Scalp Invasion by Atypical or Anaplastic Meningioma Is a Risk Factor for Development of Systemic Metastasis

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■ BACKGROUND: **Atypical and anaplastic meningiomas (AAMs) are rare and comprise approximately 5% of all meningiomas. Extracranial metastases in meningioma patients occur in 0.1% of all cases, but these lesions are difficult to treat and may be a poor prognostic factor.**

■ METHODS: **We conducted a retrospective chart review between 1990 and 2016 of patients who had surgical resection of AAM. In a cohort of 149 patients, 6 had metastatic lesions that were histologically confirmed to be meningioma. We compared baseline characteristics between patients with and without metastasis and performed a multivariate Cox regression analysis to assess risk factors for the development of systemic metastasis.**

■ RESULTS: **Six patients had histologically confirmed meningioma metastasis. We hypothesized that the presence of scalp invasion in patients could be a potential risk factor for the development of systemic meningioma metastasis. Nine out of the 149 patients without metastasis had scalp invasion, whereas 4 out of the 6 patients with metastasis had scalp invasion. Patients with metastasis had a median age of 62 ± 20. Patients without metastasis had a median age of 59 ± 15 years. Gender distribution was similar; approximately 50% of patients in each group were female. Eighty-five percent of patients with metastatic disease were white, and 65% of patients without metastatic disease were white. Among patients without metastatic disease, 77% had World Health Organization II tumors, whereas 50% of patients with metastatic disease had World Health Organization II tumors. In multivariate analysis including age, tumor grade, size, location, extent of resection, sex, and scalp invasion, the only significant predictor of systemic metastasis was scalp invasion (odds ratio = 39.67; 95% confidence interval = 3.74–421.12; $P = 0.0023$). Median overall survival (OS) with metastasis was 126 months, and median OS without metastasis was 158 months. Having metastatic disease was not significantly associated with worse OS ($P = 0.33$).**

■ CONCLUSIONS: **Metastasis development from AAM is a rare but serious event. Because scalp invasion is a strongly associated predictive factor for development of systemic metastasis in patients with AAM, it is necessary to consider strategies to prevent and to be vigilant of the development of scalp invasion.**

INTRODUCTION

Meningiomas are slow-growing and mostly benign intracranial tumors that arise from the arachnoid cap cells. They account for approximately one third of all intracranial brain tumors.[1,2] They are typically solitary tumors, they are more common in women, and the majority of meningiomas are World Health Organization (WHO) grade I, but approximately 5% are atypical and malignant (WHO II and III).[3,4] Hospital-based epidemiologic studies report higher proportions of WHO II and III meningiomas ranging from 6%–15% for WHO II meningiomas and from 2%–4% for WHO III meningiomas.[5,6] High-grade meningiomas are more aggressive than their lower-grade counterparts, they recur earlier and more often, and also invade the adjacent structures, such as the brain, cranial bone, and the scalp occasionally. Despite being aggressive tumors,

Key words
- Anaplastic meningioma
- Atypical meningioma
- Metastasis
- Scalp invasion

Abbreviations and Acronyms
AAM: Atypical and anaplastic meningiomas
MRI: Magnetic resonance imaging
WHO: World Health Organization

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they rarely metastasize. Systemic metastasis from meningioma is an extremely rare event that occurs in 1–5 for every 1000 meningioma cases.[7-10]

There is a lack of guidelines to treat patients with atypical and anaplastic meningiomas (AAM). Tumor characteristics that have prognostic implications include genetic abnormalities, extent of surgical resection, need for adjuvant radiation, and histologic features, such as mitotic rates.[11-18] Recently, advances in the molecular characterization of meningiomas have shed light on potential genetic alterations that are linked with tumorigenesis and may lead to the identification of novel therapeutic targets.[19-21] Some molecular alterations can be detected easily with immunostains and can help identify subtypes of meningiomas that may correlate with prognosis.[22,23] Additionally, some of these molecular alterations have been added to the newest WHO classification of brain tumors as diagnostic criteria.[24] Previously we identified a combination of factors, such as the ones listed earlier that are associated with worse prognosis.[25]

We previously published a series describing the clinical characteristics of patients with high-grade meningiomas that developed metastasis.[26] The goal of this study was to identify risk factors for the development of metastatic lesions in AAM patients and to determine if this affected the survival of patients harboring these difficult-to-treat tumors.

METHODS

Study Design and Patient Population

Institutional Review Board approval was obtained before the start of this study. The records of all patients undergoing surgery for AAM at a single academic tertiary care institution (Johns Hopkins Hospital) between 1993 and 2014 were retrospectively reviewed. Patients with tissue-proven diagnosis of WHO II or III meningioma were included in the study. Tumor grade was determined by a senior neuropathologist according to the 2007 WHO grading system.[27]

The clinical, operative, and hospital course records of the patients were reviewed. Information collected included patient demographics, presenting symptoms, comorbidities, preoperative and postoperative neuroimaging, postoperative neurologic function, and adjuvant therapy. Tumor characteristics on preoperative and postoperative magnetic resonance imaging (MRI) were assessed at the time of surgery by a neuroradiologist blinded to patient outcomes. The degree of resection was determined from neuroradiology reports. Subtotal resection and gross total resection were defined on postoperative MRI. Extent of resection was also recorded as Simpson grades 1 through 5 by postoperative neuroimaging and operative reports.[28] The primary outcome evaluated for each patient was the presence of systemic metastasis and overall survival. Patients were assigned a preoperative Karnofsky Performance Scale score by the chart reviewer based on preoperative symptoms. Systemic metastasis was defined as a histologically proven lesion consistent with meningioma histology distant to the intracranial compartment and the scalp, which can be invaded by local invasion. Scalp invasion was not considered metastatic disease. The date of death was recorded according to the public U.S. Social Security Death Index database (http://ssdi.rootsweb.ancestry.com/).

Statistical Methods

Patient characteristics including demographics, clinical, radiologic, and pathologic variables were analyzed to determine associations with the development of systemic metastatic disease from AAM. Counts and proportions were used to summarize categorical variables. Groups were compared using the Fisher exact test. Medians and ranges were used to summarize continuous variables, and these were compared using the Mann–Whitney U test. Univariate and multivariate binary logistic regression models were constructed to calculate odds ratios and 95% confidence limits for variables associated with systemic metastasis development. Univariate and multivariate analyses with Cox proportional hazards regression models were also used to determine associations with the development of systemic metastasis. Statistically significant variables were analyzed as covariates in the regression models. Kaplan–Meier plots using the log-rank test were used to analyze survival for the patients that developed systemic metastasis. All analyses were considered statistically significant if 2-tailed P values were less than a type I error rate set at 0.05. All statistical analyses were carried out using SAS software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient Population and Baseline Characteristics

Characteristics of the 149 patients with a diagnosis of WHO grade II or III meningiomas included in the study are summarized in Table 1. The average age (±standard deviation) of patients included in the study was 59 ± 14 years, and 70 (47%) of the patients were male. The average follow-up time was 38 ± 43 months. The median (IQR) Karnofsky Performance Scale was 80 (20–100). It is noteworthy that 114 (76%) were WHO grade II tumors and 35 (23%) were WHO grade III tumors. Seventy-eight (52%) were newly diagnosed tumors, and the rest were recurrent tumors. The most frequent tumors in the series include the convexity meningiomas accounting for 34%, followed by parafalcine meningiomas accounting for 25%. Of all the patients with grade II or grade III meningiomas, 28% of them received radiation therapy, whereas 10% received chemotherapy. Simpson grade 1 resections were performed in 65 (43%) patient, Simpson grade 2 was performed in 16 (10%) patients, Simpson 3 was performed in 6 (4%) patients, and Simpson 4 was performed in 62 (41%) of the patient's included in the cohort. Scalp involvement was identified in MRI scans in 13 (8%) patients.

Only 6 patients (4%) of the cohort presented with pathology-proven metastatic disease originating from intracranial meningioma. The mean age of patients with metastases was 55 years ±20 years, whereas the mean age of patients without metastases was 58 ± 14 years. Three (50%) patients with metastasis were male, whereas 67 (47%) of the patients without metastasis were male. The majority (5, 83%) of patients with metastases were white. Of the patients with metastases, 3 (50%) belong to the WHO grade II classification.

Risk Factors for Development of Metastatic Disease in Patients with Atypical and Anaplastic Meningiomas

We performed a univariate analysis to determine association of the collected variables with the development of metastatic disease

Table 1. Baseline Characteristics for Entire Cohort and According to Presence of Metastases

Characteristic	All	Metastases	No Metastases	*P* Value
Number (%)	149	6 (4%)	143 (96%)	
Age, year, mean (standard deviation)	59 (14)	55 (20)	58 (14)	0.92
Sex				
Male, number (%)	70 (47%)	3 (50%)	67 (47%)	1.00
Female, number (%)	79 (53%)	3 (50%)	76 (53%)	
Race				
White	99 (66%)	5 (83%)	94 (66%)	0.42
African American	34 (23%)	0 (0%)	34 (24%)	
Other	16 (11%)	1 (17%)	15 (11%)	
Karnofsky Performance Scale				0.44
≥70	124 (83%)	3 (50%)	121 (85%)	
<70	19 (13%)	1 (17%)	18 (13%)	
Missing*	6 (4%)	2 (33%)	4 (3%)	
WHO grade				0.14
II	114 (77%)	3 (50%)	111 (78%)	
III	35 (23%)	3 (50%)	32 (22%)	
Disease status				0.42
Newly diagnosed	78 (52%)	2 (33%)	76 (53%)	
Recurrent	71 (48%)	4 (67%)	67 (47%)	
Extent of resection				0.65
STR	62 (42%)	3 (50%)	59 (41%)	
GTR	86 (58%)	2 (33%)	84 (59%)	
Missing*	1 (1%)	1 (17%)	0 (0%)	
PORT				0.35
Yes	42 (28%)	3 (50%)	39 (27%)	
No	107 (72%)	3 (50%)	104 (73%)	
Tumor location				0.45
Convexity	40 (27%)	1 (17%)	39 (27%)	
Parafalcine	32 (21%)	1 (17%)	31 (22%)	
Falcine	5 (3%)	1 (17%)	4 (3%)	
Anterior skull base	13 (9%)	0 (0%)	13 (9%)	
Middle fossa	15 (10%)	0 (0%)	15 (10%)	
Posterior fossa	7 (5%)	0 (0%)	7 (5%)	
Intraventricular	5 (3%)	0 (0%)	5 (4%)	
Multiple	32 (21%)	3 (50%)	29 (20%)	
Number of lesions				0.11
1	117 (79%)	3 (50%)	114 (80%)	
Multiple	32 (21%)	3 (50%)	29 (20%)	
Largest tumor dimension, cm, mean (standard)	4.9 (1.6)	6.1 (1.8)	4.7 (1.6)	0.18
Missing*	17 (11%)	15 (10%)	2 (33%)	
Venous system invasion				0.60
Present	38 (26%)	2 (33%)	36 (25%)	
None	110 (74%)	3 (50%)	107 (75%)	
Missing*	1 (1%)	1 (17%)	0 (0%)	
Scalp invasion				<0.001
Yes	13 (9%)	4 (67%)	9 (6%)	
No	136 (91%)	2 (33%)	134 (94%)	

WHO, World Health Organization; STR, subtotal resection; GTR, gross total resection; PORT, postoperative radiation therapy.
*Missing observations not included in statistical analyzes.

from high-grade meningiomas, and the only statistically significant difference was the presence of scalp invasion ($P < 0.001$) (Table 1).

Subsequently, this variable was subjected to a multivariate analysis, and the presence of scalp invasion on MRI remained a statistically significant factor that was independently associated with development of metastases originating from WHO grade II or III meningiomas (odds ratio = 39.67; 95% CI = 3.74–421.12; $P = 0.0023$). This is summarized in Table 2.

Development of Metastasis and Survival

Importantly metastasis was not significantly associated with overall survival from initial diagnosis (Figure 1). The median overall survival of patients with metastases was 126 months, which was less than that in patients without metastases who had a median overall survival of 158 months; however, this difference was not statistically significant ($P = 0.33$).

DISCUSSION

Meningiomas are mostly benign tumors that can be cured with resection alone. The majority of these tumors are WHO grade I; however, higher-grade meningiomas display an aggressive behavior, higher incidence of recurrence, and atypical histologic characteristics. These are WHO grade II and III meningiomas. Patients with higher-grade meningiomas often require multiple surgeries and adjuvant therapies like radiation. In rare cases, chemotherapy has been tried for patients harboring aggressive meningiomas with no benefit.[29] These patients present several challenges to the treating team of physicians due to the limited availability of treatment strategies for these difficult-to-treat tumors. It has been well documented that reoperation carries increased morbidity including cognitive changes, neurologic deficits, and wound-healing complications.[30-32]

Table 2. Univariate and Multivariate Analysis for Predictors of Metastases

Characteristic	Univariate	*P* Value	Multivariate	*P* Value
Age	0.99 (0.94–1.04)	0.60	NE	
Sex				
Female	Reference		NE	
Male	1.13 (0.22–5.81)	0.88		
Race			NE	
White	Reference			
African American	—	0.94		
Other	1.25 (0.14–11.48)	0.93		
KPS			NE	
≥70	Reference			
<70	2.24 (0.22–22.7)	0.49	NE	
WHO grade				
II	Reference		NE	
III	3.47 (0.67–18.02)	0.14		
Disease status			NE	
Newly diagnosed	Reference			
Recurrent	2.27 (0.40–12.78)	0.35		
Extent of resection			NE	
STR	Reference			
GTR	0.47 (0.08–2.89)	0.41		
PORT			NE	
No	Reference			
Yes	2.67 (0.52–13.78)	0.24		
Tumor location			NE	
Convexity	Reference			
Parafalcine	1.26 (0.08–20.9)	0.92		
Falcine	9.75 (0.51–187.53)	0.97		
Anterior skull base	—	0.85		
Middle fossa	—	0.96		
Posterior fossa	—	0.97		
Intraventricular	—	0.98		
Multiple	4.03 (0.40–40.79)	0.89		
Number of lesions			NE	
1	Reference			
Multiple	3.93 (0.75–20.50)	0.10		
Largest tumor dimension	1.67 (0.88–3.19)	0.12	NE	
Venous system invasion			NE	
No	Reference			
Yes	1.98 (0.32–12.34)	0.46		

Continues

Table 2. Continued

Characteristic	Univariate	*P* Value	Multivariate	*P* Value
Scalp invasion				
No	Reference		Reference	
Yes	29.78 (4.79–185.01)	<0.001	39.67 (3.74–421.12)	0.0023

NE, not entered; KPS, Karnofsky Performance Scale; WHO, World Health Organization; STR, subtotal resection; GTR, gross total resection; PORT, postoperative radiation therapy.

In this study we sought to identify factors that may lead to the development of systemic metastatic disease in patients with WHO II and III meningiomas. We retrospectively reviewed the charts, operative reports, and imaging studies of 149 patients with histopathologic diagnosis of WHO II and III meningiomas. In our cohort of patients with high-grade meningiomas, we observed that 6 out the 149 patients reviewed (4%) had developed systemic metastatic lesions that were found in workup for other medical problems or were due to the presence of symptoms.[26] Previous studies have identified an incidence of metastatic lesions in meningioma patients of 0.14%–0.76% where patients with high-grade meningiomas are the ones at risk for metastatic disease.[7,9,33,34] Some of the previously cited studies mention worse prognosis in patients with metastatic meningioma. In our study, the results demonstrate that although the time of survival from initial diagnosis was shorter in patients with systemic metastasis, this did not reach statistical significance.

Previous studies have identified factors, such as high cellularity and mitotic rate, necrosis, and invasion of the venous system as important risk factors associated with the development of metastatic disease for meningioma patients. Another large study found that having multiple recurrences was associated with development of systemic metastasis.[34] The authors mention that multiply recurrent meningioma in the central nervous system led to the decision to obtain systemic images, and this may have led to increased discovery of asymptomatic systemic disease. Although most of the patients with metastatic disease in this series had recurrent central nervous system disease, this factor was not statistically significant (Tables 1 and 2). In this study, the only factor that was associated with development of metastatic disease was the presence of scalp invasion. Other variables in the analysis that were not associated with development of metastatic disease included venous system invasion, tumor size, tumor location, tumor grade, history of postoperative radiation therapy, extent of resection, or disease status (see Tables 1 and 2). The incidence of metastatic disease in WHO grade II and III patients was 4% in our study, whereas in the study by Della Ore et al,[34] the incidence of metastatic disease in patients with high-grade lesions was 2.95%. In our series, the tumors that metastasized were located in the convexity, in the falx or parafalcine, and in multiple locations based on local extension. None of the tumors were located in the skull base or posterior fossa. In many cases these tumors invade the calvarial bone and require placement of a cranioplasty, and this poses a risk for recurrence and invasion through the cranioplasty into the scalp. In this study, having scalp invasion resulted in an odds ratio average of 39 compared with not having scalp invasion.

Although the survival of patients with metastatic meningioma was not statistically significant in our cohort, it was shorter compared with patients with no metastatic disease. The lack of

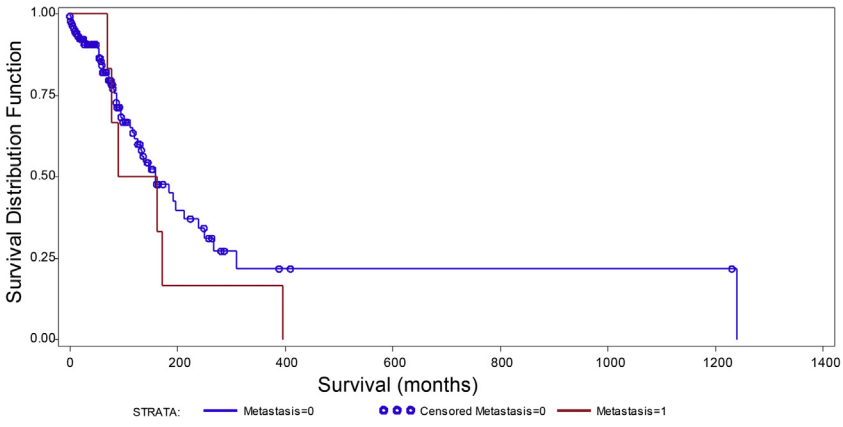

Figure 1. Kaplan-Meier curve comparing the overall survival (OS) of patients with metastatic World Health Organization grade II and III meningioma to those without metastatic disease. The median OS of patients with metastatic disease was 126 months. The median OS of patient is without metastatic disease was 158 months ($P = 0.33$).

significance is probably due to the size of our cohort. Larger, possibly multicentric, studies pooling the information of patients of multiple institutions may yield more robust results. Routine body imaging to determine the presence of systemic metastatic disease in patients diagnosed with meningioma is not performed. There are currently no guidelines for the detection of metastatic disease in the management of patients with WHO grade II and III meningiomas. Interestingly, in the study by Dalle Ore et al,[34] they began screening their patients with multiply recurrent disease to plan for further treatment. In their study, the authors found that the number needed to treat was 3.83, suggesting that when patients are selected on the basis of the presence of multiply recurrent disease, there is a significant yield of discovery of metastatic disease. Potentially, a grading scale incorporating scalp invasion, presence of recurrent disease, venous invasion, tumor location, and histologic factors including tumor grade may be useful to stratify high-grade meningioma patients to determine whether screening for metastatic disease is necessary. It has been reported that approximately 50% of the metastasis are diagnosed secondary to symptoms and approximately 30% are incidentally found on imaging for other indications.[35] Furthermore, Corniola et al[36] published an increased risk of metastasis with WHO grade III meningiomas, although the majority of high-grade meningiomas are grade II and are also at risk for development of metastasis. In our cohort, 50% of the patients with metastasis were grade II and 50% were grade III. Proportionally this reflects an incidence of metastatic disease in patients with WHO grade II meningioma of 2.6% and an incidence of metastatic disease in 8.5% of patients with WHO grade III meningioma in our cohort.

The retrospective nature of the study is one of the main limitations. In addition, the small size of our patient sample is another limitation; however, metastatic meningioma is rare. In spite of these limitations we identified a factor that can be corrected to potentially prevent the development of systemic metastatic disease in patients with high-grade meningioma. When a cranioplasty is required, it may be beneficial to perform the reconstruction with a nonporous material instead of titanium cranioplasty to prevent invasion of the scalp if the meningioma recurs. Prospective implementation of a tool to stratify patients to determine the need for screening for the presence of metastatic disease may be needed and this could also help decide whether the patient would benefit from a modified plan for reconstruction after surgery and further management.

CONCLUSIONS

Although metastases are a rare occurrence in meningioma patients, they are more common in patients with high-grade lesions. In our study, the incidence of metastatic disease in our cohort is slightly higher than that of other series. We found that scalp invasion was a significant risk factor for development of systemic metastasis. None of the other factors, such as invasion of the venous structures or CNS recurrence, were significant risk factors for development of metastatic disease. This is likely due to the small number of patients with metastatic disease in our series.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Tomas Garzon-Muvdi: Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Russell Maxwell:** Data curation, Formal analysis. **Andrew Luksik:** Data curation. **Remi Kessler:** Data curation. **Jon Weingart:** Writing - review & editing. **Alessandro Olivi:** Writing - review & editing. **Chetan Bettegowda:** Writing - review & editing. **Rafael Tamargo:** Writing - review & editing. **Henry Brem:** Writing - review & editing. **Michael Lim:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing.

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