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The impact of multiple lesions on progression-free survival of meningiomas: a 10-year multicenter experience

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OBJECTIVE Multiple meningiomas (MMs) occur in as many as 18% of patients with meningioma, and data on progression-free survival (PFS) are scarce. The objective of this study was to explore the influence of the number of lesions and clinical characteristics on PFS in patients with WHO grade I meningiomas.

METHODS The authors retrospectively reviewed the records of all adults diagnosed with a meningioma at their three main sites from January 2009 to May 2020. Progression was considered the time from diagnosis until radiographic growth of the originally resected meningioma. A secondary analysis was performed to evaluate the time of diagnosis until the time to second intervention (TTSI). Univariable and multivariable analyses were conducted to assess whether the number of lesions or any associated variables (age, sex, race, radiation treatment, tumor location, and extent of resection) had a significant impact on PFS and TTSI.

RESULTS Eight hundred thirty-eight patients were included. Use of a log-rank test to evaluate PFS and TTSI between a single and multiple lesions showed a significantly shorter progression for MM ($p < 0.001$ and $p < 0.001$, respectively). Multivariable Cox regression analysis showed significantly inferior PFS on MM compared to a single lesion (hazard ratio [HR] 2.262, 95% confidence interval [CI] 1.392–3.677, $p = 0.001$) and a significantly inferior TTSI for patients with MM when compared to patients with a single meningioma (HR 2.377, 95% CI 1.617–3.494, $p = 0.001$). By testing the number of meningiomas as a continuous variable, PFS was significantly inferior for each additional meningioma (HR 1.350, 95% CI 1.074–1.698, $p = 0.010$) and TTSI was significantly inferior as well (HR 1.428, 95% CI 1.189–1.716, $p < 0.001$). African American patients had an inferior PFS when compared to non-Hispanic White patients (HR 3.472, 95% CI 1.083–11.129, $p = 0.036$).

CONCLUSIONS The PFS of meningiomas appears to be influenced by the number of lesions present. Patients with MM also appear to be more prone to undergoing a second intervention for progressive disease. Hence, a closer follow-up may be warranted in patients who present with multiple lesions. These results show a decreased PFS for each additional lesion present, as well as a shorter PFS for MM compared to a single lesion. When assessing associated risk factors, African American patients showed an inferior PFS, whereas older age and adjuvant therapy with radiation showed an improved PFS.

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KEYWORDS age; multiple meningiomas; progression-free survival; race; radiation; survival; oncology

ABBREVIATIONS CI = confidence interval; EBRT = external-beam radiation therapy; GTR = gross-total resection; HR = hazard ratio; MM = multiple meningioma; NF2 = neurofibromatosis type 2; PFS = progression-free survival; SRS = stereotactic radiosurgery; TTSI = time to second intervention.

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The presence of multiple meningiomas (MMs) in a single patient has been reported in as many as 18% of patients with meningioma.[1,2] This entity was first reported by Harvey Cushing and Louise Eisenhardt in 1938.[3] The pathophysiology of multiple tumor occurrence in the same patient is unknown, but theories suggest that this phenomenon might be due to leptomeningeal spread of a single lesion or as a consequence of sporadic neoplasms arising in different locations.[4,5] The appearance of MMs has also been correlated with previous exposure to radiation therapy, particularly among pediatric patients.[6–8]

There are multiple factors known to influence the incidence and prognosis of patients with meningiomas, with sex being one of the most influential variables, as the incidence of meningiomas is twice as high in females as in males.[9–11] Moreover, the presence of MMs associated with vestibular schwannomas is a hallmark of neurofibromatosis type 2 (NF2), as established by the Manchester criteria.[12]

Data on the risk factors and prognosis of MM are scarce and no outcome studies on large cohorts have been conducted. Our group recently published a study from data obtained through a national database (Surveillance, Epidemiology, and End Results program from the National Cancer Institute) reporting a significant association between the number of meningiomas in a single patient, age, and sex on survival of meningioma patients.[13] As evidenced by our previous study, MMs tend to behave differently than single lesions. Although the mechanisms for these differences are still under investigation, studies suggest there are variations in the molecular characteristics of these lesions.[14,15] Nevertheless, there is a clear clinical significance for these differences, and to account for these clinical characteristics we sought to investigate the clinical outcomes of patients with MMs utilizing data from our own institution. In this study, we evaluate the progression-free survival (PFS) of patients with MMs based on our own multisite data. We test the hypothesis that the number of lesions at the time of diagnosis may have a significant influence on the PFS of patients with MMs.

Methods

Patient Selection

We retrospectively reviewed the electronic medical records of all consecutive adult patients (≥ 18 years old) who underwent an open surgical procedure for histological diagnosis of meningioma at the three main sites of our institution (Florida, Minnesota, and Arizona, Mayo Clinic) from January 2009 to May 2020. Patients with recurrent disease, or without histological diagnosis, were excluded from this study. Additionally, patients with atypical (WHO grade II) or anaplastic (WHO grade III) meningiomas, as well as patients with a previous diagnosis of NF2 or the presence of either a schwannoma or an intracranial malignant tumor, were excluded to avoid any confounding variables. This study was approved by our IRB.

Demographic and Clinical Characteristics

Demographic and clinical data were retrospectively extracted from the electronic medical records. The following variables were obtained: age, sex, race, ethnicity, date of diagnosis, histological diagnosis, WHO grade, and radiation treatment.

Radiographic Characteristics

Radiographic variables were collected from available imaging and procedure notes. For this study, preoperative MRI and all follow-up imaging were reviewed until there was radiographic evidence of progression. Frequency of imaging varied and was contingent on the clinical judgment of the treating physician. However, in our practice, at least two scans are performed in the first postoperative year followed by surveillance scans at the discretion of the physician. The following variables were obtained: number of meningiomas at diagnosis, time to progression, extent of resection, and location.

All imaging was reviewed and interpreted by an expert neuroradiologist at the time the study was performed. Radiographic progression was defined as lesion growth, and data were retrospectively gathered from the formal interpretation. PFS was considered as the time from histopathological diagnosis until radiographic progression of the lesion originally excised. A secondary analysis was conducted to evaluate the time from diagnosis to a second intervention (time to second intervention [TTSI]) with either surgery or radiation therapy for the lesion originally excised. An exploratory secondary analysis to evaluate progression of nonoperated tumors was performed, considering progression as the time from surgery to radiographic growth of any of the nonoperated lesions.

Statistical Analysis

For all statistical methods, significance was defined as $p < 0.05$. The PFS was analyzed using a log-rank test and plotted using the Kaplan-Meier method. The age between single and multiple meningioma groups was analyzed using a Mann-Whitney U-test. The differences in demographic and clinical characteristics between the two groups were compared using a two-tailed z-test of proportions for two samples. Univariable and multivariable Cox proportional hazards models were used to evaluate the association between variables (age, sex, race, WHO grade, number of meningiomas, treatment with radiation, and location in the skull base) with PFS and TTSI. On multivariable analysis we compared the number of meningiomas as a categorical variable to compare outcomes of a single lesion versus multiple lesions. A secondary analysis was performed with the number of meningiomas as a continuous variable to assess the risk of every additional lesion. The log-rank test, Kaplan-Meier curve, and Mann-Whitney U-test were performed using GraphPad Prism (version 9 for Mac, GraphPad Software, www.graphpad.com), and the Cox proportional hazards models were performed using SPSS statistical software (version 25 for Mac, IBM Corp.). For continuous variable analysis, patients with 4 or more meningiomas were grouped together as previously described.[13]

Results

Patient Selection

We screened 2093 patients with a histological diagnosis of meningioma at our institution between January

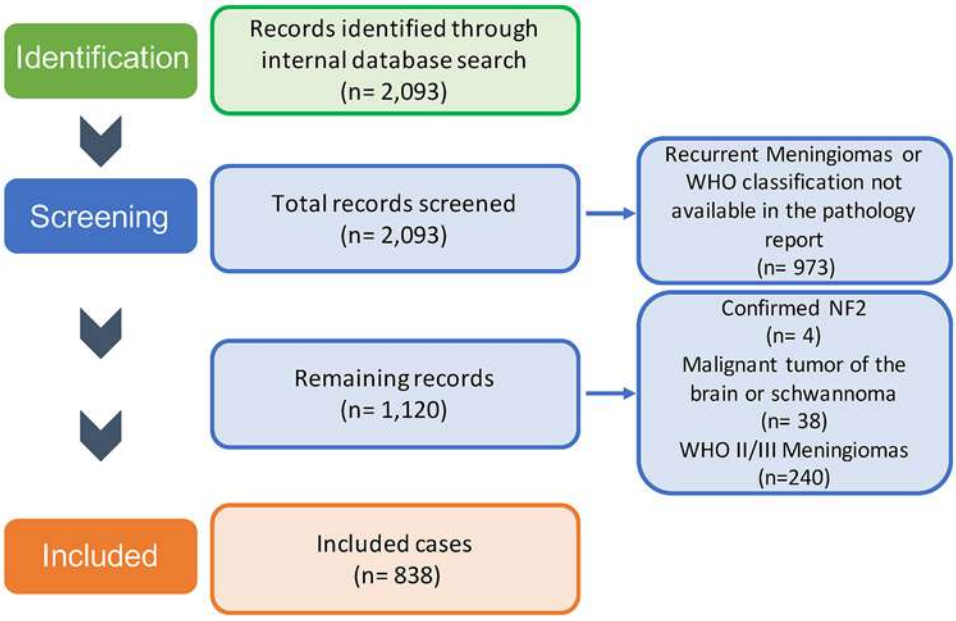

FIG. 1. Flowchart illustrating the selection criteria for this study. Figure is available in color online only.

2009 and May 2020, and 838 patients met the selection criteria for this study (Fig. 1).

Demographic and Clinical Characteristics

The demographic and clinical characteristics are described in Table 1. From our total patient cohort (n = 838), 742 (88.54%) had a single lesion and 96 (11.46%) had more than one lesion. The mean age (± SD) was 56 ± 12.85 years, the majority of patients were female (n = 640, 76.37%), and most patients (n = 770, 91.89%) were of non-Hispanic White race. Half of the patients had tumors located in the skull base (n = 462, 55.13%). All patients underwent a surgical procedure for lesion removal (n = 838), while 582 (69.45%) underwent an initial gross-total resection (GTR). Seventy-one patients received adjuvant treatment with radiation after initial resection (8.47%), and from the 71 patients who received adjuvant radiation, 23 (32.39%) underwent external-beam radiation therapy (EBRT) and 48 (67.61%) underwent stereotactic radiosurgery (SRS). In the MM group, 19 patients (19.79%) had more than 1 lesion removed during the initial procedure and 34 patients (35.42%) had radiographic progression of their nonoperated tumors. In the single meningioma group, 14 patients (1.89%) had a history of previous radiation to the head and 17 (2.29%) had a history of radiation to another section of the body. In the MM group, 4 patients (4.17%) had a history of prior radiation to the head and 6 (6.25%) had a history of radiation to another section of the body.

Univariable Analysis

A log-rank test comparing the PFS between patients with a single meningioma compared with MMs showed a significantly inferior PFS for MM ($p < 0.001$, Fig. 2) as well as an inferior TTSI for MM ($p < 0.001$, Fig. 3). Univariable Cox proportional hazards regression analysis (Table 2) showed that patients with multiple tumors had a significantly inferior PFS when compared to a single tumor (hazard ratio [HR] 2.554, 95% confidence interval [CI] 1.619–4.029, $p < 0.001$). When input as a continuous variable (i.e., separating patients with 1, 2, 3, and ≥ 4 tumors into different groups), PFS was significantly inferior as well (HR 1.588, 95% CI 1.268–1.987, $p < 0.001$). The difference in age between patients with a single meningioma (median 56 years) compared with patients with MM (median 58 years) was not statistically significant ($U = 31{,}775$, $p = 0.088$). On our secondary analysis evaluating the TTSI, the univariable Cox proportional hazards regression (Table 3) showed that patients with MMs have a significantly inferior TTSI when compared to those with a single tumor (HR 2.733, 95% CI 1.883–3.967, $p < 0.001$). When input as a continuous variable (i.e., separating patients with 1, 2, 3, and ≥ 4 tumors into different groups), TTSI was significantly inferior as well (HR 1.691, 95% CI 1.408–2.030, $p < 0.001$). An exploratory analysis evaluating overall survival by number of meningiomas was nonsignificant ($p = 0.302$). The mean PFS for nonoperated lesions was 38.12 months, whereas the mean PFS for the operated lesions was 52.21 months.

Multivariable Analysis

When taking into account other variables such as age, sex, race, number of meningiomas, treatment per type of radiation, extent of resection, and location in the skull base, multivariable Cox proportional hazards regression (Table 2) showed a significantly inferior PFS for patients with MM (Fig. 4) when compared to patients with a single meningioma (HR 2.262, 95% CI 1.392–3.677, $p = 0.001$). When input as a continuous variable, PFS was significantly inferior as well (HR 1.350, 95% CI 1.074–1.698, $p = 0.010$). Additionally, African American ethnicity was

TABLE 1. Patient demographic and clinical characteristics

Characteristic	Total (%)	Single Tumor (%)	Multiple Tumors (%)	p Value
No. of patients	838 (100)	742 (88.54)	96 (11.45)	
Age, yrs				
<65	598 (71.36)	537 (72.37)	61 (63.54)	0.071
≥65	240 (28.64)	205 (27.63)	35 (36.46)	0.071
Sex				
Male	198 (23.63)	188 (25.34)	10 (10.42)	**0.001**
Female	640 (76.37)	554 (74.66)	86 (89.58)	**0.001**
Race				
Non-Hispanic White	770 (91.89)	679 (91.51)	91 (94.79)	0.267
Hispanic/Latino	7 (0.84)	7 (0.94)	0 (0.00)	0.337
African American	18 (2.15)	16 (2.16)	2 (2.08)	0.960
Asian	11 (1.31)	10 (1.35)	1 (1.04)	0.803
Native American	3 (0.36)	3 (0.40)	0 (0.00)	0.535
Treatment w/ radiation				
None	758 (90.45)	681 (91.78)	77 (80.21)	**<0.001**
EBRT	23 (2.74)	22 (2.96)	1 (1.04)	0.276
SRS	48 (5.73)	34 (4.58)	14 (14.58)	**<0.001**
Located in skull base				
No	376 (44.87)	346 (46.63)	30 (31.25)	**0.004**
Yes	462 (55.13)	397 (53.50)	65 (67.71)	**0.009**
Extent of resection				
Subtotal	253 (30.19)	209 (28.17)	44 (45.83)	**<0.001**
GTR	582 (69.45)	531 (71.56)	51 (53.13)	**<0.001**
History of prior radiation				
Head	18 (2.15)	14 (1.89)	4 (4.17)	0.147
Other section of body	23 (2.74)	17 (2.29)	6 (6.25)	**0.026**

Boldface type indicates statistical significance.

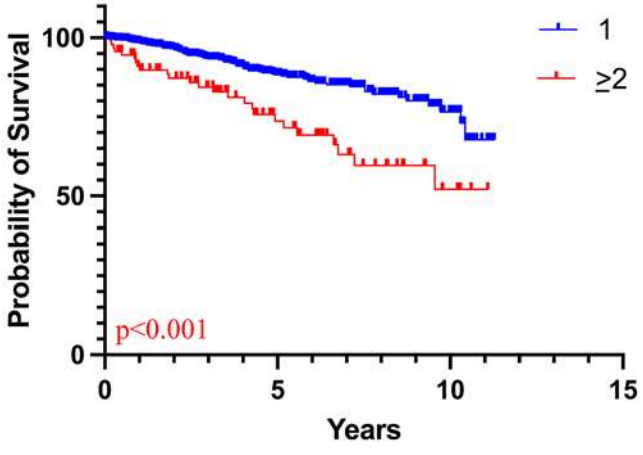

FIG. 2. Kaplan-Meier curve for PFS in patients with meningiomas. A Mantel-Cox (log-rank) test was performed demonstrating a significantly reduced PFS in patients with multiple lesions compared with those with a single lesion ($p < 0.001$). Figure is available in color online only.

associated with an inferior PFS when compared to White race (HR 3.472, 95% CI 1.083–11.129, $p = 0.036$). On our secondary analysis, the multivariable Cox proportional hazards regression (Table 3) showed a significantly inferior TTSI for patients with MM when compared to patients with a single meningioma (HR 2.377, 95% CI 1.617–3.494, $p = 0.001$). When input as a continuous variable, TTSI was significantly inferior as well (HR 1.428, 95% CI 1.189–1.716, $p < 0.001$).

When accounting for other variables, age was associated with an improved PFS (HR 0.982, 95% CI 0.966–0.998, $p = 0.029$) and with an improved TTSI (HR 0.977, 95% CI 0.964–0.991, $p = 0.001$). Adjuvant treatment with EBRT (HR 0.210, 95% CI 0.050–0.873, $p = 0.032$) and SRS (HR 0.467, 95% CI 0.230–0.950, $p = 0.035$) was associated with a superior PFS as well. Additionally, PFS (HR 0.215, 95% CI 0.136–0.339, $p < 0.001$) and TTSI (HR 0.120, 95% CI 0.080–0.179, $p < 0.001$) were superior in patients who underwent GTR compared to subtotal resection.

Discussion

Even though meningiomas are the most common pri-

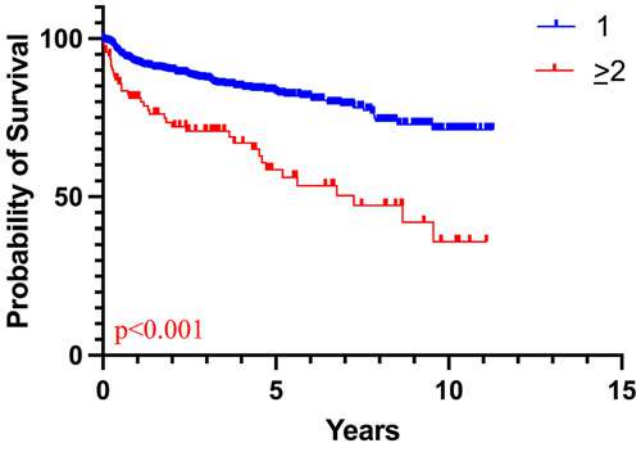

FIG. 3. Kaplan-Meier curve for TTSI in patients with meningiomas. A Mantel-Cox (log-rank) test was performed demonstrating a significantly reduced time to a second treatment course in patients with multiple lesions compared with those with a single lesion ($p < 0.001$). Figure is available in color online only.

mary intracranial neoplasm, the presence of multiple tumors in the same patient remains fairly infrequent, with reports ranging from 1% to 20% within a population of patients with meningioma.[1,2,13] The reported incidence has risen over the years, potentially due to advanced diagnostic imaging.[16] Our study found an incidence of 12.15% in our population of patients, in accordance with the previously reported ranges.[1,2,13] Limited data are available regarding the influence of number of lesions on the prognosis of these patients. Hence, in this paper we assess the effects of MM, sex, and treatment on PFS of meningioma patients.

Influence of MM in Progression: Worse PFS and TTSI for Every Additional Lesion Present

We found an inferior PFS for patients with MMs when compared to patients with a single meningioma. This remained true after taking into account other variables including demographic and clinical data, such as treatment with radiation and skull base location. Interestingly, when we input the number of meningiomas as a continuous variable in our multivariable model, we also found significantly worse PFS and TTSI, suggesting a decreasing PFS and TTSI for every additional meningioma present. This could potentially be useful when counseling patients on their middle- to long-term prognosis and the possibility of progression, as well as the need for further therapy in the future. It may also impact the follow-up times of these patients, and a closer follow-up may be required according to the number of lesions. Further studies are needed to understand if any of these changes might benefit clinical outcomes.

Even though the mechanisms associated with inferior

TABLE 2. Univariable and multivariable analyses of PFS in patients with meningiomas

Patient Characteristic (n = 838)	Univariable		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	0.986 (0.971–1.001)	0.073	0.982 (0.966–0.998)	**0.029**
Sex				
Male	Ref		Ref	
Female	0.862 (0.539–1.378)	0.535	0.658 (0.400–1.080)	0.098
Race				
Non-Hispanic White	Ref		Ref	
African American	2.756 (0.869–8.743)	0.085	3.472 (1.083–11.129)	**0.036**
No. of meningiomas	1.588 (1.268–1.987)*	**<0.001**	1.350 (1.074–1.698)*	**0.010**
1	Ref		Ref	
≥2	2.554 (1.619–4.029)	**<0.001**	2.262 (1.392–3.677)	**0.001**
Treatment w/ radiation				
None	Ref		Ref	
EBRT	0.468 (0.115–1.907)	0.290	0.210 (0.050–0.873)	**0.032**
SRS	1.277 (0.662–2.463)	0.466	0.467 (0.230–0.950)	**0.035**
Located in skull base				
No	Ref		Ref	
Yes	1.146 (0.764–1.720)	0.510	0.847 (0.550–1.306)	0.453
Extent of resection				
Subtotal	Ref		Ref	
GTR	0.258 (0.169–0.393)	**<0.001**	0.215 (0.136–0.339)	**<0.001**

Ref = reference.
Boldface type indicates statistical significance.
* As a continuous variable.

TABLE 3. Univariable and multivariable analyses of TTSI in patients with meningioma

Patient Characteristic (n = 838)	Univariable		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	0.979 (0.967–0.992)	**0.001**	0.977 (0.964–0.991)	**0.001**
Sex				
Male	Ref		Ref	
Female	0.880 (0.604–1.282)	0.505	0.744 (0.506–1.093)	0.132
Race				
Non-Hispanic White	Ref		Ref	
African American	0.866 (0.214–3.503)	0.840	0.957 (0.236–3.885)	0.951
No. of meningiomas	1.691 (1.408–2.030)*	**<0.001**	1.428 (1.189–1.716)*	**<0.001**
1	Ref		Ref	
>2	2.733 (1.883–3.967)	**<0.001**	2.377 (1.617–3.494)	**0.001**
Located in skull base				
No	Ref		Ref	
Yes	1.652 (1.175–2.325)	**0.004**	0.938 (0.657–1.339)	0.723
Extent of resection				
Subtotal	Ref		Ref	
GTR	0.109 (0.074–0.160)	**<0.001**	0.120 (0.080–0.179)	**<0.001**

Boldface type indicates statistical significance.
* As a continuous variable.

PFS and TTSI in MM are unknown, they might be related to tumor volume and the type of treatment received. They may also be related to the number of interventions needed to control the disease, as patients with MM may need to undergo more than one surgical procedure to control all disease. A previous report suggested that the larger the residual lesion is, the faster the lesion will grow if progression occurs.[17] Hence, the complexity of disease control may play a role in the difference in PFS and the risk of a second intervention of these patients. In our cohort, GTR was more common in the single-lesion group. However, this confounder was included in our multivariable analyses where a significant difference in progression was noted regardless of the tumor resection. Our analysis also included other confounders such as location in the skull base, as it is known that resections of tumors in this location tend to be more complex than lesions in the convexity.[18–20]

This difference could potentially be due to chance itself or the possibility that a certain risk factor that increases the chance of presenting with multiple lesions is also influencing the progression. There have been reports of patients with MM undergoing surgery for two different lesions showing heterogeneity in the histological subtype or the WHO grade, suggesting different behavior for every different lesion.[21–23] Conversely, some other reports have shown the same histology between two different lesions.[21,24] As the mechanisms for different progression rates for MM in a single patient are currently unknown, future studies are needed to understand the associated risk factors and whether these same risk factors contribute to progression risk.

Influence of Age, Race, and Adjuvant Treatment in Progression and Survival

Meningiomas, even though mostly considered benign lesions, carry the risk of long-term neurological morbidity and mortality.[25–28] In some cases, there is a need to reintervene through surgery or radiotherapy, which increases the risk of potential complications.[29–31] There is an established association between a remote prior history of radiation and the appearance of meningiomas.[6–8] In our cohort there was a larger number of patients from the MM group that had a prior history of radiation to either the head or another part of the body. It is also known that adjuvant treatment with radiation reduces the risk of recurrence,[32–34] consistent with the results of our cohort.

Increasing age has been associated with increased morbidity and mortality in the meningioma population.[35–37] Interestingly, we found that increasing age is associated with an improved PFS, with no differences found between the median ages in the single and MM groups. However, some retrospective studies have found no relationship between age and risk of progression; therefore, these results need to be evaluated and confirmed in a controlled experimental setting.[38,39]

Our group has previously shown, through an analysis of a national database, that within meningioma patients, African Americans have a significantly worse overall survival when compared to non-Hispanic White patients.[13,40] In this study, we found that African Americans have a higher risk of progression in benign meningiomas, although the mechanisms associated with this risk are currently unknown.[41] These disparities could be related to a variation in healthcare of at-risk populations, or to a difference in the genetic and molecular component in different subsets of populations.[40,42–45] Genetic factors have been associated with the development of meningiomas, mainly mutations in the 22q12.2 band of chromosome 22 that contains the *NF2* gene.[15] Studies suggest that the majority of multiple

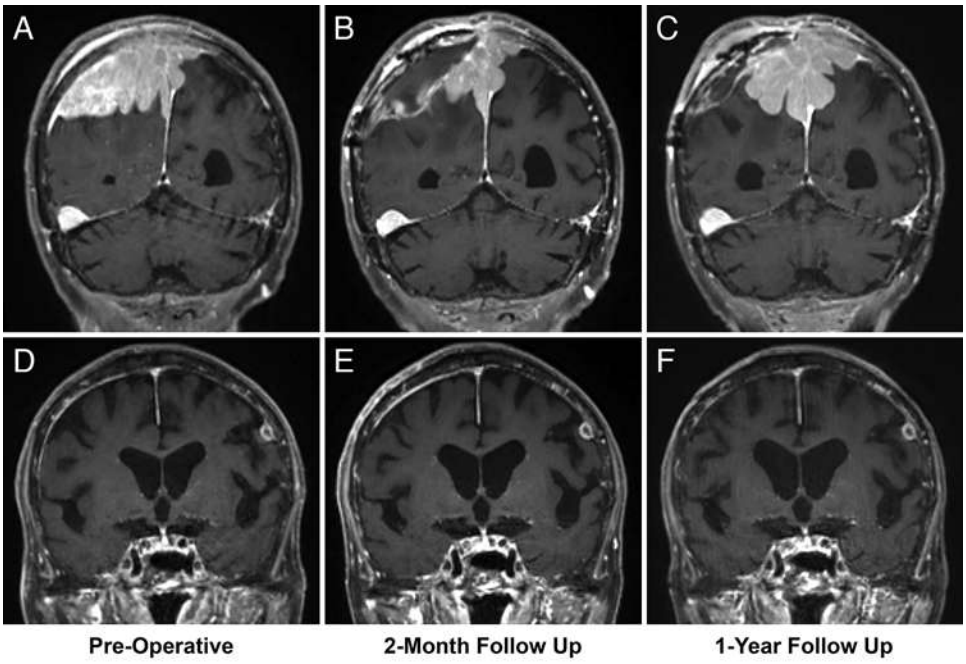

FIG. 4. Representative case of MM with radiographic progression after 1 year since diagnosis. Images from an 88-year-old woman with progressive left-sided hemiparesis and impaired ambulation. **A and D:** The initial MR images show a large, right parietal convexity meningioma, a right sigmoid sinus meningioma, and a small left parietal convexity meningioma. **B and E:** The patient underwent subtotal resection. Postoperative MR images show a residual right parietal tumor, and stable right supratentorial and left convexity meningiomas. Pathologic diagnosis was consistent with a WHO grade I meningioma with up to 3 mitoses/10 HPF. **C and F:** On 1-year follow-up, MR images show progression of the residual right parietal tumor, and stable right supratentorial and left convexity meningiomas.

meningiomas have an activation of the *NF2* gene, a phenomenon that is not seen in patients with single meningiomas.[14] Genetic analysis on MMs taken from the same patient has shown a clonal expansion with the same mutations found, suggesting that multiple lesions arise from the same population of cells.[14]

Limitations

This study has inherent limitations of a retrospective analysis and is prone to bias due to inconsistent or inaccurate medical records. Another limitation is that our institution is a tertiary referral center; thus, the population included in our study might not reflect the normal distribution found in the general population. Another limitation is the inclusion of meningiomas with histological confirmation only, as this may skew the incidence of MM because many patients with asymptomatic findings of small meningiomas are followed without surgical intervention. The fact that both scan frequency and the decision to reintervene (as well as the treatment modality) are influenced by clinical judgment and patient preference poses a limitation to this study, as the endpoints might be affected by this hidden bias. To account for advances in science and patient care, we only collected institutional data from the past 10 years. Although we provide an exploratory analysis on overall survival, the design of this study is not optimal for evaluating this parameter as meningiomas are known to affect patients in the long term. Alternatively, strengths of this study are the large number of patients included and the data collected from three different regions within the US. Due to the retrospective nature of this study, strong conclusions cannot be drawn to guide our clinical rationale. However, it establishes a baseline and adds scientific evidence that could guide the clinical rationale in future studies.

Conclusions

The PFS in patients with meningiomas appears to be influenced by the number of lesions present in a single patient. Patients with MM also seem to be more prone to undergoing a second intervention for progressive disease. Hence, a closer follow-up may be warranted in patients who present with multiple lesions. Our results show a decreased PFS and TTSI for every additional lesion present, as well as a decreased PFS and TTSI for patients with MM when compared to patients with a single meningioma. When assessing for associated risk factors, African Americans showed an inferior PFS. Age and adjuvant therapy with radiation were associated with an improved PFS. Future studies are warranted to elucidate the factors that contribute to these findings.

Acknowledgments

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Author Contributions

Conception and design: all authors. Acquisition of data: Ramos-Fresnedo, Domingo, Sanchez-Garavito, Perez-Vega, Akinduro. Analysis and interpretation of data: Sherman, Ramos-Fresnedo, Domingo, Jentoft, Vora, Brown, Porter, Bendok, Link, Middlebrooks, Trifiletti, Chaichana, Quiñones-Hinojosa. Drafting the article: all authors. Critically revising the article: Sherman, Ramos-Fresnedo, Domingo, Perez-Vega, Akinduro, Jentoft, Vora, Brown, Porter, Bendok, Link, Middlebrooks, Trifiletti, Chaichana, Quiñones-Hinojosa. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sherman. Statistical analysis: Ramos-Fresnedo. Administrative/technical/material support: Sherman, Ramos-Fresnedo, Jentoft, Quiñones-Hinojosa. Study supervision: Sherman, Quiñones-Hinojosa.

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