Incidence, Risk Factors, and Prognosis of Meningiomas With Distant Metastases at Presentation

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Abstract

Introduction

Distant metastases (DM) at presentation in meningiomas is a very rare event, and the incidence and factors predicting this are uncertain. This population-based study also aimed to investigate the prognostic implication of DM at presentation and clinical parameters to prognosticate the overall survival (OS) of meningiomas presenting with DM (M1).

Methods

We accessed the Surveillance, Epidemiology, and End Results program to search for patients who were diagnosed with meningioma between 2004-2016. The log-rank test was used to compare Kaplan-Meier survival curves and multivariate Cox regression model was utilized to evaluate the prognostic parameters of meningiomas with DM at presentation.

Results

The incidence of DM at presentation among all meningiomas was 0.18%. Clinical variables associated with this event were male gender, large tumor size, and WHO grade III. The presence of DM at diagnosis conferred a shorter survival in comparison to those without DM (HR = 2.015; 95% CI = 1.600-2.536). Older patient age, male gender, malignant histology, and the lesser extent of resection were independent prognostic factors that could negatively impact OS of M1 meningiomas. Radiotherapy and chemotherapy were not associated with an improved outcome for these patients.

Conclusion

Our study highlighted the clinical and prognostic factors of M1 meningiomas. These data suggest that a greater extent of resection is associated with increased OS across a nationwide analysis and emphasize the need to establish the standards of care in these patients.

Introduction

Meningioma is the most frequently reported primary brain tumor in the United States with an annual age-adjusted incidence rate of 8.58 per 100,000 persons ¹. Meningioma is typically seen in females at lower grade and its incidence increases with age. The 10-year overall survival (OS) of benign and malignant meningiomas is 83.7% and 61.7%, respectively ¹. The current World Health Organization (WHO) classification has divided this tumor entity into three different grades with distinct prognoses; most meningiomas are grade I and associated with a benign clinical course, although there are subgroups with more varied courses. Grades II and III are associated in most cases with aggressive behavior and higher rates of recurrence ², with grade III representing frank malignancy. Meningiomas with remote metastases are rare and have been described in the literature as case reports or small-sized case series ³⁻⁶. The most

frequent metastatic sites of meningioma are the lung, bones, spinal cord, and liver³. The majority of metastatic meningiomas are identified after the primary tumor has diagnosed and resected (93%) and only 6% of metastases are found simultaneously with the primary tumor at time of diagnosis³.

Because of its uncommon nature, the risk factors and prognostication of meningiomas with distant metastasis (DM) at presentation are still unclear among this common tumor. In this study, we aimed to explore the incidence, risk factors, clinical relevance, and prognosis of meningiomas with DM at presentation in the Surveillance, Epidemiology, and End Results (SEER) program.

Materials And Methods

The SEER 18 registries custom database was used to search for meningioma cases from 2004–2016 without age restriction. The year 2004 was selected as the cut-off year because the data of DM at diagnosis was added in SEER from this year onward. Patients who had autopsy or death certificate only were excluded. Cases with missing information for demographic (age, gender, and race), clinical (WHO grade, primary tumor site, and DM at presentation), treatment (extent of resection, radiotherapy, and chemotherapy), and follow-up data were also removed. Our selection criteria resulted in a final cohort of 71,906 meningiomas.

DM at presentation was categorized as M0 (without DM) and M1 (with DM). M0 meningiomas included the Collaborative Stage (CS) code of 00. M1 cases included the CS codes of 10, 20, 30, 40, 50, and 60. Cases with the code of 99 were regarded as missing data and subsequently deleted from the analyses. The associations of DM at presentation with baseline patient characteristics were compared using the Mann-Whitney test and student t-test for continuous variables, and Chi-square test and Fisher's exact test for categorical covariates. The Kaplan-Meier curve and log-rank test were computed to analyze all-cause mortality differences between patients with M0 and M1. A multivariate Cox proportional hazards regression was used to assess the impact of DM at presentation on all-cause mortality. To assess prognostic parameters for M1 meningioma, we computed a multivariate Cox regression model adjusted for relevant parameters. The median follow-up of patients was 50 months. All *p*-value are two-sided and a value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 20 (IBM, New York, NY).

Results

Baseline patient characteristics

We included a total of 71,906 meningiomas for analyses with a mean age of 64 years. 133 patients were identified to have DM at presentation and the incidence of M1 among all meningiomas was 0.18%. Table 1 shows the association of DM at presentation with clinicopathological parameters. We found significant associations of DM at presentation with gender, tumor size, WHO grades, extent of resection, administration of radiotherapy, and chemotherapy (*p*-value < 0.001). There were no correlations of M1

with age and race. M1 meningiomas were also associated with an increased mortality rate and a compromised overall survival (OS).

Table 1

The associations of clinicopathological parameters, treatments, and survival with distant metastasis at presentation in meningiomas

DM at presentation	All cases	Entire cohort (n = 71,906)		
		M0	M1	p-value
Patient no. (%)	71906	71773 (99.8)	133 (0.2)	
Age, median (IQR) (years)	65 (53–76)	65 (53–76)	62 (53–72)	0.078
Gender				< 0.001
Female, no. (%)	53169	53094 (74.0)	75 (56.4)	
Male, no. (%)	18737	18679 (26.0)	58 (43.6)	
Race				0.107
White, no. (%)	57540	57441 (80.0)	99 (74.4)	
Non-white, no. (%)	14366	14332 (20.0)	34 (25.6)	
Tumor size, median (IQR) (cm)	22 (14–36)	22 (14–36)	45 (34.5–60)	< 0.001
WHO grade				< 0.001
Grade I, no. (%)	67531	67492 (94.0)	39 (29.3)	
Grade II, no. (%)	2729	2720 (3.8)	9 (6.8)	
Grade III, no. (%)	1646	1561 (2.2)	85 (63.9)	
Extent of resection				
Biopsy, no. (%)	43638	43598 (60.7)	40 (30.1)	< 0.001
STR, no. (%)	13815	13766 (19.2)	49 (36.8)	
GTR, no. (%)	14453	14409 (20.1)	44 (33.1)	
Radiotherapy, no. patients (%)	6510	6467 (9.0)	43 (32.3)	< 0.001
Chemotherapy, no. patients (%)	187	178 (0.2)	9 (6.8)	< 0.001
Patient mortality, no. patients (%)	17703	17626 (24.6)	77 (57.9)	< 0.001
Survival, median (IQR) (months)	50	50 (25–84)	35 (8–69)	< 0.001
Abbreviations:				
GTR, gross total resection; IQR, interquartile range; SD, standard deviation; STR, subtotal resection; WHO, World Health Organization				

Subgroup analyses stratified by WHO grades

TableS1 shows the associations of DM at presentation status with clinical and treatment covariates in different WHO grades. Gender and tumor size were no longer significant risk factors for the occurrence of DM in each grade. In WHO grade I meningiomas, the presence of DM at time of diagnosis was associated with more aggressive treatments (wide extent of resection, use of radiotherapy, and chemotherapy) whereas treatments in WHO grade II and III meningiomas were mostly similar between patients with and without DM at presentation. In WHO grade I and II, the mortality rate and patient survival were not statistically different between meningiomas with and without DM. On the other hand, the presence of DM at presentation conferred poorer outcomes in malignant meningiomas (WHO grade III).

Impact of DM at presentation on patient OS

Kaplan-Meier curve and the log-rank test demonstrated that the presence of DM at time of diagnosis is associated with a dismal outcome (p -value < 0.001) (Fig. 1). The negative impact of DM at presentation on patient OS was further confirmed by a multivariate Cox regression model adjusted for age, gender, race, WHO grades, extent of resection, radiotherapy, and chemotherapy (HR = 2.015; 95% CI = 1.600-2.536; p -value < 0.001).

Prognostic factors of meningiomas presenting with DM at time of diagnosis

Among 133 M1 meningiomas, older age, male gender, non-white race, large tumor size, malignant histology, and the administration of chemotherapy were significantly associated with an increased mortality rate (Table 2).

Table 2

The associations of clinicopathological parameters and treatment modalities with all-cause mortality of M1 meningiomas

Meningioma with M1	Patient mortality		
	Dead (n = 77)	Alive (n = 56)	p-value
Age, median (IQR) (years)	66 (57–72)	55.5 (48.8–70)	0.002
Gender			0.003
Female, no. (%)	35 (45.5)	40 (71.4)	
Male, no. (%)	42 (54.5)	16 (28.6)	
Race			0.032
White, no. (%)	52 (67.5)	47 (83.9)	
Non-white, no. (%)	25 (32.5)	9 (16.1)	
Tumor size, median (IQR) (cm)	49.5 (40–60)	35 (15.5–47.5)	< 0.001
WHO grade			< 0.001
Grade I, no. (%)	14 (18.2)	25 (44.6)	
Grade II, no. (%)	1 (1.3)	8 (14.3)	
Grade III, no. (%)	62 (80.5)	23 (41.1)	
Extent of resection			0.370
Biopsy, no. (%)	26 (33.8)	14 (25.0)	
STR, no. (%)	29 (37.7)	20 (35.7)	
GTR, no. (%)	22 (28.6)	22 (39.3)	
Radiotherapy, no. (%)	26 (33.8)	17 (30.4)	0.678
Chemotherapy, no. (%)	9 (11.7)	0 (0.0)	0.01
Abbreviations: GTR, gross total resection; IQR, interquartile range; SD, standard deviation; STR, subtotal resection; WHO, World Health Organization			

In a multivariate Cox regression model adjusted for age, gender, race, WHO grade, extent of resection, receipt of radiation, and chemotherapy, we demonstrated several significant prognostic factors that can impact patient OS of M1 meningioma (Table 3). Older age at diagnosis, male gender, and malignant histology conferred a negative impact on patient survival. In addition, meningioma patients treated with STR or GTR were also associated with a superior OS in comparison to patients treated with biopsy only. The administration of radiation or chemotherapy added no survival benefits to metastatic meningiomas.

Table 3
Multivariate Cox proportional hazards model for all-cause mortality in M1 meningiomas

Variable		Hazard Ratio (95% CI)	p-value
Age (per year increase)		1.030 (1.011–1.050)	0.002
Gender	Male	Reference	
	Female	0.355 (0.209–0.602)	< 0.001
Race	Non-white	Reference	
	White	0.644 (0.383–1.060)	0.096
WHO grade	Grade I-II	Reference	
	Grade III	3.209 (1.789–5.758)	< 0.001
Extent of resection	Biopsy	Reference	
	STR	0.504 (0.271–0.938)	0.031
	GTR	0.370 (0.203–0.676)	0.005
Radiation	No	Reference	
	Yes	1.349 (0.775–2.346)	0.290
Chemotherapy	No	Reference	
	Yes	2.029 (0.930–4.426)	0.076

Abbreviations: CI, confidence interval; GTR, gross total resection; STR, subtotal resection; WHO, World Health Organization

Discussion

Distant metastasis is an extremely uncommon event in patients with meningioma with an estimated incidence of less than 1% of meningiomas^{3,7,8}. In an institutional study with 396 meningiomas, the incidences of DM among all cases and malignant meningiomas were 0.76% and 43%, respectively. As opposed to previous hypotheses that only malignant meningiomas develop DM⁷, our findings unexpectedly revealed that about one-third of metastatic meningiomas were grade I. Earlier studies reported metastatic meningiomas only in clinically symptomatic patients^{7,8}. With the preponderance and ease of surveillance imaging studies and the increased use of whole-body imaging, more metastatic meningiomas identified incidentally have been reported^{3,9–11}.

Several clinical parameters have been linked to the development of systemic spread in meningiomas such as venous sinus invasion, nuclear pleomorphism, tumor necrosis, high mitotic rate, papillary and malignant histology, and tumor relapse^{8,12,13}. However, these criteria are mainly seen in malignant meningiomas and may not explain the metastatic occurrence in benign cases. Of note, the majority of

metastases develop during the follow-up period ³, and limited data are known regarding the clinical importance of DM at presentation in meningioma. We demonstrated several risk factors of this rare event including male gender, large primary tumor size, and high-grade tumor. Additionally, patients with DM at presentation had a significantly higher rate of a greater extent of resection, radiotherapy, and chemotherapy administration.

Stratified by WHO grades, however, we failed to identify significant risk factors for DM at presentation, probably due to the small sample size in each grade. Treatment modalities were only statistically different for benign meningiomas (WHO grade I) with and without DM. In high-grade tumors, the treatment approaches were comparable between M0 and M1 groups with the only exception of radiotherapy administration in WHO grade II cases. Our findings signify that high tumor grade were associated with aggressive treatment plans regardless of DM status.

Medulloblastoma and atypical teratoid/rhabdoid tumor (ATRT) were among the newly diagnosed primary brain tumors with the highest risk for DM ¹⁴. In contrast, glioma and meningioma are associated with the lowest risk ¹⁴. The most common metastatic site of meningiomas is the lung ³, indicating that the hematogenous spread via the jugular veins may be the most frequent pathway for tumor dissemination. Metastasis to the liver may occur if the tumor cells enter the inferior vena cava system via the right atrium ¹⁵. Less commonly, meningioma cells may also spread through the paravertebral venous plexus to the vertebrae, kidney, and adrenal glands or through the lymphatic vessels and cerebrospinal fluid ^{16–18}.

Because meningiomas presenting with DM are very rare, there are no guidelines or consensus on staging and management of these cases. It is of clinical interest to determine the prognostic factors to predict the survival of these patients and to identify molecular features which may be associated with metastatic potential. Our results highlighted some independent parameters that can negatively influence patient survival of M1 meningioma including increased age, male gender, WHO grade III, and biopsy only of primary tumor. The use of radiation and chemotherapy in M1 cases did not benefit patients with metastases and tended to have a higher risk of mortality; however, the results were not statistically significant, underscoring the importance of aggressive surgical resection of the primary tumor. Our findings can help clinicians better evaluate patient prognosis and consider appropriate treatment plans for patients presenting with remote metastasis at diagnosis.

Our study has several limitations that need to be outlined. First, we could not include primary tumor locations in our analysis since most of M1 cases were found in meninges, not otherwise specified (70%). Second, other important covariates including multifocality, metastatic sites, patient performance status, and comorbidities that can affect the survival analysis were not available. The study also is subject to the inherent limitations of large population-based datasets. And finally, the rarity of this event resulted in difficulty identifying meaningful risk factors in each tumor grade. Future SEER cohort analyses should aim to reinvestigate these risk factors in different WHO grades.

Specific biological attributes of meningioma are likely to govern metastatic potential. Indeed, efforts have been made to characterize the genomic profiles of metastatic meningiomas to better understand the biologic nature of this event. There were no differences in incidence of *NF2*, *CDKN2A*, *BAP1*, *ARID1A*, and *TP53* mutations between meningiomas with and without dissemination¹⁹. *TERT* promoter mutations were associated with a significantly higher risk for DM in thyroid cancer or melanoma^{20,21}, but this association was not found in meningioma¹⁹.

In conclusion, DM at presentation was an exceedingly rare event of meningiomas, but surprisingly can be seen in all grades. Meningiomas presenting with DM were associated with compromised outcome as compared to those without this event. In this population-based study, we identified several risk factors that help predict the occurrence of DM at presentation. Our study also highlighted important parameters which are of prognostic significance among M1 meningiomas. The extent of resection remains an important concept in improving patient survival while radiotherapy and chemotherapy added no discernable survival advantage to patients.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interest

The authors declare no conflicts of interest.

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Authors' contributions

HGV: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation, writing-review, and editing.

TNMN: data curation, formal analysis, investigation, software, writing-review, and editing.

IFD: project administration, validation, writing-review, editing, and supervision.

All authors have read and approved the manuscript.

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Figures

Figure 1

Kaplan-Meier curve illustrating the overall survival of M0 and M1 meningiomas

Supplementary Files

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