Surgical management of metastatic sarcoma to the brain

Clinical article

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Object. Metastatic sarcoma to the brain is rare and represents a therapeutic challenge due to its relative resistance to radio- and chemotherapy. Resection has traditionally been the mainstay of treatment. The authors reviewed a series of patients with metastatic sarcoma to the brain treated surgically to determine outcomes and identify predictors of survival in these patients.

Methods. A retrospective review of prospectively collected data was undertaken on patients undergoing surgery between 1993 and 2005 for metastatic sarcoma to the brain at The University of Texas, M.D. Anderson Cancer Center.

Results. During the study period, 62 patients underwent 84 operations for metastatic sarcoma to the brain. The median postoperative overall and progression-free survival rates were 7.5 and 4.7 months, respectively. Fifty-nine (95%) of 62 patients had a gross-total resection. The 30-day mortality rate was 4.2%. The Karnofsky Performance Scale scores at discharge from the hospital and 3 months postoperatively were the same or improved in 50 (85%) of 59 and 26 (51%) of 51, respectively. Overall postcraniotomy survival was 62% at 6 months, 39% at 1 year, 21% at 2 years, and 8% at 5 years. In multivariate and univariate analysis, control of systemic disease, and sarcomas originating from bone, cartilage, or soft tissue were predictors of survival. Patients with control of systemic disease had survival advantage when compared with those who did not. In patients with alveolar soft-part sarcoma, there was a significantly increased survival advantage compared with all other histological subgroups.

Conclusions. The authors’ results suggest that in selected patients, resection of metastatic sarcoma to the brain is associated with a relatively low risk of operative death and results in improvement in neurological function. Patients with systemic control of their primary disease and certain histological subtypes (specifically alveolar soft-part sarcoma) have improved overall and progression-free survival. (DOI: 10.3171/2008.4.17505)

Key Words • gross-total resection • metastatic brain tumor sarcoma • sarcoma

METASTATIC brain disease occurs in 10–30% of patients with cancer.6 However, sarcoma metastases to the brain are relatively rare with a reported incidence of 1–8%.1,3,9,11,12 Metastatic sarcoma to the brain represents a therapeutic challenge as these tumors are generally refractory to radiation therapy and systemic chemotherapeutic regimens, which have been shown to prolong survival of patients with extracranial metastatic sarcoma.2 Surgery, when possible, has generally been the mainstay for treatment, and the results from small series of patients in the literature suggest resection as an effective treatment modality.1,12 In the present study we review our surgical experience in patients with metastatic sarcoma to the brain at a tertiary cancer center. Patient outcomes and predictors of survival are specifically addressed. Our results indicate that resection remains an effective component of the treatment regimen for metastatic sarcoma to the brain.

Methods

A retrospective review of prospectively collected data from patients undergoing resection for metastatic sarcoma to the brain was performed. The Multidisciplinary Brain and Spine Center Database at The University of Texas M.D. Anderson Cancer Center was used. Patients treated between 1993 and 2005 were included in this study. Patients with intracranial parenchymal sarcoma metastases were included in this series and those with exclusively dural or skull metastases and those with intraparenchymal glial sarcomas (gliosarcomas) were excluded.

Histological Characteristics

Sarcomas are malignant tumors arising from the connective tissues (such as fat, bone, muscle, blood vessels, nerves, and fibrous tissues of the body). The various histological entities included in the study were as follows:
ASPS, angiosarcoma, chondrosarcoma, epithelioid sarcoma, Ewing sarcoma, high-grade undifferentiated sarcoma, leiomyosarcoma, malignant fibrous histiocytoma, malignant schwannoma, meningeval sarcoma, neurofibrosarcoma, osteosarcoma, rhabdomyosarcoma, sarcomatoid carcinoma, sarcomatous transformation of teratoma, small cell sarcoma, spindle cell sarcoma, and synovial cell sarcoma. Patients were divided into 5 groups based on histological similarities: nerve sheath tumors, bone/cartilage tumors, soft-tissue sarcomas, undifferentiated sarcomas, and other sarcomas.

**Variables**

The status of the systemic sarcoma (including both primary and distant, nonbrain metastases) at both the time of surgery and at the time of death was characterized in each patient as either controlled or progressing. The receipt of radiation therapy (either WBRT or SRS) as part of the surgical plan (periorperative radiotherapy) or to treat a postsurgical recurrence was also recorded. The KPS score was determined by performing neurological assessment preoperatively, at the time of discharge from the hospital, and, when possible, at 1 and 3 months postoperatively. Operative mortality was defined as death due to any cause within 30 days of surgery.

**Tumor Recurrence**

Recurrences were identified on postoperative MR imaging. Disease that progressed at the site of a resection was considered a recurrence. In the instance of multiple tumors, disease at the site of a resection was considered a recurrence.

**Surgical Outcomes**

Resections were characterized as either gross total or incomplete. These distinctions were based on the surgeon’s intraoperative impression and postoperative MR imaging.

**Statistical Analysis**

Data were analyzed using SPSS (version 12.0, SPSS Inc.). The Pearson chi-square tests were used to evaluate associations in frequency tables. Univariate and multivariate predictors of survival were assessed using the Cox proportional hazards model. Rate ratios and their 95% CIs were computed. Survival curves were calculated using Kaplan-Meier product limits. Log-rank tests were used to assess survival function curves. Statistical significance was defined as a probability value of \( \leq 0.05 \).

**Results**

**Patient Characteristics**

We identified 62 patients who underwent 84 operations for metastatic sarcoma to the brain during the study period. There were 37 males (60%) and 25 females (40%). Forty-three (69%) of the 62 patients had a single brain metastasis. The median age at diagnosis was 38 years (range 5–67 years) and at surgery it was 41 years (range 7.5–70 years). For patients with a single metastasis, the most common brain location was the frontal lobe (19 [30.6%]), followed by the occipital lobe (10 [16.1%]), parietal lobe (9 [14.5%]), temporal lobe (4 [6.5%]), and cerebellum (1 [1.6%]). Multiple metastases were detected in 19 patients (30.6%). The most common primary sarcoma site was an extremity (27 [43.5%]), followed by chest (15 [24.2%]), head/neck (10 [16.1%]), abdomen/pelvis (5 [8.1%]), genitourinary (4 [6.5%]), and unknown (1 [1.6%]). The distribution of patients by various histological entities was as follows: nerve sheath tumors (in 3 patients), bone/cartilage tumors (in 10), soft-tissue sarcomas (in 18), unclassified sarcomas (in 17), and other sarcomas (in 14). The most common specific histological entity was alveolar soft-part sarcoma (in 12 patients). Forty-eight (77%) of the 62 patients had evidence of distant, nonbrain metastasis at the time of brain metastasis diagnosis. The most common distant (nonprimary, nonbrain) metastasis location was lung (24 [39%]), and 20 patients (32%) had evidence of multiple organ system metastases. The median interval of time from diagnosis of primary sarcoma to diagnosis of brain metastasis was 18 months. At the time of study completion, 8 patients were alive (13%), and 54 had died (87%).

**Survival**

Fifty (81%) of 62 patients had a GTR of all their intracranial lesions. Ten of the 12 remaining patients had multiple intracranial metastases, and only some of these lesions were targeted for surgery due to their correlation with symptoms and increasing size. Of these 10, 9 underwent GTR of the targeted lesions resulting in a GTR rate of the targeted lesions in 59 patients (95%). The median postoperative survival in these 59 patients was 7.5 months (95% CI 2.97–12.03 months; Fig. 1). Overall survival was 62% at 6 months, 39% at 1 year, 21% at 2 years, and 8% at 5 years. Eleven of the 59 patients had multiple craniotomies for tumor recurrences; 8 patients underwent 2 operations, 2 patients underwent 3 operations, and 1 patient underwent 5 operations.

There was no statistically significant difference in survival between GTR of 1 or more masses in patients with newly diagnosed or recurrent tumors. However, there were not enough incomplete resections (only 3) to make statistically valid comparisons of complete versus incomplete resections. We found no statistical difference in survival between the group of GTRs of all lesions (50 patients, median survival 9 months) and the group of GTR of only specifically targeted lesions (increasing in size or symptomatic tumors) with other tumors not targeted (9 patients, median survival 7.5 months; \( p = 0.51 \)). There was no statistical difference in survival for patients who underwent 1 craniotomy when compared with those who underwent ≥ 2 (\( p > 0.05 \)). The anatomical location of the tumor did not influence survival (\( p > 0.05 \)).

The median survival was 7.5 months (95% CI 0.00–17.6 months) from the time of surgery in patients whose tumor was newly diagnosed and 6.7 months (95% CI 1.5–12 months) in patients undergoing surgery for a recurrent tumor. This difference was not statistically significant (\( p = 0.88 \), log-rank test).
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Fig. 1. Kaplan-Meier survival curve showing the overall survival of the 59 patients who had GTR of their metastatic sarcoma lesions. The median survival was 7.5 months.

Fig. 2. Kaplan-Meier survival curve comparing patients with control of systemic disease with those without. The difference between the curves is statistically significant (p = 0.03, log-rank test).

Karnofsky Performance Scale

Fifty (84.7%) of the 59 patients had a preoperative KPS score of ≥ 70. The KPS score was the same or improved in 54 (91.5%) of 59 at discharge (p = 0.034, chi-square test) and same or improved in 26 (51%) of 51 patients at 3 months postoperatively. The difference in preoperative and 3-month postoperative KPS remained statistically significant (p < 0.001, chi-square test).

There were 52 patients with a KPS score ≥ 70 prior to surgery. These patients had a median survival of 10.2 months (95% CI 4.8–15.6 months). There were 10 patients with a KPS score < 70. These patients had a median survival of 2.6 months (95% CI 0.00–9.4 months). This difference was not statistically significant (p = 0.21, log-rank test).

Recurrence and PFS

Twenty-two patients (in 84 surgeries, 26%) developed a local recurrence after surgery as identified on postoperative MR imaging. Of these local recurrences, 17 occurred in patients with a single metastasis who underwent GTR, and 5 were from resected lesions in patients with multiple tumors. The median PFS was 4.7 months (95% CI 0.71–8.63). Overall PFS at 6 months was 48%, at 1 year was 27%, and at 2 years was 16%. The median time to recurrence for histological subgroups was as follows: nerve sheath tumors, 2.3 months (95% CI not defined); bone/cartilage, 4.4 months (95% CI 0.0–8.8 months); unclassified, 7.2 (95% CI 0.0–7.1 months); soft tissue, 22 months (95% CI 5.2–39 months); and other, 1.8 months (95% CI 1.4–2.2 months).

Radiation Therapy

Nineteen (32%) of the 59 patients received perioperative radiation therapy as part of their treatment. Of these 19, 16 (84%) received WBRT and 3 (16%) received perioperative SRS. Three patients underwent SRS preoperatively, whereas only 1 patient underwent WBRT preoperatively. The median survival for patients receiving perioperative radiation was 6.1 months (95% CI 0.0–12.8 months). The median survival for patients who did not receive perioperative radiation was 10.2 months (95% CI 2.5–17.9 months). There was no statistically significant difference in survival between those patients who received radiation versus those who did not (p = 0.44, log-rank test).

Systemic Disease

At the time of surgery, 25 (42%) of 59 patients had no evidence of progression of their systemic disease (including extracranial metastatic disease). Of the 34 patients (58%) without control of their systemic disease at the time of surgery, 33 (97%) had progression of their distant (nonprimary, nonbrain) metastatic disease and the remaining one (3%) had progression of the primary sarcoma. The median survival was 13.7 months for those patients with stable disease at the time of surgery (95% CI 9.62–17.72 months) and 6.1 months for those with progressing systemic disease at the time of surgery (95% CI 0.64–11.50 months). This difference was statistically significant (p = 0.03, log-rank test; Fig. 2).

Site of Primary Disease

The site of primary disease did not influence overall survival. The median survival for patients in whom the extremity was the source of their metastasis was 7.5 months (95% CI 0.00–16.4 months); for patients with a chest primary sarcoma, the median survival was 5.2 months (95% CI 1.8–8.6 months); for patients with an abdomen/pelvis primary sarcoma, median survival was 2.3 months (95% CI 0.0–6.6 months); for patients with a head and neck primary sarcoma, median survival was 16.2 months (95% CI 7.4–25 months); for patients with a genitourinary primary sarcoma, median survival was...
11.5 months (95% CI 0.0–25.8 months); and the patient with an unknown primary sarcoma survived 10 months.

**Histological Findings**

Patients with sarcomas derived from bone/cartilage or soft tissue had a survival advantage (median 15 and 20 months, respectively) compared with sarcomas from other locations (3.0 months, p = 0.03). Patients with an unclassified or soft-tissue–derived sarcoma had a longer PFS (median 7.2 and 7.8 months, respectively) than those with sarcomas from other locations (2.6 months, p = 0.05). Table 1 summarizes the patient demographics and surgical characteristics of these groupings.

Alveolar soft-part sarcoma was part of the histological subgroups found to have a survival advantage and a longer PFS than sarcomas from other locations. We analyzed ASPS independently as other authors have found that patients with this histological type have a survival advantage (see Discussion). There was a statistically significant increase in survival in patients with ASPS histology (median survival 27 months) when compared with all other tumors (6.1 months, p = 0.003; Fig. 3).

**Predictors of Survival**

Variables evaluated in the univariate and multivariate analyses included age, sex, histology, site of origin of the primary sarcoma, number of metastases, histological grouping, KPS score, perioperative radiation therapy, and control of systemic disease. In this analysis, the variables predicting improved survival included bone/cartilage or soft-tissue–derived sarcoma, and control of systemic disease.

**Complications**

The 30-day mortality rate was 4.2% (2 of 47 patients with adequate follow-up). Neither patient died of direct or secondary neurological complications of the craniotomy and resection of the tumor or of neurological progression of the tumor. One of the patients died prior to discharge from the hospital following surgery of uncontrollable bilateral spontaneous hemorrhage of his diffuse lung metastases. The second patient was discharged postcraniotomy with an improved KPS score and subsequently developed pancreatic obstruction due to an intraabdominal tumor and opted for palliative care and died shortly thereafter.

**Discussion**

Sarcomas are a group of malignant tumors arising from the connective tissues (fat, bone, muscle, blood vessels, nerves, and fibrous tissues of the body). Sarcomas are rare, accounting for < 1% of all adult cancer cases and have an incidence of 6–7000 nonskeletal and 2000 skeletal sarcomas diagnosed annually in the US.3,6 In the context of metastatic brain disease, metastatic sarcoma to the brain is also relatively rare.1,3,9,11,12 Furthermore, treatment of metastatic sarcoma to the brain is complicated by its relative radio- and chemoresistance.2 Thus, surgery is considered an important part of the management of this disease, and an appropriate plan of care should take into account the status of the patient’s systemic disease, the overall neurological and clinical status of the patient, as well as number, size, location, and histological and radiographic features.5 This retrospective review of 62 patients with metastatic sarcoma to the brain treated surgically is, to our knowledge, the largest series to date. In this select population of patients, we show that survival is consistent with other published reports, and identify predictors of survival such as certain sarcoma histological subtypes.

In this study, the median postcraniotomy survival for all tumors was 7.5 months. Our reported median survival is consistent with 2 previously reported studies by Wronska et al.11 and Espat et al.3 These studies also concluded that resection is associated with an increase in survival. Espat et al. reported their experience with metastatic soft-tissue sarcoma to the brain at Memorial Sloan-Kettering Cancer Center and found that 27 patients who underwent resection of their tumor had a median survival of 9.6

<table>
<thead>
<tr>
<th>Histological Subgroup</th>
<th>No. of Patients (%)</th>
<th>Median Age at Diagnosis (yrs)</th>
<th>Median Age at Op (yrs)</th>
<th>Median Survival in Mos (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>nerve sheath</td>
<td>3 (4.8)</td>
<td>25.3</td>
<td>25.8</td>
<td>1.9 (not defined)</td>
</tr>
<tr>
<td>bone-cartilage</td>
<td>10 (16.1)</td>
<td>30.8</td>
<td>30.7</td>
<td>14.9 (1.0–28.9)</td>
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<tr>
<td>unclassified</td>
<td>18 (29)</td>
<td>49.5</td>
<td>50.3</td>
<td>14.3 (3.3–25.3)</td>
</tr>
<tr>
<td>soft tissue</td>
<td>17 (27.4)</td>
<td>28.2</td>
<td>33.3</td>
<td>5.4 (0.5–10.3)</td>
</tr>
<tr>
<td>other</td>
<td>14 (22.6)</td>
<td>46.4</td>
<td>47.7</td>
<td>2.9 (2.4–3.5)</td>
</tr>
</tbody>
</table>
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months. The 13 patients who did not undergo resection had a median survival of 2.7 months. In addition, they reported a 2-year postcraniotomy survival rate of 27 versus 0% in those patients who did not undergo craniotomy. Wronska et al. 11 reported 1- and 2-year postcraniotomy survival rates of 40 and 16%, respectively, in 25 patients. Our postcraniotomy survival rate was similar with an overall rate of 62% at 6 months, 39% at 1 year, 21% at 2 years, and 8% at 5 years. Our overall PFS at 6 months was 48%, at 1 year was 27%, and at 2 years was 16%.

Previous series have cited a significant increase in survival in patients with ASPS, 1, 9, 12. This sarcoma is a rare malignant soft-tissue neoplasm with a prevalence of < 1% of all primary soft-tissue sarcomas. It is more common in adolescents and young adults and commonly originates from deep tissues of proximal extremities particularly the lower limbs. 13 Alveolar soft-part sarcoma is generally much less responsive to chemotherapy than other soft-tissue sarcomas and has a predilection for metastasizing to the brain, and ~ 30% of patients with Stage IV ASPS develop brain metastases during the course of their disease. 8

In our study, ASPS was part of the group histological entities found to have a survival advantage (bone/cartilage or soft tissue) and a longer PFS when compared with sarcomas from other locations. Furthermore, there was also a statistically significant increase in survival in patients with ASPS when compared with all other tumors. Alveolar soft-part sarcoma was the most common tumor in our series, which may have influenced our overall survival data. Other published series have reported only a few cases of ASPS. The most common sarcomas in previously reported series include hemangiopericytoma and Ewing sarcoma as reported by Yoshida et al., 12 liposarcoma as reported by Espt et al., 1 osteosarcoma as described by both Bindal et al. 1 and Salvati et al., 9 and embryonal rhabdomyosarcoma as reported by Wronska et al. 11 The differences in histological representation between these studies may be due to the overall rarity of sarcoma as well as referral patterns.

Previous studies have reported preoperative KPS scores > 70 as a prognostic indicator. 9, 12 Salvati et al. 12 reported a statistically significant survival difference of 12.8 versus 5.3 months for KPS scores ≥ 70 and KPS scores < 70, respectively. Although in our study there was longer survival in patients with KPS scores ≥ 70 versus KPS scores < 70, this difference was not statistically significant and it did not predict survival in multivariate analysis. Our results are consistent with Bindal et al. 1 who also noticed an increase in median survival (15.7 vs 6.6 months), which was not statistically significant. It is possible that this previously reported finding of increased survival associated with preoperative KPS scores ≥ 70 was due to statistical variation or the small number of patients in the previously reported series. In our series, at least 2 patients with a preoperative KPS score < 70 presented acutely moribund due to hemorrhagic conversion of their mass and signs of acute increased intracranial pressure. These patients’ conditions improved to a postoperative KPS score of ≥ 70 at the time of discharge due to prompt and effective surgical decompression. Although patients such as these alter the prognostic value of the KPS score and affected our survival data in the patients with KPS scores < 70, they also highlight the point that in the acute setting, control of systemic disease was a more significant prognostic indicator. Regardless of the number or location of metastases, those patients who had control of their systemic disease had a statistically longer median survival than those who did not.

Our overall GTR rate of 95% (59 of 62 patients) is comparable to previously reported GTR rates for metastatic brain tumors. In a retrospective review of 194 consecutive craniotomies performed at M.D. Anderson for brain metastases, postoperative MR images using volumetric measurements revealed that GTR was achieved in 94% of the cases. 10 Other authors have shown that GTR is associated with a statistically significant survival advantage. 1, 9 At least 1 study has shown that patients who have had complete resection of a sarcoma metastasis, even in the setting of other brain metastases, survival is comparable to patients who have had complete resection of a single metastatic sarcoma. 1

In general, intracranial sarcomas are considered resistant to conventional fractionated radiation. Because of this “radioresistance,” SRS has been suggested as an effective alternative. 4 However, Chang et al. 2 reporting on their experience of SRS in 9 patients with sarcoma noted a 1-year actuarial survival rate of 22% and a 1-year crude and actuarial rate of local tumor control of 42 and 0%, respectively. In comparison with other radioresistant tumors (melanoma and renal cell carcinoma) treated in their study with SRS, sarcoma had the highest degree of local failure, the lowest 1-year survival rate, and the highest rate of death attributed to neurological disease progression.

Nineteen (32.2%) of the 59 patients in our series received perioperative radiation therapy as part of the treatment plan with the majority receiving WBRT. We found no statistically significant difference in survival in the patients receiving perioperative radiation therapy given as part of the treatment plan versus those who did not receive perioperative radiation therapy. Similarly, Yoshida et al. 13 reported on 5 patients at their institution who received external-beam radiation therapy as the sole treatment for their metastatic sarcoma to the brain. These 5 patients had a mean survival of 4.2 months, which was significantly lower than the 10 postcraniotomy patients in their series who had a mean survival of 25.4 months. However, these studies (including ours) are retrospective and suffer from small numbers of patients; thus, no definitive comparison can be made. We believe that SRS should remain an acceptable alternative for patients with small tumors who are not operative candidates.

To the best of our knowledge, this is the largest surgical series on metastatic sarcoma to the brain to date. This study was performed at a major tertiary cancer center, which allowed for a large number of patients in a relatively short time frame; however, the referral pattern of a multidisciplinary cancer center may alter patient selec-
tion and could conceivably attract individuals with more aggressive and complex tumors when compared with the average hospital setting and may have affected our results. Although retrospective, this series reviews a rare pathological entity and yields valuable data on survival and predictors of survival to aid clinicians and patients in the decision-making process.

Conclusions

Our results, from the largest surgical series to date, indicates that resection of metastatic sarcoma to the brain results in an improvement in neurological function, is safe, and is associated with a relatively low risk of perioperative death. Histological subtypes such as ASPS have a significant impact on overall and PFS. Patients with systemic control of their sarcoma have a significant survival advantage compared with those without. Further studies are needed to further define the role of adjuvant and alternative therapies such as radiation therapy and SRS in the treatment of metastatic sarcomas to the brain.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References


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