rare tumors

Brain metastases from Truncal and extremity bone and soft tissue sarcoma: Single institution study of oncologic outcomes

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Abstract

Brain metastases are a rare occurrence in patients with sarcoma. The prognosis for patients is poor, and treatment can contribute to considerable morbidity. We sought to examine the experience of our institution in managing these patients over a period of 17 years. We performed a retrospective cohort study of patients managed for sarcoma of the extremity or trunk who developed brain metastases from 2000 to 2017. Clinical data were analyzed and we assessed survival outcomes. 14 patients presenting at a mean age of 46.7 years were included. All patients were treated with radiotherapy for their brain metastases. 3 patients underwent surgical excision of their intracranial metastases. Two patients were treated with radium-223 dichloride. Kaplan–Meier survival analysis and the log rank test were used to calculate the survival probability, and to compare patient subgroups. All patients in this study developed lung or bone metastases at a mean interval of 13.3 months prior to the development of brain metastasis. The median interval from diagnosis of a brain metastasis to death was 3.6 months. The Kaplan–Meier survival probability at 6 months was 28.6%, and 14.3% at 1 year. Surgery was not found to be associated with increased survival. Patients with cerebellar metastasis had increased survival probability as compared to those with cerebral metastasis. Patients with extremity or trunk sarcoma who develop brain metastases frequently develop lung or bone metastases in the year preceding their diagnosis of brain metastasis. Patients with cerebellar metastasis may have better survival than those with cerebral metastasis, and an aggressive treatment approach should be considered. Despite aggressive treatment, the prognosis is grim.

Keywords

brain, intracranial, metastasis, osteosarcoma, sarcoma

Introduction

Brain metastases occurring in patients with bone and soft tissue sarcoma are rare events for which screening is not routine. Their development portends a poor prognosis with published survival ranging from 1.67 to 9.8 months after diagnosis.[1–7] Some studies advocate for aggressive management of patients despite demonstrated uniformly poor outcomes. The paucity of literature regarding this unique subset of patients with sarcoma makes the counseling of such patients regarding the utility of intervention challenging, especially when one considers the morbidity of certain modalities of treatment. The purpose of this study is to describe the contemporary University of Florida experience with this unusual subset of sarcoma patients, their outcomes and to compare them to the existing literature.

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Materials and methods

This study is a retrospective case series. The prospectively collected musculoskeletal oncology database of the University of Florida was queried to identify patients who had been treated for bone or soft tissue sarcoma and who developed brain metastasis. We identified 14 patients (11 males and 3 females) managed from 2000 to 2017. All patients died during the study period and the mean duration of follow-up from diagnosis of their primary sarcoma to death was 47.3 months (±60.9). Patients who had been diagnosed with a sarcoma were followed for routine surveillance for metastasis with computed tomography of the chest and, in certain patients, bone scan. Patients only underwent radiological evaluation for possible brain metastases when clinical suspicion indicated. Where radiological findings were concerning for metastasis, patients were discussed at a multidisciplinary tumor board to decide on treatment recommendations. Tissue diagnosis was obtained in 3 of the 14 patients in the study group.

Descriptive statistical analysis was performed for the study group to better characterize the group with respect to demographic characteristics, disease characteristics, treatment, and the time course of their disease from initial diagnosis. Kaplan–Meier survival analysis was performed to assess the probability of mortality following the diagnosis of a sarcomatous brain metastasis. The log rank test was used for the comparison of survival in patient subgroups. Statistical analysis was performed using EZR; a statistical software package based on R (Easy R, Version 2.13.0; Jichi Medical University, Saitama, Japan).[8]

Results

Patients were diagnosed at a mean age of 46.7 years (±21.0) for their primary sarcoma. The 14 patients had the primary diagnoses of high-grade sarcoma of the bone or soft tissue; osteosarcoma (6), undifferentiated pleomorphic sarcoma (UPS) (3), Ewing's sarcoma, leiomyosarcoma of bone, myxofibrosarcoma, spindle cell sarcoma, and malignant peripheral nerve sheath tumor (MPNST) (Table 1).

Brain metastasis were diagnosed at a median interval of 26 months (Range: 2–209 months) from the diagnosis of the primary sarcoma. The presentation of the brain metastasis were neurologic symptoms including hemiparesis, headaches, visual disturbances, unilateral hearing loss, dizziness and nausea. The metastases were cerebellar in two patients, leptomeningeal in four, and parenchymal in the remaining eight.

All 14 patients had prior development of metastases in the bone, lung or both. Four of the patients presented with metastatic disease at the time of initial diagnosis, and the other 10 developed brain metastases following the diagnosis of these other metastasis. No patient had brain metastases at time of initial sarcoma diagnosis. The mean time interval from the diagnosis of metastatic disease to the

diagnosis of the brain metastasis was 13.3 months (±13.1). Those presenting with metastatic disease developed brain metastasis at a mean of 5.4 months (±2.8). This is in contrast to those who initially presented with localized disease in whom brain metastasis developed at a mean of 16.4 months (±14.4) (p=0.165).

Seven of 14 patients (50%) developed brain metastasis within 2 years of diagnosis, with 6 of the remaining 7 developing brain metastasis within 5 years of diagnosis. The last patient developed lung and brain metastasis 17 years after his diagnosis of osteosarcoma, and after successfully completing his course of treatment for the primary disease and being continually disease free.

Four of 14 patients developed local recurrence; these patients suffered from telangiectactic osteosarcoma, Ewing's sarcoma, UPS, and MPNST. The mean time interval from the diagnosis of local recurrence to the diagnosis of the brain metastasis was 20.9 months (±2.5).

Five out of the six patients with soft tissue sarcomas were managed with radiotherapy and wide local excision for their primary. The sixth patient had presented with metastatic disease, declined amputation for local control and underwent definitive radiotherapy of her primary site of disease. Five out of the six patients who were diagnosed with osteosarcoma were treated with chemotherapy and wide resection of the tumor. The sixth patient with osteosarcoma of the right ilium had presented with widespread metastases and the primary disease was managed with chemotherapy and radiation therapy.

Treatment for the brain metastasis included surgical excision with adjuvant radiotherapy or radiation therapy alone. The modalities of radiation included whole brain radiotherapy, intensity modulated radiation therapy and stereotactic body radiotherapy. Patients were also under treatment for their lung and bone metastases and all but two were receiving chemotherapy.

The median interval from diagnosis of a brain metastasis to death was 3.6 months. By Kaplan–Meier survival analysis, the 6-month probability of survival was 28.6%, and the 1 year probability of survival was 14.3% (Figure 1).

On analysis of patient and treatment related factors, no statistical difference was found in median survival following the brain metastasis diagnosis of patients who had osteosarcoma versus other primaries, who did or did not undergo resection of their metastasis, who initially presented with localized versus metastatic disease, or who did or did not receive radium-223 radionuclide therapy. The two patients who had cerebellar metastasis did survive longer than those who developed supratentorial disease, with a median survival of 38.4 months as compared to 3.1 months (p=0.02).

Only two patients in our series survived more than 8 months after the diagnosis of brain metastases. Both of them had developed cerebellar metastasis, and had noteworthy courses of their disease. The first patient had developed lung metastasis 14 months after being managed for a

Table 1. Summary of patient characteristics.

Case #	Primary sarcoma diagnosis	Site of disease	Age at diagnosis (y)	Gender (M/F)	Treatment of primary	Location of brain met	Management of brain met	Local recurrence?	Location of other metastasis	Interval to extracranial met (m)	Interval from extracranial met to brain met (m)	Interval to brain met (m)	Survival following diagnosis of brain mets (m)	Interval from initial diagnosis to death (m)
1	Undifferentiated Pleomorphic Sarcoma	Right shoulder (around coracoid)	51	M	RT, WLE	Right cerebellum	Gross total resection and SRS	No	Lung	14.7	38.5	53.1	47.1	100.2
2	Undifferentiated Pleomorphic Sarcoma	Left anterior thigh	56	M	RT, WLE	Right frontal lobe	3D-CRT	Yes	Lung	8.5	10.1	18.6	1.1	19.7
3	Leiomyosarcoma of bone	Right distal femur	56	M	CTX, WLE	Frontal lobe	Whole brain RT	No	Bone/Bilateral lungs	9.1	22.0	31.1	7.5	38.6
4	Osteosarcoma, Fibroblastic	Left distal femur	18	M	CTX, WLE	Inferior right temporal lobe	SRS	No	Lung/Bone	17.4	27.0	44.4	2.1	46.6
5	Osteosarcoma, Chondroblastic	Left distal femur	68	F	CTX, WLE	Bilateral frontal	Pazopanib, Sirolimus	No	Bilateral lung/Bone	0.0	8.7	8.7	1.5	10.3
6	Undifferentiated Pleomorphic Sarcoma	Right posterior thigh	56	F	RT, WLE	Right Frontal lobe	IMRT	No	Lung/Bone	12.2	39.6	51.8	1.2	53.0
7	Osteosarcoma, telangiectactic	Right distal femur	78	M	CTX, WLE	Right frontal; parafalcine	Gross total resection	Yes	Lung	15.2	6.4	21.6	3.7	25.3
8	Myxofibrosarcoma	Left posterior thigh	67	M	RT, WLE	Right parietal	SRS	No	Lung	4.4	5.5	9.9	3.6	13.4
9	Spindle cell sarcoma	Left navicular	55	F	Palliative RT	Right occipital lobe. Bilateral frontal lobes	Whole brain RT	No	Lung/Lymph node	0.0	6.9	6.9	3.5	10.5
10	Malignant peripheral nerve sheath tumor	Left sciatic nerve	55	M	RT, WLE	Left parieto-occipital lobe	Gross total resection and Whole brain RT	Yes	Lung	44.1	5.5	49.7	2.6	52.3
11	Osteosarcoma	Left distal femur	12	M	CTX, WLE	Bilateral cerebellar hemispheres, bilateral frontal lobes	Radium-223 radioisotope/SRS	No	Bone/Lung	208.9	0.4	209.3	29.8	239.0
12	Ewing's	Right femur	22	M	CTX, RT	Left frontal lobe	SRS	Yes	Bilateral lungs	37.7	8.9	46.6	7.3	53.9
13	Osteosarcoma, telangiectactic	Right ilium	42	M	CTX, RT	Right occipital lobe	SRS	No	Bilateral lungs	0.0	2.7	2.7	4.0	6.8
14	Osteosarcoma	Left distal femur	18	M	CTX, WLE	Right occipital lobe	SRS/Radium-223	No	Lung/Bone	0.0	3.4	3.4	2.4	5.8

CTX: chemotherapy; WLE: wide local excision; RT: radiotherapy; SRS: stereotactic radiosurgery; 3D-CRT: 3D conformal RT; IMRT: intensity modulated RT. All sarcomas high-grade.
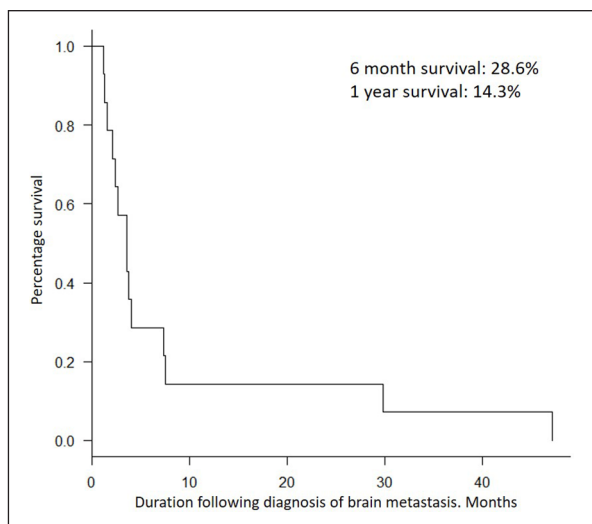
Figure 1. Kaplan–Meier survival plot: Time of diagnosis of brain metastasis to death.

UPS of the coracoid with neoadjuvant radiation therapy and wide excision of the primary tumor. He was managed for the lung metastasis with surgical excision of the metastasis and chemotherapy. He was diagnosed with a cerebellar metastasis 38 months after his lung metastases. Management for the brain metastasis included gross total tumor excision, adjuvant radiation, and chemotherapy. He eventually succumbed to disease 47 months after his diagnosis of a brain metastasis. The second patient had osteosarcoma, and following treatment including resection and chemotherapy for localized disease had been in continuous remission until development of lung and bony metastasis 17 years after the initial diagnosis. The metastases were confirmed to be osteosarcoma, and he was diagnosed with cerebellar metastasis within 1 month of the diagnosis his other metastases. He underwent a variety of treatments including chemotherapy, radiotherapy, and radionuclide therapy with Radium-223 Dichloride. He eventually succumbed to disease 30 months after the diagnosis.

Discussion

Brain metastasis is an uncommon occurrence in patients with sarcoma, with estimates of incidence ranging from <1 to 8%.[1,6,7,9–11] Studies to date comprised mostly retrospective case series, and few large studies that include patients who were treated across a long enrollment period.[2,8] The largest study to date[7] is a multicenter retrospective study involving 17 centers comprising 246 patients managed from 1992 to 2012. As with all uncommon conditions, contemporary studies add further understanding of these conditions and provide valuable insights to survival outcomes as systemic treatment approaches and modalities evolve.

All patients in this study presented with neurological symptoms. Al Sannaa et al.[12] however reported a 12% rate of asymptomatic presentation which was detected on screening. In this study, imaging of the central nervous system was not part of the standard surveillance protocol for sarcoma patients and thus may account for the diagnosis only in symptomatic patients. Our patients presented at a median of 26 months post primary sarcoma diagnosis, which is comparable to that in the literature.[2,12,13]

Brain metastasis developed at a mean of 13.3 months after the detection of lung or bone metastatic disease. This interval is similar to that in other studies.[7,12,14,15] However, the longest interval from diagnosis of primary to diagnosis of brain metastasis was 17 years, and similarly long disease free intervals have also been reported in other studies.[12,16]

All patients in this study had presented with or developed metastatic disease in the lung or bone prior to their diagnosis of brain metastasis. This finding is consistent with that in other studies[12,15,17] where the rates of metastatic disease at other sites range from 77 to 100%. Salvati et al.[2] reported a lower rate of 51% of concurrent pulmonary metastasis in their series and this may reflect a referral bias, owing to their study being a consecutive series of patients who underwent surgical excision of their brain metastasis.

The lack of patients presenting with brain metastasis does contrast with other studies that have reported between 23 and 52.5% of their study population developed brain metastasis.[1,12] Three reasons may account for this. Firstly, screening for pulmonary metastasis was routine in our study, but not for brain metastasis. This may have led to a lag to diagnosis in asymptomatic brain metastasis. Secondly, this study included only patients with the extremity, or trunk as the site of primary disease, and it is known that in extremity and trunk sarcoma the lung as the first site of metastasis in the vast majority of cases.[18,19] Notably, the study by Al Sannaa et al. featured 41% of patients having their primary sarcoma originating from sites other than the trunk or extremities. Thirdly, the higher rate of brain metastasis on presentation in other studies may represent a referral bias of patients with brain metastasis to a referral center for subspecialized oncologic services or neurosurgical services.

The findings of this study support a high index of suspicion for brain metastasis following the diagnosis of extracranial metastasis. All subjects developed lung or/and bone metastasis prior to brain metastasis, and the time interval from extracranial to intracranial metastasis was less than one year in the majority of patients. Several authors have recommended considering routine screening for brain metastases in patients with extensive disease, and in those with short disease-free intervals.[17,20]

This study did not show a significant difference in survival for those patients undergoing excision of their intracranial metastasis. This in contrast to the study by Espat et al.[1] that did show a significant difference in median post metastasis survival favoring patients with metastasectomy over unresected patients (9.6 months vs 2.7 months). Several other studies focusing on surgical treatment have

shown favorable results in patients deemed appropriate candidates for surgical treatment, with the major positive preoperative prognostic factor being a Karnofsky performance score >70.[2,9,12,18] The brain has been regarded as a "sanctuary" site[21] owing to the inability of many therapeutic agents to cross the blood brain barrier and the need for a multidisciplinary approach cannot be overstated.

Survival following the diagnosis of brain metastasis is generally very short. Median survival after diagnosis of brain metastasis in this study was 3.6 months. Only 2 of 14 patients (14%) in our series survived over 8 months; One osteosarcoma patient surviving 30 months and one UPS patient surviving 47 months after their diagnosis of brain metastasis. In the large multicenter series by Chaigneau et al., the median overall survival was 2.7 months, and only 6.9% of their study group had an overall survival of more than 2 years, with the median survival in that group being 47 months. Several studies have shown a longer survival after brain involvement with alveolar soft parts sarcoma (ASPS)[2,4,13] likely due to the slow but inexorable nature of this subtype of sarcoma. In our series there were however no cases of ASPS. The poor survival outcomes in this study mirror those in numerous other studies that document the grim prognosis that sarcomatous brain metastasis carry.[1,5,13–15]

This study does have several limitations. The size of the series is small, a limitation inherent to the study of this uncommon event. Only sarcomas arising from extremities and pelvis were included, thus possibly excluding anatomic sites with a higher incidence of central nervous system metastasis. Lastly, we included a diverse range of sarcomas. That said, this study does provide valuable contemporary data on the survival of this unique group of patients.

Conclusion

Sarcomatous brain metastases are a rare occurrence. Patients with extremity or trunk sarcoma who develop brain metastases most often demonstrated lung or bone involvement during the year prior. Patients with sarcoma brain metastasis do very poorly; with most patients succumbing very soon after diagnosis. Patients with cerebellar metastasis may have better survival than those with cerebral metastasis, and should be seriously considered for an aggressive treatment approach. Owing to the significance and grave prognosis associated with brain metastasis, our study supports formal radiological evaluation for brain metastasis in patients with a history of sarcoma with neurologic symptoms and especially those with established local or distant recurrence.

Contributorship

All authors of this original work have directly participated in its conception, and authorship. All authors have read and approved the final version submitted.

Conflict of interest

Ethical approval

Approval was obtained from the Unversity of Florida institutional review board for this study. Approval number **IRB201400812.**

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Informed consent

Written patient informed consent is required to publish case reports or case series in *Rare Tumors*. Please also refer to the ICMJE Recommendations for the Protection of Research Participants.

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References

1. Espat NJ, Bilsky M, Lewis JJ, et al. Soft tissue sarcoma brain metastases. Prevalence in a cohort of 3829 patients. *Cancer* 2002; 94: 2706–2711.
2. Salvati M, Cervoni L, Caruso R, et al. Sarcoma metastatic to the brain: a series of 15 cases. *Surg Neurol* 1998; 49: 441–444.
3. España P, Chang P and Wiernik PH. Increased incidence of brain metastases in sarcoma patients. *Cancer* 1980; 45: 377–380.
4. Chou YS, Liu CY, Chen WM, et al. Brain, the last fortress of sarcoma: similar dismal outcome but discrepancy of timing of brain metastasis in bone and soft tissue sarcoma. *J Surg Oncol* 2011; 104: 765–770.
5. Ogose A, Morita T, Hotta T, et al. Brain metastases in musculoskeletal sarcomas. *Jpn J Clin Oncol* 1999; 29: 245–247.
6. Shweikeh F, Bukavina L, Saeed K, et al. Brain metastasis in bone and soft tissue cancers: a review of incidence, interventions, and outcomes. *Sarcoma* 2014; 2014: 475175.
7. Chaigneau L, Patrikidou A, Ray-Coquard I, et al. Brain metastases from adult sarcoma: prognostic factors and impact of treatment. A Retrospective Analysis from the French Sarcoma Group (GSF/GETO). *Oncologist* 2018; 23: 948–955.
8. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; 48: 452–458.
9. Bindal RK, Sawaya RE, Leavens ME, et al. Sarcoma metastatic to the brain: results of surgical treatment. *Neurosurgery* 1994; 35: 185–190; discussion 190–191.
10. Salvati M, D'Elia A, Frati A, et al. Sarcoma metastatic to the brain: a series of 35 cases and considerations from 27 years of experience. *J Neurooncol* 2010; 98: 373–377.
11. Wroński M, Arbit E, Burt M, et al. Resection of brain metastases from sarcoma. *Ann Surg Oncol* 1995; 2: 392–399.

12. Al Sannaa G, Watson KL, Olar A, et al. Sarcoma brain metastases: 28 years of experience at a single institution. *Ann Surg Oncol* 2016; 23: 962–967.

13. Fox BD, Patel A, Suki D, et al. Surgical management of metastatic sarcoma to the brain. *J Neurosurg* 2009; 110: 181–186.

14. Urakawa H, Tsukushi S, Kozawa E, et al. Postoperative brain metastases in soft tissue sarcomas. *Clin Exp Metastasis* 2015; 32: 345–351.

15. Chua C, Raaj J, Pan S, et al. Brain metastasis in sarcoma: does metastasectomy or aggressive multi-disciplinary treatment improve survival outcomes. *Asia Pac J Clin Oncol* 2016; 12: e16–e22.

16. Lillehei KO, Kleinschmidt-DeMasters B, Mitchell DH, et al. Alveolar soft part sarcoma: an unusually long interval between presentation and brain metastasis. *Hum Pathol* 1993; 24: 1030–1034.

17. Marina NM, Pratt CB, Shema SJ, et al. Brain metastases in osteosarcoma. Report of a long-term survivor and review of the St. Jude Children's Research Hospital experience. *Cancer* 1993; 71: 3656–3660.

18. Billingsley KG, Lewis JJ, Leung DH, et al. Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. *Cancer* 1999; 85: 389–395.

19. Gadd MA, Casper ES, Woodruff JM, et al. Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. *Ann Surg* 1993; 218: 705–712.

20. Yonemoto T, Tatezaki S-I, Ishii T, et al. Longterm survival after surgical removal of solitary brain metastasis from osteosarcoma. *Int J Clin Oncol* 2003; 8: 340–342.

21. Palmieri D, Chambers AF, Felding-Habermann B, et al. The biology of metastasis to a sanctuary site. *Clin Cancer Res Off J Am Assoc Cancer Res* 2007; 13: 1656–1662.