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Resection of Brain Metastases from Sarcoma

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Background: Brain metastases from sarcoma are rare, and data concerning the treatment and results of therapy are sparse.

Methods: We retrospectively reviewed 25 patients with brain metastases from sarcoma of skeletal or soft-tissue origin, surgically treated in a single institution during 20 years.

Results: In 18 patients the brain lesion was located supratentorially, and in 7 patients infratentorially. Median age at brain metastasis diagnosis was 25 years. Median time from primary diagnosis to diagnosis of brain metastasis was 26.7 months. Lung metastases were present in 19 patients and in 8 patients they were synchronous with the brain lesion. Pulmonary metastases were resected in 12 patients (48% of total, and 63% of those with pulmonary lesions). The overall median survival from diagnosis of the primary sarcoma was 38 months and from craniotomy was 7 months. The presence or absence of lung lesions did not alter the median survival as calculated from diagnosis of brain metastasis. Overall percent survival was 40% at 1 year and 16% at 2 years.

Conclusions: Because brain metastases from sarcoma are refractory to alternative treatment, surgical excision is indicated when feasible. Brain metastases from sarcoma are uncommon, usually occurring with or after lung metastasis. Long-term survival is possible in some patients.

Key Words: Brain metastasis—Sarcoma—Brain neoplasms.

Despite aggressive surgical therapy and recent advances in chemotherapy (1), distant metastases develop in many patients with soft-tissue sarcoma (2–4) and osteosarcoma (5). The occurrence of brain metastases in different histologic types of sarcoma is rare (6–8). Sarcomas of all types accounted for <3% of brain metastases in an autopsy series reported in 1964 (9). There is some evidence that the incidence of brain metastasis from sarcomas has increased to 6% (10), possibly due to improved treatment and survival (11). Data concerning the surgical treatment and therapeutic results for patients harboring brain metastases from sarcoma are sparse (12). There are ~70 published cases of resected cerebral metastases of bone and soft-tissue sarcoma (13–15).

We present our experience with 25 patients neurosurgically treated in a single institution during 20 years.

MATERIAL AND METHODS

Among 670 patients who had brain metastases and who underwent resection of parenchymal lesions between January 1972 and December 1992 at Memorial Sloan-Kettering Cancer Center, pathology reports revealed 28 patients (4%) with histologically diagnosed sarcoma of skeletal or soft-tissue origin. The records of 25 patients were available for review and were retrospectively analyzed. Three records or their microfilms could not be found and are excluded from analysis. Additionally, all patho-

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TABLE 1. *Characteristics of 25 patients with sarcoma metastatic to brain*

Pts.	Sex/age (yrs)	Primary site	Lung mets./ resection	Mets.[a] to brain (in mos)	Site in brain	Sarcoma pathology	Survival[b] (mos)
			BONY AND CARTILAGINOUS SARCOMA				
1	M/26	Maxilla	N/N	63	T	Osteosarcoma	2.4
2	F/7	Femur	N/N	21	O	Osteosarcoma	13
3	M/15	Femur	Y/Y	33	PO	Osteosarcoma	7
4	F/10	Humerus	Y/Y	18	PF	Osteosarcoma	3
5	F/17	Femur	Y/Y	27	PO	Osteosarcoma	3
6	F/30	Hand	Y/Y	35	PF	Chondrosarcoma	4
7	F/27	Skull	N/N	11	F	Chondrosarcoma	1.6
8	F/15	Fibula	Y/N	72	F	Ewing's sarcoma	22
9	M/17	Femur	Y/N	0.3	F	Ewing's sarcoma	1
			SOFT-TISSUE SARCOMA				
10	F/28	Scalp	Y/N	27	O	Malig. fibr. hist.	10.2
11	M/67	Thigh	Y/Y	3	PF	Malig. fibr. hist	65
12	M/47	Pulm. artery	Y/Y	6	P	Malig. fibr. hist.	19
13	M/66	Thigh	Y/Y	34	PO	Embr. rhabdomyo.	6.6
14	F/2	Mediastinum	Y/Y	2	PO	Embr. rhabdomyo.	3
15	M/18	Calf	Y/N	147	P	Embr. rhabdomyo.	64
16	M/29	Thigh	Y/N	6	PO	Embr. rhabdomyo.	4
17	F/67	Nasopharynx	N/N	12	F	Embr. rhabdomyo.	2.3
18	M/17	Perineum	N/N	11	PF	Embr. rhabdomyo.	4
19	F/14	Thigh	Y/Y	23	PF	Alv. soft part sar.	73
20	M/7	Tongue	Y/Y	23	T	Alv. soft part sar.	23
21	M/24	Thigh	Y/N	16	PF	Leiomyosarcoma	2.7
22	F/38	Vagina	Y/Y	28	F	Leiomyosarcoma	14.5
23	F/60	Uterus	Y/N	69	P	Leiomyosarcoma	30
24	M/51	Thigh	N/N	74	PF	Liposarcoma	6.5
25	M/38	Thigh	Y/Y	50	T	Liposarcoma	0.6

T, temporal; O, occipital; F, frontal; P, parietal; PF, posterior fossa; Mets, metastases.
[a] Time from diagnosis of primary until diagnosis of brain metastasis.
[b] Survival postcraniotomy.

logic slides were reviewed and the diagnosis confirmed.

Follow-up was obtained in 100% of patients to June 1994. This was accomplished by reviewing outpatient records or contacting the patient, family member, friend, or personal physician by letter or telephone. Survival analysis was done by the Kaplan-Meier method (16), and comparisons of survival were done by log-rank analysis (17). Significance was defined as $p < 0.05$. All survival data were calculated from the time of resection of brain metastasis. Because the number of analyzed patients was too small and statistical considerations therefore were seriously biased, we do not report the multivariate analysis by the Cox proportional hazards model (18).

RESULTS

There were 13 men and 12 women (M:F = 1). The characteristics of the patients are shown in Table 1. In 18 patients (72%) the brain lesion was located supratentorially, and in seven patients infratentorially. Five patients had multiple brain metastases; four had two lesions (patients 10, 13, 14, and 16 in Table 1) and one patient had three lesions (patient 9 in Table 1). The median age at time of primary sarcoma diagnosis was 22.2 years (range 2.4–67.7). The median age at brain metastasis diagnosis was 25 years (range 2.6–68 years). Median time from primary diagnosis to diagnosis of brain metastasis was 26.7 months (range 0–147 months). The primary site was not controlled in five patients. Lung metastasis occurred in 19 patients (76%) and 8 were synchronous with the brain lesion. For metachronous lesions the median time to development after lung metastases was 10 months. There was no difference in survival between women and men (median 7 months versus 6.6 months, respectively, $p < 0.6$). None of our patients received chemotherapy after craniotomy for resection of brain metastasis. Thirteen patients received whole-brain radiation therapy (WBRT) after surgery and their median survival was 6.5 months (mean 10.2 months).

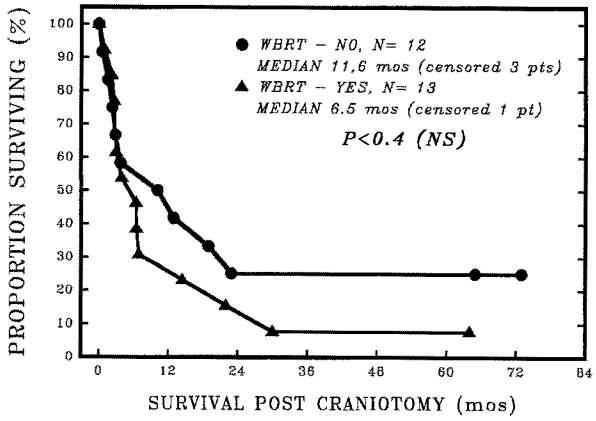

FIG. 1. Impact of whole-brain radiation therapy (WBRT) on survival in 25 patients with resected brain metastases from sarcoma. The difference is not statistically significant.

Twelve patients were not treated postoperatively with WBRT and their median survival was 11.6 months (mean 12.1 months). The difference in survival was not statistically significant ($p < 0.4$) (Fig. 1).

Median time from diagnosis of pulmonary metastases to brain metastasis was 2.5 months (mean 11.6 months). Pulmonary metastases were resected in 12 patients (48%). The presence or absence of lung lesions did not change the median survival calculated from time of diagnosis of brain metastasis (7 and 4.5 months, respectively; $p < 0.48$, log-rank test).

Median preoperative Karnofsky performance score (KPS) was 70 (mean 64, range 30–100). Postsurgical KPS measured after 30 days from surgery was 80 (mean 70, range 20–100). Two patients (8%) died within 30 days of operation and were excluded from further analysis. The overall median survival time from diagnosis of primary sarcoma was 38.8 months and from craniotomy was 7 months. The overall survival is depicted in Fig. 2. One-year survival was 40% and 2-year survival was 16%. Three patients (12%) survived >5 years. Of the 20 patients who have died, 6 (30%) died of neurological causes alone, 9 (45%) of systemic disease alone, and 4 (20%) of combined neurological and systemic diseases. One patient died of pulmonary embolism. Nine patients (40%) had recurrence of disease in the brain, but none underwent reoperation for recurrent tumor.

DISCUSSION

Primary sarcomas can be divided into skeletal, with 2,000 cases diagnosed yearly (19), and soft tissue, with 6,000 new cases yearly (19). Based on published data, brain metastases from sarcoma are very rare. Progress in surgical treatment of brain metastases has improved the overall survival rate in the last 10 years (20,21). Also, major changes occurred in the surgical management of the primary tumor, adjuvant radiotherapy and chemotherapy, and the multimodal approach to metastatic disease. Detection of brain metastases from sarcoma has increased in the last two decades, because of new diagnostic techniques and prolonged survival due to multimodality treatment. However, the number of brain metastases reported in the literature is small. In one series (7) published in 1980, the authors reviewed 517 cases of sarcoma treated between 1961 and 1970 at the Royal Marsden Hospital in London, and were able to find only 12 patients with brain metastases. No patient underwent craniotomy and most died within 2 months after diagnosis, with three patients dying by 12 months (7).

Two major review articles on brain metastasis from sarcoma were published in the mid-1980s. The first was written in 1985 by Sarno and co-workers (14). The authors described their own case of endometrial sarcoma metastatic to brain and reviewed 55 cases from the literature. In 1988, Lewis (15) reviewed all reported cases of pathologically verified brain metastases from sarcoma and found only 50 cases. Another 44 reported cases were not pathologically verified. Recently Bindal and colleagues (22) reported the results of surgery in 21 patients with brain metastases from different histological types of sarcoma, treated at M. D. Anderson Cancer Center (MDACC) between 1980 and 1992.

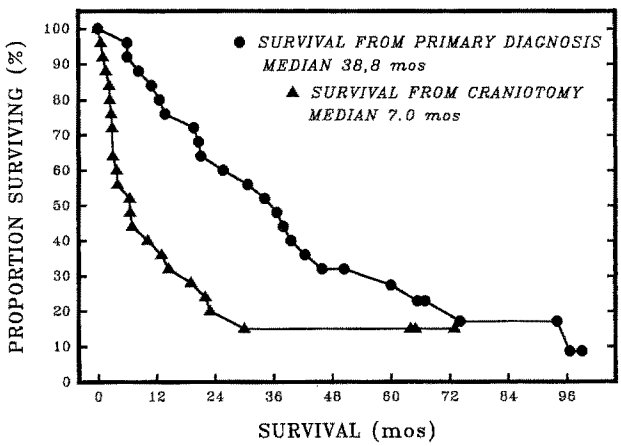

FIG. 2. Overall survival in 25 patients with brain metastases from sarcoma calculated from primary diagnosis of sarcoma (upper curve—median 38 months) and from resection of brain metastases (lower curve—median 7 months).

Reviewing the literature, Lewis was able to find only six patients, in whom the intracranial metastasis was the first evidence of sarcoma presence (15). Brain metastases frequently are associated with pulmonary metastasis (23).

In a previous article from our institution on brain metastases from solid tumors in young patients, the records of 31 patients younger than age 21 years were reviewed (24). Among them, 16 patients had brain lesions from sarcoma, mostly osteogenic sarcoma (9 patients), rhabdomyosarcoma (5 patients), and Ewing's sarcoma (2 patients). Pulmonary metastasis was present in 88% neurologically symptomatic patients with brain metastases (n = 25). The median interval between diagnosis of lung metastasis and brain metastasis in the whole group of 31 patients was 10 months (range 0–60).

Osteosarcoma is a malignant bone tumor that is characterized by atypical cells that produce osteoid—a matrix protein produced by bone cells (25). Although this is one of the most common malignant bone tumors in children and adolescents (5), it rarely metastasizes to the CNS (23). Giuliano et al. (6) had only 2 cases of brain metastases in his series of 111 patients treated with osteosarcoma between 1971 and 1984. Baram et al. (26) found only 5 patients with brain metastasis among 87 osteosarcoma pediatric patients, in contrast to 39 patients with pulmonary metastasis. Recently, Bindal and coworkers from the same institution reported that their six patients with resected intraparenchymal brain lesions from osteosarcoma survived 3.1, 6.6, 7.5, 10.5, 22, and 39 months after craniotomy (22). Marina et al. (27) reported a case of a 3-year-old boy with histologically proven osteosarcoma of humerus, in whom a computed tomography (CT) scan of the head 4 months later showed low-density lesions that were consistent with cerebral metastases. This diagnosis was not confirmed by the biopsy, but after eight courses of ifosfamide there was complete resolution of brain and thoracic lesions. The same authors also reported 13 other patients (of 254 treated for osteosarcoma between 1962 and 1989) in whom brain metastases from osteosarcoma were diagnosed but none of which were biopsy proven or resected (27). Among our five patients, only two survived 6 months after surgery (7 and 13 months).

Ewing's sarcoma is a rare, highly malignant neoplasm of bone, accounting for ~10% of all the skeletal sarcomas. This tumor most frequently affects children and young adults, generally occurring in the bones of the extremities and the pelvis, and is well known for a high incidence of metastasis at the time of initial diagnosis (28). CNS involvement in Ewing's sarcoma is uncommon, and is estimated that 5% of patients have intraparenchymal brain involvement (29). In the literature the number of histologically proven cases with parenchymal metastases (22,30–40) approached 30. Many patients had multiple brain metastases at autopsy, and widespread metastatic disease. Surgical resection is not common, and very few patients survived >1 year (41) after surgery. Our 15-year-old patient survived 22 months and died because of pneumonia after intensive chemo- and radiotherapy treatment of L3 vertebral and epidural metastases.

Metastatic chondrosarcoma to the brain is also a rarity and only seven cases have been published to date (11,42–46). Our first patient with metastasis to the right cerebellar hemisphere survived only 4 months after resection, and died because of diffuse metastatic disease in both lungs. Our second patient died in the 7th week, because of recurrence of highly malignant tumor in craniofacial area.

Malignant fibrous histiocytoma (MFH) is the most common extremity soft-tissue sarcoma of late adult life, manifesting a broad range of histological appearances (47). Most often it arises in the soft tissues of the trunk and extremities, although the bone may also be a primary site (48). Weiss and Enzinger (8) found only 2 cases (1%) of brain metastases among 200 cases of MFH seen in consultation at the Armed Forces Institute of Pathology from 1952 through 1975. In a series of 167 patients reported in 1980 by Kearney et al. (49), only 3 persons developed brain metastasis. Rosemberg et al. (50), reporting a case of cerebral metastasis from a primary MFH of the lung, found only 10 cases of cerebral metastasis from MFH. Another case of cerebral metastasis from pulmonary MFH was published earlier by Epstein et al. (51). Nikaido et al. (52) in 1986 published a case and found in the literature an additional nine cases including three patients with MFH originating from lung or mediastinum. One pulmonary case was also reported by Lewis (15) together with his fourth case to originate from the left scapula. Lewis also found in the literature another five verified and three clinical cases of MFH metastasizing to the brain. Others reported two autopsy cases (53,54). We found another 4 cases (55–57), so our case brings to 12 the reported patients with brain metastases from pulmonary MFH. The large series of 21 cases from MDACC (22) had three patients with MFH, with the primary

tumors originating from the trunk, shoulder, and heart. Their latter case is rare and only five other reports of cardiac MFH metastasizing to brain have been published to date (58–62). Recently Biegel et al. (63) reported a first case in which brain metastasis from MFH was subjected to cytogenetic analysis. The tumor demonstrated a complex karyotype, with a variety of numerical and structural abnormalities. There are also reports on primary intracranial MFH (64).

Intracranial metastasis of soft-tissue fibrosarcoma is rare and to date only a few cases have been reported (65–69). Lewis, in his excellent review (15), cited seven other cases, mainly from the German literature.

Alveolar soft part sarcoma (ASPS) is a rare tumor accounting for <1% of all soft-tissue sarcomas (47). Among 102 patients treated in the period from 1923 to 1986 at Memorial Sloan-Kettering Cancer Center, Lieberman et al. (12) identified 15 patients (15%) with brain metastases. In 11 patients (75%) it was synchronous with metastases in other sites, mostly in the lung. Lewis (15) in his review up to 1987 found only nine histologically verified cases with brain metastases and another six patients were diagnosed clinically. Recently Perry and Bilbao (70) reported a case of a 28-year-old man who presented with seizures. CT of the head revealed a dural-based, left frontal mass, and small round, a dural-based occipital lesion, which suggested multiple meningiomas. The patient underwent craniotomy: histopathology, electron microscopy, and immunohistochemical studies showed the tumor to be an ASPS. The patient later had multiple pulmonary lesions and a large maxillary mass, but search for a primary lesion was unsuccessful (70). Another interesting report (71) describes a patient with ASPS resected from pectoralis major muscle at the age of 10 years, a lung metastasis at the age of 31, and brain and renal masses at the age of 43. The patient was treated by surgical resections each time, but never received radiotherapy or chemotherapy. Researchers from MDACC reported (22) that their two patients with ASPS are alive at 16 and 25 months after surgery. Through a literature review they collected the data of another seven cases of surgically treated brain metastases from ASPS, and found that including their patients, only two of all these patients died, with survival from 12 months to 5 years (22). We added to their bibliographical collection four other long-time surviving patients after brain surgery, as searched from the literature (11.8 years [72], 3 years [73], 2.2 years [74], 12 months [75]). Including two of our own cases who survived 6 years and 23 months, respectively, we concur with Bindal's suggestion (22), that the patients with metastatic brain tumor from ASPS may have a relatively good prognosis if they are surgically treated.

Rhabdomyosarcoma is the most common soft-tissue sarcoma in childhood and young adults, but can also occur in almost all sites and age groups (76). Even with the most effective regimens, >50% of the patients will die of disease progression and distant metastases (77). Cerebral metastasis is very rare. Ho (13) in 1979 reported a single case of brain metastasis from a primary pulmonary rhabdomyosarcoma and reviewed another 22 cases of different sarcomas from the literature. Douvin et al. (78) published one case and reviewed the literature. Kleinert et al. published an autopsy case of alveolar rhabdomyosarcoma from the left forearm, metastasizing to the brain (79). Anderson-Ranberg and Helmer-Hansen (80) published a case of alveolar rhabdomyosarcoma from the left foot that presented with subarachnoidal bleeding from cerebral and cerebellar metastases. Recently six other cases were published (81–83), including three reported by Bindal et al. (22). Recalculating an estimate of Uyeno, who found that up to 1992 only 16 cases of rhabdomyosarcoma metastasizing to the brain have been reported, the current number is ~30 cases, including 6 patients from this report.

Liposarcoma is similar in frequency to MFH among soft-tissue sarcomas (84). It occurs almost exclusively in adults and is found most often in the thigh or retroperitoneum (4,85). Metastatic liposarcoma to the brain is extremely rare. The first surgical case was published in 1933 by Fender (86), and later by Lu and Lee (87). Although the presence of brain metastasis is mentioned in several general series of patients treated for liposarcomas, crucial details are not given. Haft and Wang (88) described a patient who had a 20-year history of liposarcoma originating in the thigh and metastatic to the brain 18 years later. A huge 9 × 7 × 5-cm mass was surgically removed, but the patient died 10 months later.

Leiomyosarcomas are uncommon malignant tumors of smooth-muscle origin that rarely metastasize to the brain (89). Lewis reviewed the literature up to 1987 and found six cases with metastatic involvement in brain parenchyma (15). We found another two cases originating in the thigh (90), or from an unknown primary (91). Our case of uterine leio-

myosarcoma was published elsewhere (92), and reviewing the literature we found seven similar cases, including four in which brain metastases were resected.

It is worth mentioning that a new kind of radiation therapy, radiosurgery, is emerging as a useful therapeutic modality for brain metastases (93,94). This noninvasive technique (95) may be applied to one or several brain metastases with a diameter not exceeding 2.5–3 cm. It can be performed on an outpatient basis and is cost effective. The control rate for small metastases exceeds 90%, and steroid requirements are reported to be reduced (96). Large lesions so treated may result in radiation injury (necrosis) (97). The efficacy of stereotactic radiosurgery compared with conventional surgery remains to be proven by a prospective randomized study.

Comparing our series of 25 cases with the series from MDACC, we found a difference in median survival (7 versus 12 months). Interestingly, we have three patients who are still alive after 5 years, in comparison to the MDACC series, in which there are no 5-year survivors.

This study confirms that brain metastases from sarcoma are uncommon, and usually occur in association with or after lung metastasis. Because brain metastases from sarcoma are refractory to alternative treatment, surgical excision is indicated when feasible. Long-term survival is possible in a small percentage of patients. Of those surviving >1 year, no identifying prognostic factor related to primary tumor site, sex, age, and pathology could be found. Elements of the biological behavior, histopathology, and clinical staging, together with careful planning and collaboration between oncologist and neurosurgeon, play a key role in achieving optimal results.

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