by bone ($n = 11$; 10 %). Only three cases (3 %) showed synchronous brain and lung metastases at presentation. The overall time from primary tumor diagnosis to the diagnosis of brain metastasis was quite variable (range, 0–16.7 years; median, 2.2 years). The median time from the diagnosis of initial distant metastasis (when other than brain) to the first brain metastasis was 1.1 years (range, 0–10.6 years). Alveolar soft part sarcoma was noted to develop brain metastasis significantly later during the course of the disease (median, 4.6 years; range, 0.1–16.7 years) compared with all other sarcomas (median, 1.8 years; range, 0–13.0 years; p value $= 0.043$). Karnofsky performance scores (KPS) were available for 49 patients (44 %). Twenty patients had hemorrhagic metastatic brain tumor deposits, whereas 29 presented with nonhemorrhagic metastases. The median KPS score was 90 (range, 60–100). We found no significant difference in the KPS score between the two groups ($p = 0.973$).

TABLE 1 Summary of clinical characteristics of patients with sarcomas brain metastases

Variable	No. of cases	%
Gender		
Total	112	
Female	50	45
Male	62	55
Location of primary sarcoma		
Total	106	
Head and neck	12	11
Trunk	13	12
Intra-thoracic, intra-abdominal or retroperitoneal	28	27
Extremities	53	50
Metastatic status		
Total	107	
Brain is initial site	22	20
Prior distant metastasis	82	77
Synchronous distant metastasis	3	3

Characterization of Metastases

Primary Diagnosis The histopathological diagnoses of the 112 sarcoma cases with brain metastasis are enumerated in Table 2. Undifferentiated sarcoma of various types was the most commonly encountered diagnosis seen in 27 % of cases, followed by alveolar soft part sarcoma (16 %), osteosarcoma (13 %), Ewing sarcoma (8 %), leiomyosarcoma (7 %), synovial sarcoma (5 %), rhabdomyosarcoma and angiosarcoma (4 % each), malignant peripheral nerve sheath tumor and chondrosarcoma (3 % each), liposarcoma and epithelioid sarcoma (2 % each), tailing off into other rare subtypes (6 %).

Clinicopathologic Features Table 3 summarizes the clinicopathological characteristics of the brain metastatic foci. Most were unifocal ($n = 83$; 78 %), parenchymal ($n = 103$; 92 %), and nonhemorrhagic ($n = 78$; 70 %; Fig. 1). Leptomeningeal dissemination was seen occasionally. The frontal lobes were the predominant initial location for the brain metastatic foci. Frontal lobe involvement was seen in 40 % of cases, followed by parietal lobe (23 %), occipital lobe (16 %), temporal lobe (13 %), and cerebellum (8 %).

TABLE 2 Histological diagnoses of 112 cases of sarcoma brain metastases

Diagnosis	No. of cases	%
Undifferentiated sarcoma	30	27
Not otherwise specified	16	
Spindle cell pleomorphic	9	
Small/round cell	4	
Epithelioid	1	
Alveolar soft part sarcoma	18	16
Osteosarcoma	15	13
Ewing sarcoma	9	8
Leiomyosarcoma	8	7
Synovial sarcoma	6	5
Rhabdomyosarcoma	5	4
Angiosarcoma	5	4
Malignant peripheral nerve sheath tumor	3	3
Chondrosarcoma	3	3
Liposarcoma	2	2
Myxoid	1	
Pleomorphic	1	
Epithelioid sarcoma	2	2
Clear cell sarcoma of kidney	2	2
Malignant myoepithelioma of soft tissue	1	1
Clear cell sarcoma	1	1
Sarcomatous component of immature teratoma	1	1
Heterologous sarcomatous component of mixed mullerian tumor	1	1

TABLE 3 Summary of sarcoma brain metastases characteristics

Variable	No. of cases	%
Parenchymal versus leptomeningeal foci		
Total	112	
Parenchymal	103	92
Leptomeningeal	9	8
No. of metastatic foci		
Total	107	
One	83	78
Two	17	16
Multiple	7	6
Hemorrhage status		
Total	112	
Hemorrhagic	34	30
Nonhemorrhagic	78	70

Outcome and Survival Analysis

Thirty-one percent ($n = 34$) of brain metastases locally recurred. All recurrences manifested within 5.3 (median, 0.3) years. Compared with nonhemorrhagic deposits, hemorrhagic metastatic foci were found to be more likely to recur locally (27 % vs. 38 %, respectively). They also recurred within a significantly shorter time interval when compared to nonhemorrhagic metastases (median, 0.2 and 0.6 years, respectively; range in years, 0.1–5.3 vs. 0–0.6, respectively; $p < 0.001$). The outcome for the entire cohort of patients was very poor. Eighty-five of the 112 patients (76 %) succumbed to metastatic disease. Disease-specific survival is summarized in Table 4. The median survival time from primary sarcoma diagnosis was 3.0 (range, 0.3–14.4) years, from first metastasis diagnosis (if other than brain) was 2.3 (range, 0.3–10.3) years, and from first brain metastasis diagnosis was 0.6 (range, 0.1–10.1) years. At the time of last follow-up available, 19 patients (17 %) were alive with disease and only 6 (5 %) were alive without current clinical or radiologic evidence of disease. We found no difference in post-brain metastasis survival based on gender ($p = 0.904$), age (pediatric vs. adult; $p = 0.120$), primary tumor location ($p = 0.737$), number of initial brain metastatic foci ($p = 0.653$), or parenchymal ($n = 103$) and leptomeningeal ($n = 9$) metastatic brain tumor deposits ($p = 0.477$). Hemorrhagic metastatic brain tumor deposits were found to be associated with a significantly lower post-brain metastasis survival than their nonhemorrhagic counterparts ($p = 0.004$). When we compared outcomes by primary sarcoma histopathological diagnosis, we found no difference in post-brain metastasis

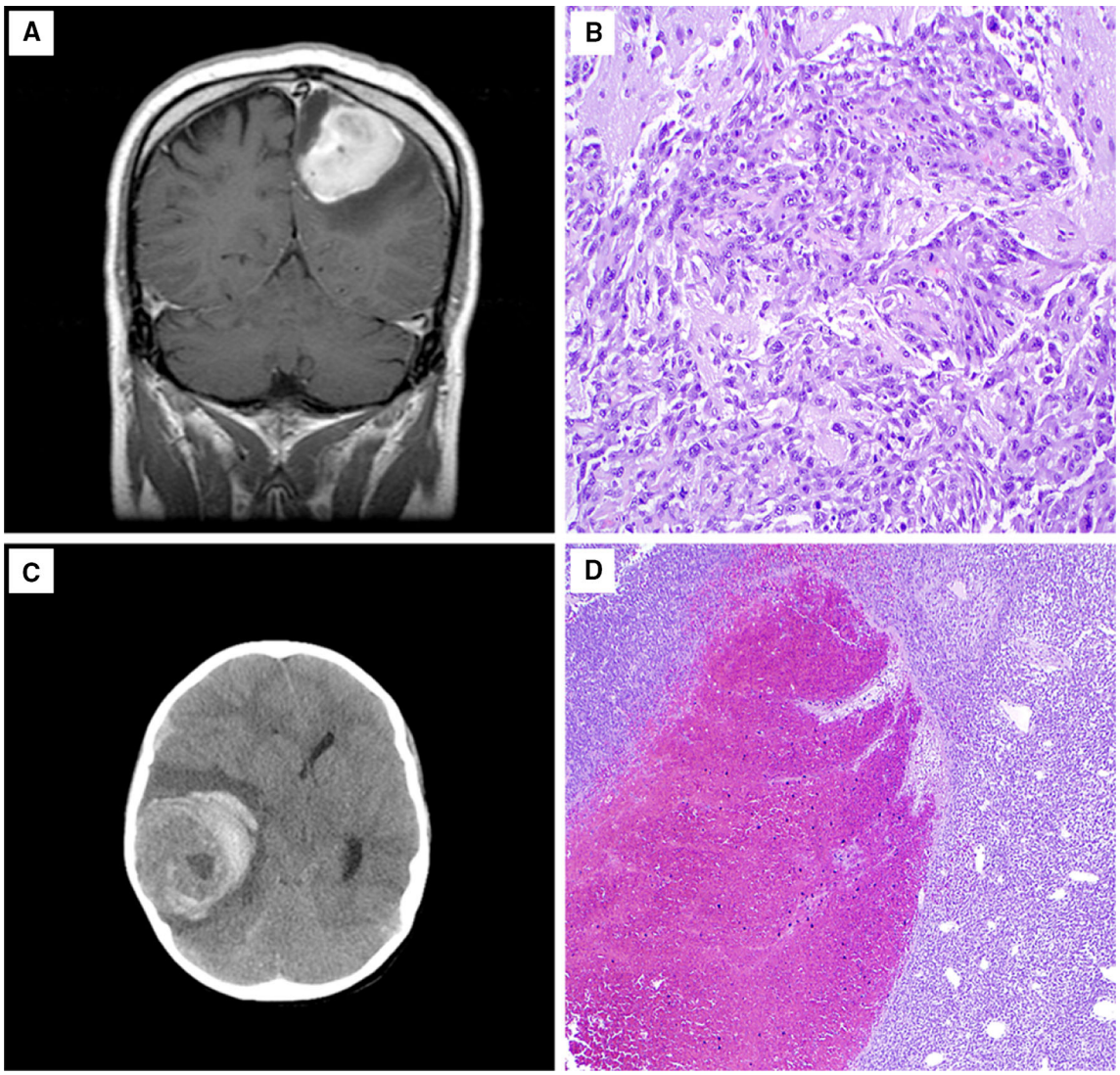

FIG. 1 **a** Post-contrast coronal T1 view brain MRI of a 27-year-old male featuring a large, solid, enhancing mass in the left parietal lobe with perilesional vasogenic edema. **b** Histological picture of the lesion in image (**a**) representing an undifferentiated pleomorphic sarcoma (UPS) exhibiting interdigitating infiltrative borders into brain parenchyma. **c** Noncontrast axial view head CT scan showing a hemorrhagic lesion within the right frontotemporal and parietal lobe with surrounding hypodensity reflecting edema. The patient is a 10-year-old female. **d** The lesion in image (**c**) is a metastatic synovial sarcoma with extensive areas of hemorrhage

TABLE 4 Summary of survival outcome for patients with sarcoma brain metastases

Time to death	Median (year)	Range (year)
From primary sarcoma diagnosis	3.0	0.3–14.4
From first metastasis diagnosis (if other than brain)	2.3	0.3–10.3
From first brain metastasis diagnosis	0.6	0.1–10.1

survival between primary soft tissue and bone sarcomas ($p = 0.301$). Therapeutic measures employed for patients are summarized in Table 5. Of the 55 patients who received radiation therapy to manage their initial brain metastases (49 % of our total cohort of 112), the radiotherapy protocol was well documented for 44 patients (80 % of those receiving radiation). The majority received whole brain radiation ($n = 30/55$; 54 %). Gamma knife stereotactic radiosurgery was performed on eight patients (15 %), whereas four patients (7 %) underwent intensity

TABLE 5 Summary of modality of treatment of first brain metastasis

Modality of treatment	No. of cases	%
Metastasectomy alone	36	32
Metastasectomy with chemotherapy	10	9
Metastasectomy with radiation	46	41
Metastasectomy with chemotherapy and radiation	5	5
Metastasectomy with other targeted therapy	1	1
Radiation alone	3	2
Chemotherapy and radiation alone	1	1
Unknown	10	9

modulated radiotherapy (IMRT). Additionally, one patient was managed using proton beam radiotherapy and another one using stereotactic external beam radiation. In 11 patients, the precise radiation regimen was uncertain (20 %). The modality of treatment of brain metastases and whether metastasectomy was solely employed or combined with radiotherapy was not found to have a statistically significant effect on survival ($p = 0.718$). When chemotherapy was combined to metastasectomy, a significantly better survival was observed ($p = 0.019$). There were insufficient numbers of patients treated with radiotherapy alone ($n = 3$) or with multimodality therapy composed of surgery, radiotherapy, and chemotherapy ($n = 5$) to do meaningful comparisons. In addition selection bias is likely significant as patients are generally apportioned therapies based on the perceived severity of disease rather than under a prospective and unbiased approach. Local recurrence of brain metastasis was not found to affect survival ($p = 0.603$).

DISCUSSION

Brain metastasis is commonly seen in advanced carcinoma and melanoma but is an unusual and most often late event in sarcoma. Giving their rarity, the exact incidence of sarcoma brain metastases has been difficult to estimate. Reports of brain metastases from sarcomas, however, have increased recently. This increase is likely due to increased use of cranial imaging studies and perhaps prolonged survival in patients with advanced disease. Other than a series of 40 sarcoma brain metastases presented by Brennan and colleagues at the Memorial Sloan-Kettering Cancer Center, only isolated case reports and small, retrospective studies are available in the literature.[3,6–10] To the best of our knowledge, our report of 112 cases of sarcoma brain metastases is by far the largest cohort in the literature describing this rare event.

Brain metastases from sarcomas were previously reported to show a slight male predilection.[3,7,9,11–13] In our study, we confirmed this finding and report a 1.2:1 male-to-female ratio. Half of our cases had the primary sarcoma located in the extremities, which is higher than previously reported.[5] Interestingly, we found notably variable timing of occurrence of brain metastasis in our sarcoma patients. Brain metastasis usually occurred late during the course of the disease, but a few cases presented initially with brain metastasis (range, 0–16.7 years). The median interval from primary disease diagnosis to brain metastasis was 2.2 years and from systemic disease to brain metastasis was 1.1 year. Alveolar soft part sarcoma patients developed brain metastasis significantly later during the course of the disease, with a median interval of 4.6 years from primary sarcoma diagnosis. A relatively favorable course has been described for these patients particularly following metastasectomy.[5,12,13] However, we were not able to demonstrate this within our cohort perhaps due to the limited number of cases with sufficient outcome data. Concordant with previous reports, the majority of our patients showed evidence of systemic involvement, mostly to the lungs, prior to developing brain metastases.[9,10] However, 20 % of our patients had brain metastasis as the first manifestation of systemic dissemination. With 12 % of patients being asymptomatic at diagnosis, an argument could be made for routine brain surveillance in patients with high grade sarcomas. This strategy may help in early detection of brain metastatic foci when they are more amenable to surgical excision. Although the effect of brain metastasectomy on survival appears to be limited, this procedure can have valuable palliative effects.[5]

Of the 17 different histological sarcoma types that constituted our cases, we found undifferentiated sarcoma to be the most common source of brain metastasis, followed by alveolar soft part sarcoma. The two sarcoma types represent contrasting ends of the brain metastatic continuum. Undifferentiated sarcomas metastatic rates are very low, but these are relatively common sarcomas. Alveolar soft part sarcoma is one of the most rare sarcoma types, but the metastatic rates to brain are very high. Alveolar soft part sarcoma is estimated to develop brain metastasis in up to 30 % of cases.[7,13] Osteosarcoma ranked third on our list of cases. Amongst other bone tumors, chondrosarcomas seldom metastasize to the brain. Only rare case reports of chondrosarcoma brain metastases are found in the literature.[14,15] Thus, worthy of note is our encounter of three chondrosarcoma brain metastases, constituting 3 % of our cases. In contrast to previous reports, leiomyosarcomas and liposarcomas were not amongst the most common sources in our series.[6] Initial sarcoma brain metastases have been reported as single rather than multiple deposits. Multiple brain metastases from sarcomas have been reported in 13–40 % of cases.[3,7,9,11,12] In our study as well, the majority of brain metastases were solitary, with 22 % of

cases presented as multiple metastatic deposits (16 % showed 2 foci, and 6 % showed 3 or more).

Generally, the prognosis for patients with sarcoma metastases to the brain is very poor. In our study, the presence of peritumoral brain hemorrhage was associated with significantly lower disease-specific survival. This dismal outcome did not seem to be influenced by the number of initial metastatic foci in the brain. Additionally, the leptomeningeal/parenchymal involvement did not significantly influence outcome, albeit this finding is limited by the small number of cases ($n = 9$, 8 %) with leptomeningeal spread in our cohort. Interestingly, we noted that hemorrhagic sarcoma brain metastases were more likely to recur locally following metastasectomy, and over a shorter period of time, compared with nonhemorrhagic foci. Similar to previous reports, we found bone sarcomas and soft tissue sarcomas to have similarly dismal outcomes once they develop brain metastasis.[3] Metastasectomy and focused stereotactic irradiation has become the mainstay of management of brain metastases. They are currently employed even in the setting of multiple metastatic foci for control of symptoms. Radiotherapy, commonly utilized in conjunction with surgical resection, did not show a significant effect on survival in our study. Additional chemotherapy, used when there is evidence of systemic involvement, appeared to be effective in these patients, although the vagaries of patient selection bias and limited patient numbers in certain categories in this retrospective series complicate these interpretations. In general, the outcome of patients with brain metastasis remains dismal. Metastasectomy and chemotherapy are the only options to control symptoms and hopefully to prolong survival in affected patients.

CONCLUSIONS

We report a large series of sarcoma brain metastases diagnosed and treated at a single institution. Although limited by the extended time period, through which different multidisciplinary management protocols evolved and the preclusion of multivariate analysis, this cohort represents a major contribution to the literature. This is a single-institution experience, which allows for high-quality case selection and follow-up, but lacks the strength of seeing equivalent findings from multiple institutions. Sarcoma brain metastases are very rare. They occur primarily following systemic progression of the disease but can be the initial manifestation of hematogenous spread. The majority of patients present with headaches and other neurological manifestations, but a subset of patients remain asymptomatic and are discovered solely by periodic neuroradiologic surveillance. Sarcomas originating in the extremities are the most common source of brain metastases. Typically, brain metastasis in sarcoma heralds a discouraging outcome, but the post-brain metastasis survival period is quite variable.

FUNDING All authors have nothing to disclose.

DISCLOSURE All authors have no conflict of interest.

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