

## Biology and treatment of metastasis of sarcoma to the brain

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### 1. ABSTRACT

Sarcomas are rare tumors with devastating clinical consequences, often affecting children as well as adults. Brain metastasis in sarcoma is frequently preceded by lung metastasis. Common offenders include Ewing sarcoma, osteosarcoma and leiomyosarcoma. Although our understanding of sarcoma metastasis remains limited, several cellular factors and signaling pathways appear to play regulatory roles and/or exhibit prognostic values in sarcoma metastasis. In addition, MicroRNAs have been shown to have either positive or negative impact on sarcoma biology and metastasis. Sarcoma is considered one of the classic radio- and chemo-resistant brain metastasis, hence the use of multiple modalities in order to improve the therapeutic ratio and overcome the inherent resistance. Treatment modalities include surgical resection, chemotherapy, gamma knife radiosurgery and/or fractionated whole-brain radiotherapy. The efficacy of chemotherapy is limited by the ability of the drug(s) to cross the blood-brain barrier (BBB), and the chemosensitivity of the tumor to the chemotherapeutic agent. In this review, we discuss the pathology, biology and therapy for sarcoma brain metastasis.

### 2. INTRODUCTION

Sarcomas are malignant mesenchymal neoplasms with an incidence of 2/100,000 population per year, and constitute 0.7.% of all cancers (1). The most

frequent malignant intracranial neoplasms are secondary ones, particularly carcinomas metastasizing from extracranial primary sites. In adults, the most common primary sites are lung, breast, melanoma, colorectal and renal cell carcinoma (2). Sarcomas are heterogeneous neoplasms and have much less potential for intracranial metastasis than epithelial tumors (2). The most frequent metastatic sites for sarcoma are lung, bone and liver (3). The reported incidence of sarcoma brain metastases ranges from 1-7% in adults (1, 3-6), and from 4.3-8% in children (7-9). Sarcoma types known to metastasize to the brain include Ewing sarcoma, Osteosaroma, leiomyosarcoma, rhabdomyosarcoma, alveolar soft part sarcoma and pleomorphic undifferentiated sarcoma (1,3-9).

Similar to other patients with intracranial metastases, patients with sarcoma metastases usually present with signs of increased intracranial pressure, symptoms like headache and nausea, or neurologic manifestation like hemiparesis and seizures. The diagnosis is usually suspected in the presence of the appropriate history of primary sarcoma, and the finding of new intracranial lesion/lesions using imaging techniques. Furthermore, it can be confirmed histologically if a resection is attempted as part of the treatment plan. Treatment options include surgical resection, chemotherapy, gamma knife radiosurgery or fractionated whole-brain radiotherapy (10). Recent studies show

**Table 1.** Intracranial locations for brain sarcoma metastases

Study	Reference	N	Single	Multiple	Frontal	Temporal	Parietal	Occipital	Cerebellar	Dural/meningeal
Flannery	10	21	9	12						6
Salavati	1	35	27	8	17	3	4	2		
Espat	4	40								9
Kebudi	7	12	5	7						
Paulino	8	20	14	6	6	4	3	1		
Postovsky	9	18	11	7		2	2	2	1	1
Yoshida	5	27	19	8	4	5	6	2	2	
Bindal	11	21	18	3	4	1	7	3	1	
			103	51	31	15	22	10	4	16

**Table 2.** Sarcoma brain metastases in adults

Study	Reference	N	LMS	ASPS	ES	LS	OS	CS	SS	MFH (UPS)	RMS	NS	HPC	Other
Hoiczkyk	3	21	5	5	3	3								5
Flannery	10	17	4	2	1	1	1	1	1			1		5
Salavati	1	26	7	2	4	1	4			4	1			3
Espat	4	40	8			5				4	4			19
Yoshida	5	18		2	2	2	1			4		1	4	2 FS
Bindal	11	14	4	2	1		2			3				2
All		136	28	13	11	12	8	1	1	15	5	2	4	36
%			20	10	8	9	6	1	1	11	4	1	3	26

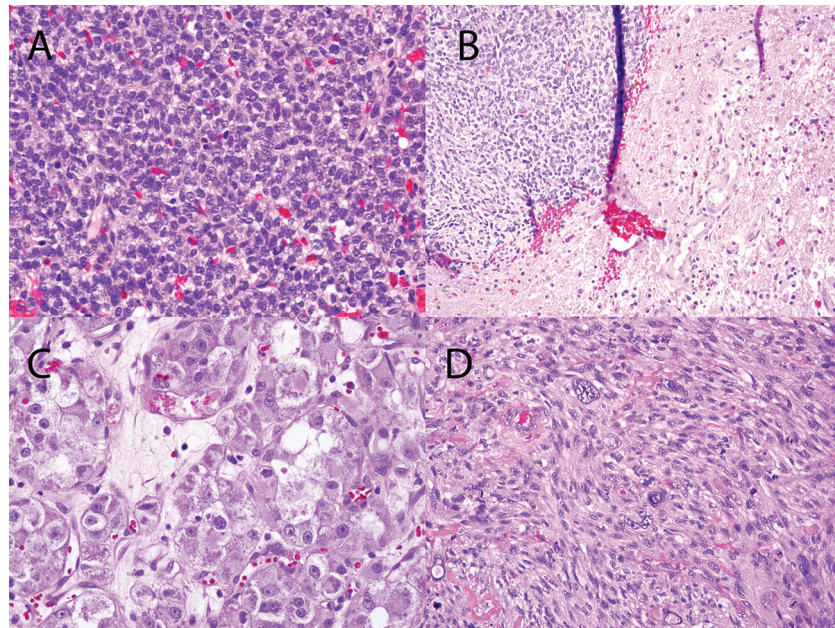
LMS: Leiomyosarcoma; ASPS: Alveolar soft part sarcoma; ES: Ewing sarcoma; LS: Liposarcoma; OS: Osteosarcoma; CS: Chondrosarcoma; SS: Synovial sarcoma; MFH: Malignant fibrous histiocytoma (also known as undifferentiated pleomorphic sarcoma "UPS"); RMS: Rhabdomyosarcoma; NS: Neurosarcoma (also known as MPNST); HPC: Hemangiopericytoma; ST: Soft tissue; FS: Fibrosarcoma

the median time from diagnosis to metastasis to be 12 months, and the median survival after diagnosis in the range of 8-16 months. The best survival is achieved in patients with isolated brain sarcoma metastases who undergo local treatment such as surgical resection and gamma knife (3, 10).

Brain metastases from sarcoma often follow lung metastases in 57-80% of patients (1, 4, 10-12). Almost all pediatric patients have metastasis to other sites, mostly lung, at the time of brain metastasis (7, 8). This led some authors to suggest that the presence of lung or other sites of metastasis is a predisposing factor for brain metastasis in children (7). Sarcoma metastasis tends to be single rather than multiple, with single metastatic lesions being twice as common (1, 5, 7-11). Intracranial sarcoma metastases are parenchymal in most of the cases, and less commonly leptomeningeal or dural based. Parenchymal metastases are mainly supratentorial; they most commonly involve the frontal lobes, followed by parietal and temporal lobes and least likely the occipital lobes (1, 5, 8, 9, 11). Metastatic lesions to meninges or dura are less frequent (10-23% of cases) (4, 10) (Table 1).

### 3. PATHOLOGY OF SARCOMA METASTASIS

In our review of the literature, leiomyosarcoma (LMS) appears to be the most common metastatic sarcoma to the brain in adults (20%), followed malignant fibrous histiocytoma (MFH)/undifferentiated pleomorphic sarcoma at 10% and alveolar soft part sarcoma (ASPS) at 9% (Table 2). In children, Osteosarcoma (OS) and Ewing sarcoma (ES) are the most common types (36% and 35% respectively), followed by Rhabdomyosarcoma (RMS) at 17% (Table 3). The most common histologic types to give brain metastases, overall, are ES, OS and LMS. The other less frequently reported types are RMS, ASPS, malignant fibrous histiocytoma (MFH)/pleomorphic undifferentiated sarcoma, liposarcoma (LS), synovial sarcoma (SS), chondrosarcoma (CS), and malignant peripheral nerve sheath tumor (MPNST)/neurosarcoma. Figure 1 illustrates several examples of brain sarcoma metastasis. They vary morphologically and include round cell, spindle cell, epithelioid and pleomorphic subtypes (Figure 1). Cytological analysis of cerebrospinal fluid (CSF) has been found to be a useful method to exclude or establish leptomeningeal involvement (7).



**Figure 1.** Pathology of sarcoma metastasis to the brain. A, Ewing sarcoma. A small round blue cell tumor. B, synovial sarcoma. Notice the normal brain tissue on the right side of the picture. C, alveolar soft part sarcoma. Nests of large epithelioid cells with abundant pink cytoplasm. D, pleomorphic undifferentiated sarcoma (malignant fibrous histiocytoma). Notice the large bizarre nuclei. (Hematoxylin and eosin, 20X magnification)

**Table 3.** Sarcoma brain metastases in children

Study	Reference	N	ASPS	ES	OS	CS	RMS	Other
Flannery		4			2	1	1	
Salavati		9	1	1	6		1	
Yoshida		9	1	4	2		2	
Bindal		7		2	5			
Kebudi		12	1	4	5		1	1
Paulino		20		6	5		7	2
Postovsky		19	1	11	4	1	2	
All		80	4	28	29	2	14	3
%			5	35	36	3	17	4

ASPS: Alveolar soft part sarcoma; ES: Ewing sarcoma;  
OS: Osteosarcoma; CS: Chondrosarcoma; RMS: Rhabdomyosarcoma

## 4. BIOLOGY OF SARCOMA METASTASIS

Current understanding of the biology of sarcoma metastasis remains limited (13). A literature review revealed that several cellular factors and signaling pathways play regulatory roles and/or exhibit prognostic values in sarcoma metastasis. These include angiogenic factors, tumor suppressors, oncoproteins, transcription regulators, and non-coding microRNAs, as summarized below. It is important to note that many of these signaling pathways are not particularly specific to sarcoma brain metastasis.

### 4.1. Angiogenic factors

Neovascularization has been shown to positively correlate with sarcoma metastasis (14). Several angiogenic factors can promote sarcoma metastasis, likely through enhancing neovascularization. For example, the vascular endothelial growth factor-A (VEGF-A) gene is frequently amplified (64%) in osteosarcoma (OS) tumors (15) and overexpressed in more than 50% of Ewing's sarcoma (16). VEGF-A expression was found to be positively associated with lung metastasis of OS (17). Furthermore, VEGF-A has been shown to serve as a prognostic factor for poor overall and disease-free survival in OS patients (15, 17) and ES patients (16). In contrast, no correlation was found between VEGF-A expression and histological subtype, stage, or response to neoadjuvant chemotherapy in patients with OS (17).

In soft tissue sarcomas (STSs), VEGF-A is also highly expressed (18). Ectopic VEGF-A expression promoted lung metastasis of STS xenografts, and anti-VEGFR2 (vascular endothelial growth factor receptor 2) monoclonal antibody DC101 in combination with doxorubicin inhibited STS tumor growth and lung metastasis (18). Interestingly, ES-specific EWS-FLI1 fusion oncogenic transcription factor activates VEGF-A gene expression in ES. In addition to VEGF-A, the expression of a positive G1 regulator, cyclin D1, can also be enhanced by EWS-FLI1(16).

Despite the positive correlation between VEGF-A and sarcoma lung metastasis, microvessel density was

not found to be associated with lung metastasis or overall survival of ES patients (19) or STS patients (20). Another more recent study confirmed that a high tissue VEGF expression, but not microvessel density, was associated with poor overall survival of STS patients and a higher probability of local recurrence and metastasis (21).

Another angiogenic factor, hypoxia-inducible factor-1 (HIF-1), has been shown to promote UPS metastasis to the lung through enhancing expression of the intracellular enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (PLOD2) (22). This is in agreement with the notion that intratumoral hypoxia correlates with metastasis and poor survival in patients with sarcoma. Pharmacologic inhibition of PLOD2 enzymatic activity suppresses UPS lung metastases, suggesting the potential use of PLOD2 and HIF-1 as novel therapeutic targets for the treatment of metastatic UPS (22).

Matrix metalloproteinases (MMPs) play an important role in remodeling extracellular matrix and facilitating tumor motility and invasion (23). Proteins associated with matrix remodeling have been shown to be elevated in STS bone metastases compared to healthy bones (24). MMP-9 (gelatinase B or the 92-kDa gelatinase/type IV collagenase) expression has been associated with sarcoma lung metastasis (25). MMP-9 inhibition using a ribozyme has been shown to block lung metastasis in a rat sarcoma model system (25). However, the results of existing literature on MMP-9 in OS have been mixed (26). More studies are needed to better define the importance of MMPs in sarcoma metastasis.

#### 4.2. Tumor suppressor p53

Loss of p53 tumor suppressor and gain of mouse double minute 2 homolog (MDM2), a E3 ubiquitin-protein ligase that degrades p53, are frequent events in a wide spectrum of human cancers, including sarcomas (27). Although germline p53 mutations were found in only about 3.0.% of children with OS (28), positivity for p53 expression (indicative of mutant dysfunctional p53 expression) was found in approximately 27% of 86 OS patients (29). MDM2 gene amplification was detected in 6.6.% of these OS patients (29). While aberrant p53-MDM2 pathway is critical for tumorigenic events towards OS (29), p53 mutation status did not differentiate between patients who presented with a localized OS and those who presented with metastases at the time of diagnosis (30). However, some recent evidence suggests that loss of wild-type p53 may also be involved sarcoma progression. For example, wild-type p53 was found to inhibit NFkappaB-induced MMP-9 promoter activation in STS (31). Meta-analysis suggests the use of p53 as an effective biomarker for survival in OS patients (32); however, additional studies are needed to solidify this suggested use.

Overexpression of COP9 signalosome subunit 3 (COPS3), which possesses kinase activity, has been linked to p53 protein degradation. Interestingly, COPS3 overexpression is frequently detected in high-grade OS tumors and this high level of expression can be attributed to frequent amplification of the region of 17p11.2. ~p12 amplicon (25%) in the disease (33). Interestingly, a more recent study reported that RNAi-mediated COPS3 gene silencing inhibited OS metastasis (34). In the genetic background of p53 mutation, mice with CD44 knockout aborted OS metastasis while tumorigenesis and tumor growth were not affected, suggesting a functional crosstalk between p53 and CD44 in mediating OS metastasis (35).

#### 4.3. Oncoproteins

Platelet-derived growth factor receptor (PDGFR) has been shown to be highly expressed in OS (36). In ES, PDGFR is frequently overexpressed and has been shown to promote motility and growth of ES cells (37). Consistent with this report, it has been found that silencing PDGFR led to reduced spontaneous tumor growth and lung metastasis of ES xenografts (38).

Src family tyrosine kinases (SFK) play an important role in promoting growth and metastasis of many types of cancer (39). It has been shown that c-Src mediates mitogenic signals in Kaposi's sarcoma cells (40). Lyn, a member of the SFK family of proteins, is highly expressed and activated in ES tumors (41). Targeting Lyn using siRNA and AP23994, a small-molecule SFK inhibitor, led to reduced ES tumor growth and metastasis (41). A more recent study showed that SFK inhibition by a selective SFK inhibitor SI221 suppressed rhabdomyosarcoma cell growth and invasiveness *in vitro* and *in vivo*, and also triggered p38 MAP kinase-mediated differentiation (42).

The oncogene astrocyte elevated gene-1 (AEG-1), also known as metadherin (MTDH), is a multifunctional protein involved in tumorigenesis, development, neurodegeneration, and inflammation (43). AEG-1/MTDH can localize in the cell membrane, cytoplasm, endoplasmic reticulum, nucleus, and nucleolus, contributing to diverse signaling pathways such as PI3K-AKT, NF-kappaB, MAPK and Wnt (43). AEG-1/MTDH protein can be detected in primary and metastatic sarcoma samples (44). Interestingly, high levels of both MTDH/AEG-1 and HOTAIR, a long non-coding RNA, in primary sarcomas are correlated with a high probability of metastasis. In contrast, lower levels of expression of both MTDH/AEG-1 and HOTAIR were correlated with a better response to treatment (44).

#### 4.4. Additional protein factors

Tumor necrosis factor receptor-1 (TNFR1) has been shown to be elevated in sarcoma bone metastases (45). TNFR1 and its ligand *TNFα* in bone



metastasis were positively correlated with poor survival following initial development of brain metastasis (45). Wilms' tumor 1 (WT1) is a zinc finger transcription factor that has been found to express in high-grade metastatic OS specimens. Importantly, high WT1 expression was shown to associate with poor survival of patients with OS metastasis (45).

Through comparative gene profiling analysis, the homeodomain only protein X (HOPX) was found to be expressed at a higher level in the metastatic sarcoma cells compared to the non-metastatic counterparts (46). HOPX knockdown inhibited sarcoma tumor cell mobility and *in vivo* metastasis (46). A RING finger E3 ubiquitin ligase Gp78 (also known as AMFR or RNF45) was reported to be involved in sarcoma metastasis (47). Gp78 possesses the ability to degrade KAI (also known as CD82), a transmembrane protein functioning as a metastasis suppressor, thereby promoting sarcoma metastasis (46).

Zinc finger E-Box homeobox (ZEB) proteins are E-box binding transcription factors that play an important role in epithelial-mesenchymal transition (48). Specifically, ZEB1 and ZEB2 can repress expression of E-cadherin, an important protein maintaining the epithelial phenotype of cells, thereby promoting the mesenchymal cell phenotype. Of note, sarcoma cells are cells of the mesenchymal phenotype. Interestingly, ZEB2 has been shown to repress the epithelial phenotype of ES cells and facilitate ES metastasis (49). ZEB2 expression knockdown reduced the metastatic potential of EW xenografts. Interestingly, several microRNAs have been shown to be expressed at lower levels in OS, including the miR-200 family of microRNAs (50), and miR-200 can suppress ZEB1/2 expression (48). By upregulating the miR-200 family of microRNAs, busulfan downregulated ZEB1/2 and displayed anti-osteosarcoma effects (51). MiR-141, a member of the miR-200 family of microRNAs, was found to be expressed at a lower level in OS tumors (52). Ectopic overexpression of miR-141 inhibited OS cell proliferation and induced apoptosis, likely through downregulating expression of ZEB1/2 (52).

#### **4.5. MicroRNAs**

The role of microRNAs in sarcoma has been intensively studied in recent years and the results are intriguingly interesting (53, 54). MicroRNAs can have positive or negative impact on sarcoma biology and metastasis. Through microRNA expression profiling, a microRNA signature has been reported for OS tumors (55). The signature includes high expression of miR-181a/b/c combined with reduced expression of miR-16, miR-29b, and miR-142-5p. Higher expression of miR-27a and miR-181c in pre-treatment biopsy samples characterized patients who developed clinical metastatic disease. Another microRNA profiling study reported that miR-199b-5p and miR-100-3p were downregulated in the

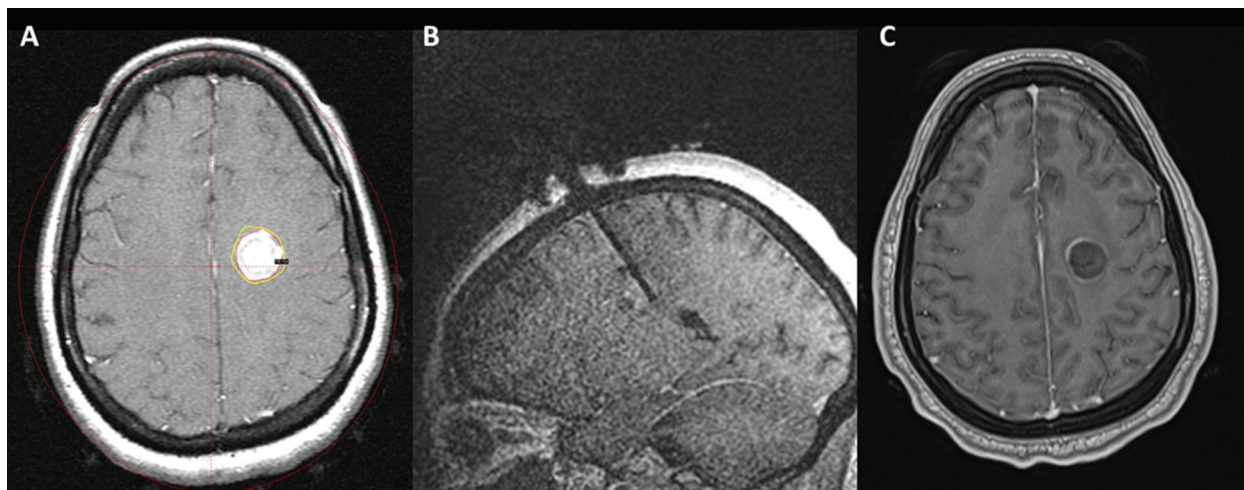
highly aggressive OS cell lines, whereas miR-155-5p, miR-135b-5p and miR-146a-5p were upregulated (56). Interestingly, miR-135b-5p and miR-146a-5p were potentially linked to the metastatic potential of OS.

A number of microRNAs have been identified to promote sarcoma progression. MiR-17 was frequently increased in OS tissues and cell lines; inhibition of miR-17 in OS cell lines substantially suppressed cell proliferation, migration, and invasion (57). miR-17 appeared to directly downregulate expression of the tumor suppressor phosphatase and tensin homolog (PTEN). An inverse correlation was observed between expression of miR-17 and PTEN in OS tissues (57). Furthermore, miR-181 was shown to increase circulating tumor cells and promote OS metastasis (52). MiR-210 expression was significantly increased in OS tumors compared to corresponding non-cancerous bone tissues; the increased expression correlated with large tumor size, poor response to preoperative chemotherapy, decreased overall survival and progression-free survival, and metastasis (58). In a clinical study, it was observed that high expression levels of CD133 and miR-133a were significantly correlated with poor prognosis of OS patients (59). Conversely, silencing miR-133a expression combined with chemotherapy suppressed OS metastasis to the lung (59).

Several microRNAs have the propensity to negatively regulate sarcoma growth and metastasis. As discussed earlier, miR-200 family of microRNAs downregulates ZEB1/2 expression leading to reduced tumor progression (48, 51, 52). MiR-145 was found to inhibit VEGF-A expression, contributing to reduced invasion and metastasis of OS (60). MiR-126 was reported to inhibit OS cell growth, invasion, and migration by downregulating ADAM-9, a disintegrin and metalloprotease 9 (61). Decreased miR-206 expression was significantly associated with advanced clinical stage, T classification, metastasis and poor histological differentiation of OS (62). MiR-218 has been shown to inhibit TIAM1, MMP-2 and MMP-9 protein expression, leading to OS cell migration and invasion (63).

#### **5. SURGERY AND RADIATION THERAPY FOR SARCOMA METASTASIS**

Sarcoma is considered one of the classic radioresistant brain metastases (64). As sarcoma brain metastases are rarer than the other radioresistant histologies such as renal cell carcinoma and melanoma, extrapolation of data from the more common radioresistant histologies is often used in the management of sarcoma brain metastases. A common theme in management is the use of radiosurgery as well as multiple modalities in order to improve the therapeutic ratio and overcome the inherent resistance of sarcoma brain metastases. The choice of modalities depends on the particular situation.



**Figure 2.** Patient with metastatic malignant peripheral nerve sheath tumor (MPNST). A, axial T1 weighted MRI with contrast on day of Gamma Knife planning. The patient received a dose of 18 Gy prescribed to the 50% isodose line in the pre-operative setting. B, sagittal T1 weighted MRI on day of laser interstitial thermotherapy (LITT). LITT procedure was performed 1 month after Gamma Knife as a planned consolidative treatment because of the known radioresistance of sarcoma brain metastases. C, axial T1 weighted MRI performed 2 months post-LITT showing decreased central enhancement consistent with treatment response. Rim of enhancement at the periphery of the tumor is a common finding for patients who receive LITT.

Brain metastases in radioresistant histologies, if not managed successfully, can lead to a high rate of death from brain metastases (64).

Stereotactic radiosurgery is commonly applied in cases of sarcoma brain metastases either alone or in combination with whole brain radiotherapy. Radiosurgery delivers a single high dose of radiation to a limited volume of brain. The advantage of radiosurgery for sarcoma is that by increasing the amount of radiation given in a single fraction, it appears to increase the efficacy of the radiation by increasing the number of targets to radiation damage (65) (Figure 2A). When radiosurgery is combined with whole brain irradiation, the local control of radiation is improved because of the increase in cumulative dose delivered to the metastases (66). Radiosurgery is generally used without whole brain irradiation in scenarios where there are fewer metastases in the brain (<5). Whole brain radiotherapy is added to radiosurgery when there are a greater number of lesions and when lesions are of a size where local control with radiosurgery alone may be compromised (>2cm) (66).

Surgery also plays a common role in the management of sarcoma brain metastases as surgery allows the immediate decrease of tumor burden. Surgery alone for brain metastases commonly leads to local failure, and the use of either radiosurgery (67) or whole brain radiotherapy (68) in the adjuvant setting can decrease this risk. Surgery is generally most useful in scenarios of large or symptomatic brain metastases, and in these situations has even been found to increase survival of patients (69). Limitations of surgery include surgical accessibility of the metastases and whether surgical intervention would significantly affect post-operative

functionality and quality of life. For surgically inaccessible lesions, laser interstitial thermotherapy (LITT) can be used to ablate radioresistant lesions to increase the local control of radiation alone (Figure 2B-C). Other means to optimize local control of radioresistant brain metastases like sarcoma are the use of concurrent systemic therapies with radiosurgery (70,71).

## 6. CHEMOTHERAPY FOR SARCOMA METASTASIS

CNS metastases from sarcomas are uncommon complications of stage IV sarcoma. Hence, clinical trials addressing the use of chemotherapy are lacking, and most reports are anecdotal in nature. Many retrospective analyses (in other tumors) have determined that the two most significant factors in determining the likelihood of achieving a meaningful response when using chemotherapy to treat CNS metastases are the ability of the drug(s) to cross the blood-brain barrier (BBB), and the chemosensitivity of the tumor to the chemotherapeutic agent(s) being used (72).

Unfortunately, the most active drugs in sarcomas - ifosfamide, doxorubicin, gemcitabine, and docetaxel - do not readily cross the blood-brain barrier, and hence penetrate CNS metastases poorly. Although limited reports exist in other solid tumors suggesting at least some of these drugs cross the BBB adequately enough to treat CNS metastases (73-76), the nature of these reports do not support the routine use of the anti-sarcoma drugs cited above in the treatment of CNS metastases.

Chemotherapy has been reported to be active, and is even incorporated into, front-line management

of certain solid tumors; these tumors tend to be highly chemosensitive, and many are considered chemocurable. Examples are germ cell tumors, gestational trophoblastic tumors (77), and non-Hodgkin's lymphoma. Unfortunately, chemotherapy is considered palliative in the treatment of (most) advanced sarcomas, with (systemic) response rates hovering around 30-35% and median durations of response being in the order of 1-2 years.

Molecular targeted therapies may change the landscape of systemic therapy in the management of CNS metastases, as many agents are "small enough" to penetrate the BBB adequately, and many reports now exist of targeted therapies resulting in CNS responses of appropriate tumors (78). Of note regarding sarcomas, is a report of pazopanib resulting in CNS response of a renal cell carcinoma, potentially prolonging the overall survival of the patient (79).

In summary, the two most important factors in determining the efficacy of systemic chemotherapy in the management of CNS metastases – ability to cross the BBB and the chemosensitivity of the tumor – are lacking in the arena of sarcomas. Thus, systemic options for treatment of CNS metastases should be regarded as investigational, or certainly not the treatment of choice. The emerging role of therapeutic, targeted, small molecules may change this in the future.

## 7. SUMMARY

Sarcomas infrequently metastasize to the brain, often in the setting of other systemic metastasis. Patients with localized metastasis and radiosurgery have relatively better prognosis; however, the prognosis is poor overall. The biology of sarcoma metastasis is not well understood. Angiogenic factors and loss of P53 appear to have a role; meanwhile oncoproteins and miRNAs are currently under study. Targeted therapy and personalized multimodality treatment planning appears to have a promising role in the treatment of certain types of sarcomas.

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