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REVIEW

A systematic review of extraneural meningioma metastasis: timing, evolution and outlook

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Abstract

Purpose Extraneural meningioma metastasis is a rare occurrence and may pose a clinical challenge due to its unclear prognosis. In this systematic review, we analyze patient demographics, clinical characteristics, management strategies, and outcomes.

Methods PubMed, EMBASE, Scopus, Cochrane, and Web of Science databases were searched from inception to February 23, 2024 for cases of metastatic meningioma according to PRISMA guidelines. Descriptive statistics, Mann–Whitney U test, Fisher's exact tests, Kaplan–Meier curves, and log-rank tests were used for selected analyses.

Results A total of 288 patients (52% male) were included with an average age of 49 years at meningioma diagnosis. Tumors were distributed across WHO grade 1 (38%), 2 (36%), and 3 (26%). Most patients experienced intracranial recurrence (79%) and mean time to first metastasis was approximately 8 years. No change in WHO grade between primary and metastasis was observed for most cases (65%). Treatment of the initial metastasis was most often with surgery (43%), chemotherapy (20%), or no treatment (14%). Half of the patients were alive (50%) with an average follow-up of 3 years following metastasis. Overall median survival was 36 months for the entire cohort. This differed significantly between WHO grade 1 versus 2/3 meningioma primaries (168 vs. 15 months, $p < 0.005$).

Conclusion Metastatic meningioma appears to be associated with more positive prognosis than other brain tumor types with extra-neural metastasis or metastasis in general. This is particularly true for cases arising from a WHO grade 1 meningioma.

Keywords Extraneural metastasis · Meningioma · Oncology · Survival

Introduction

Although the vast majority of meningiomas are histologically benign and slow-growing, extraneural metastasis can occur in less than 1% of cases [1–3]. Due to the extreme rarity of this event, routine screening is often not performed, and diagnosis can be challenging. Presentation, time to metastasis, and outcomes can be highly variable, though in general an extracranial metastasis portends worse prognosis than a typical World Health Organization (WHO) grade 1 neoplasm [4]. Current evidence suggests that meningioma metastasis may be more common among men despite a higher incidence of meningiomas occurring in females, with the lungs being the most common site of metastasis, followed by lymph nodes, abdominal viscera, and bone which parallels that of metastatic locations from other intracranial tumors such as glioma and ependymomas [5, 6]. Although these older series provide valuable information on extraneural meningioma metastasis, an updated systematic review

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with more detailed analysis of clinical course is lacking. In this systematic review, we comprehensively summarize and analyze patient demographics, clinical characteristics, management strategies, and outcomes of patients with extraneural meningioma metastasis.

Methods

Literature search

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. PubMed, EMBASE, Scopus, Cochrane, and Web of Science databases were searched from inception to February 23, 2024 using the following search query: (metastasis OR metastases OR metastatic OR metasta*) AND (meningioma). The search was performed on February 23, 2024. This review was not registered and a protocol was not prepared.

Study selection

A priori inclusion criteria included articles reporting a central nervous system meningioma with metastasis located outside of the central nervous system, patient demographics, clinical course, and outcomes. Non-English studies, book chapters, autopsy studies, invasive but non-metastasizing tumors, cases of iatrogenic seeding, intradural or “drop” metastases, unclear histologic type, tumor-to-tumor metastasis, and all other primary tumors besides meningioma were excluded. Two authors independently reviewed titles and abstracts and assessed the full text of articles to determine if they met inclusion criteria. Disagreements were resolved with discussion.

Data extraction

Data was extracted by two authors and confirmed independently by two separate authors. Missing data was either not reported by the study or could not be differentiated from an aggregate result or other non-relevant data. The following data was extracted: authors, year, age, gender, symptoms, location, treatment, histologic grade, histologic type, intracranial recurrence, number of recurrences, months between primary and extracranial metastasis, metastasis location, evolution of meningioma histologic grade, and survival or follow-up time from diagnosis of primary and metastasis. When a grade was not explicitly specified, the descriptive report (if available) was assessed and compared to the grading criteria of the WHO 2021 classification for grade assignment by the reviewer. If the terms "benign" or "atypical"/"chordoid"/"clear cell" or "malignant"/"anaplastic" were used without an explicit grade described in-text, the tumor was assigned a grade of 1, 2, and 3, respectively.

Data synthesis, quality assessment, statistical analysis

Outcomes included patient demographics, clinical characteristics of the primary tumor and metastasis, management strategies, and survival. The level of evidence of each article was assessed using the 2011 Oxford Centre For Evidence-Based Medicine guidelines [8]. A meta-analysis was not conducted as all included studies were of level IV or V of evidence. Risk of bias was independently assessed by two authors using the Joanna Briggs Institute Checklist for case reports and case series [9]. Number of patients with available data was described in the tables. Descriptive statistics and subgroup analyses were performed comparing outcomes by grade of primary (1 vs 2 or 3), treatment of metastasis, and location of metastasis. The non-parametric Mann–Whitney U test was performed for interval (numerical) data, while the Fisher's exact test was performed for categorical data. Kaplan–Meier curves were generated to visualize survival probability by primary meningioma grade and location, and a log-rank test was used for univariate analysis. P-values less than 0.05 were deemed significant.

Results

Study selection

The study selection is described in Fig. 1.

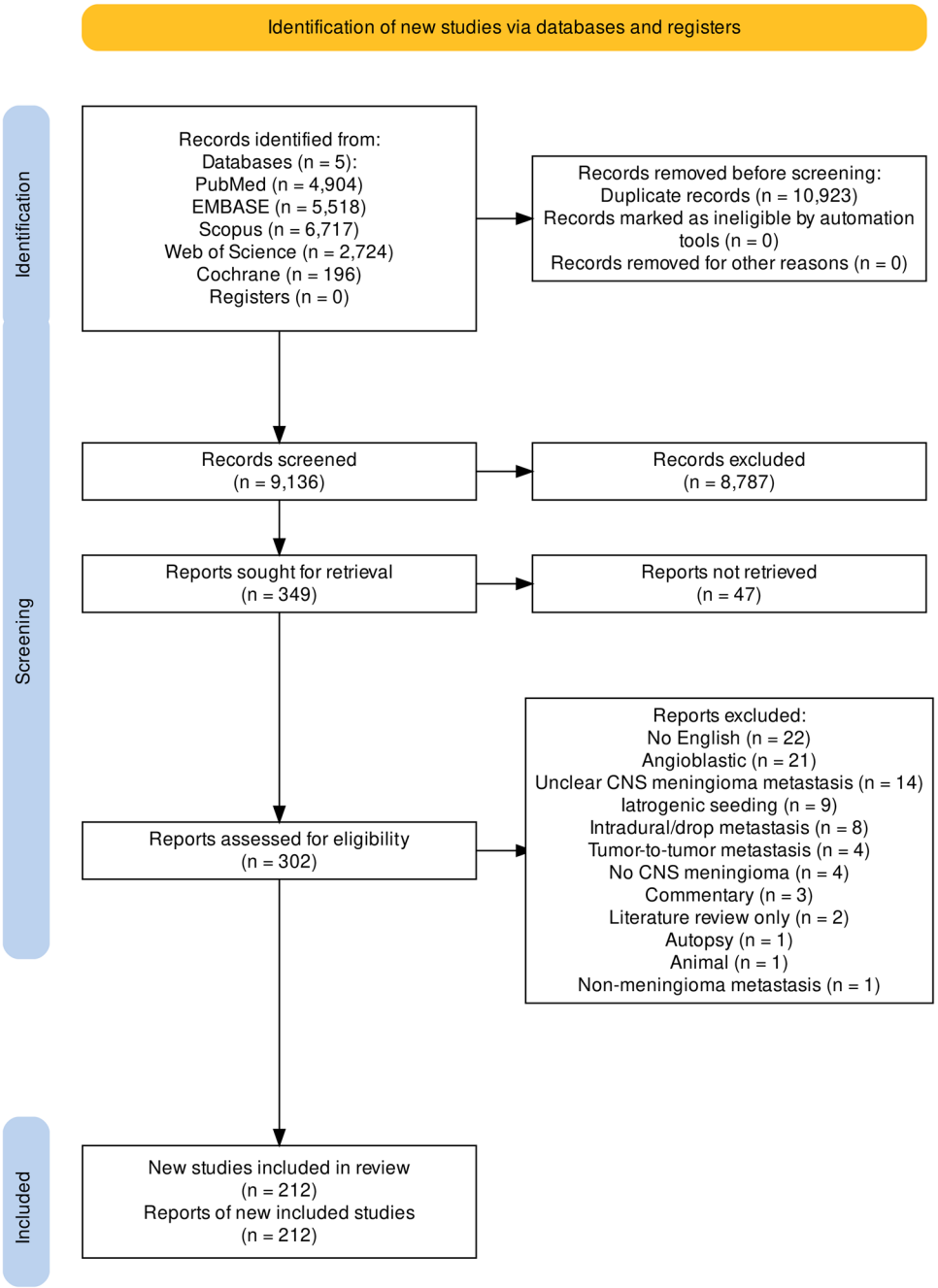
The initial search consisted of 20,059 reports (PubMed: 4904, EMBASE: 5518, Scopus: 6717, Web of Science: 2724, Cochrane: 196). Following full-text review, 212 reports were included based on the pre-specified inclusion criteria. There were 11 case series and 201 case reports, categorized as level IV and V of evidence, respectively (Supplementary Table 1), for a total of 288 patients. Risk of bias was low in most studies (Supplementary Table 2 and 3). Data in spreadsheet format is available upon request.

Clinical characteristics

There was a total of 288 patients harboring extraneural meningioma metastasis (Table 1).

The mean age at initial diagnosis of the primary meningioma was 49 years old, while that of presentation (typically around the time of metastasis diagnosis) was 53 years old. Gender distribution was nearly equal, with 52% being male. Asymptomatic, incidentally found, meningiomas were diagnosed in 7% of cases (Table 2).

Fig. 1 PRISMA Flowchart



Most meningiomas were located on a convexity (52%), parasagittal (17%), or associated with the falx (5%). Meningioma grades were distributed mostly between Grades 1 (38%) and 2 (36%), with a minority reportedly Grade 3 (26%). Common histologic types of the initial tumor included meningothelial (16%) for Grade 1, atypical for Grade 2 (38%), and anaplastic for Grade 3 (18%).

Intracranial meningioma recurrence occurred in 79% of cases, with a mean number of 1.7 recurrences per patient (Table 3).

The average time to metastasis was 7.9 years but varied widely from 2 months to 38 years. The most common locations for the first metastasis were the lungs (43%), bone (24%), and liver (13%). If another metastasis was found, this was discovered an average of 18 months after the first. When comparing the histological grade of the primary meningioma and the metastasis, most cases exhibited no change in grade (65%). A higher histologic grade was observed in 33% of cases and this was more frequently found with a grade 2 evolving to a grade 3.

Table 1 Summary of patient demographics. The number of patients for which values are reported are denoted in parenthesis (n = # patients)

Characteristics	Value
Cohort Size	288
Age	
Age (n = 285) Mean ± SD, range (years)	53 ± 16, 3 – 91
Age at Diagnosis of Primary (n = 234) Mean ± SD, range (years)	49 ± 16, 3 – 91
Gender (n = 285)	
Male (%)	149 (52%)

SD Standard Deviation.

Among cases without change in grade, a meningothelial primary and meningothelial metastasis was most commonly observed (16%) for Grade 1, atypical for Grade 2 (30%), and anaplastic for Grade 3 (25%).

Management & outcomes

Surgery alone was the most common treatment for the primary meningioma (72%), followed by surgery and radiation therapy (22%) (Table 4).

Surgery, radiation, and chemotherapy combined were utilized in 4% of cases. Gross total resection was performed in most cases (73%). For treatment of the initial metastasis, surgery (43%) or chemotherapy (20%) alone were most common, followed by no treatment (14%). Half of the patients were alive at the time of publication (50%) for approximately an average of 11 years after the initial primary diagnosis, and 3 years after the diagnosis of metastasis. Among individuals that succumbed to disease, survival from the primary meningioma averaged 8.8 years, though ranged widely between 4 months and 32 years. Meanwhile, survival time from diagnosis of the first metastasis was a mean of 1.4 years, ranging from 2 weeks to 14 years.

The median survival after diagnosis of metastasis for the entire cohort was 36 months by Kaplan–Meier analysis (95% CI 19—56). When comparing outcomes between benign (grade 1) and more malignant meningioma primaries (grade 2 or 3), high-grade primaries were associated with significantly shorter median times to first metastasis (46 vs. 96 months, $p < 0.001$) and a lower proportion of patients alive at last follow-up (42% vs. 63%, $p = 0.01$). Median survival times were significantly different between grade 1 and grade 2/3 meningioma primaries (15 vs. 168 months, $p < 0.005$) (Supplementary Fig. 1). Most patients with grade 1 (84%) and grade 2 or 3 (90%) meningioma primaries received treatment for their metastatic disease. When comparing survival between groups receiving treatment for metastasis versus no treatment, there were no significant differences between the proportion of patients alive (51% vs. 53%, $p = 0.98$). By location of metastasis, most patients were alive (59%) when the metastasis was present in only a single site.

Table 2 Summary of clinical and primary tumor characteristics. The number of patients for which values are reported are denoted in parenthesis (n = # of patients)

Characteristics	Value
Symptoms (n = 136)	
Asymptomatic (%)	10 (7%)
Location of Primary (n = 242)	
Convexity (%)	127 (52%)
Parasagittal (%)	41 (17%)
Falx (%)	13 (5%)
Middle fossa (%)	10 (4%)
Sphenoid (%)	9 (4%)
Posterior fossa (%)	7 (3%)
Ventricular (%)	7 (3%)
Anterior fossa (%)	6 (3%)
SSS (%)	6 (3%)
Multiple (%)	3 (1%)
Tentorial (%)	3 (1%)
Other[1] (%)	10 (4%)
Histologic WHO Grade (n = 233)	
Grade 1 (%)	88 (38%)
Grade 2 (%)	84 (36%)
Grade 3 (%)	61 (26%)
Histologic Type (n = 159)	
WHO Grade 1	
Meningothelial (%)	26 (16%)
Fibrous/Fibroblastic	11 (7%)
Transitional	11 (7%)
Psammomatous	2 (1%)
Microcystic	1 (1%)
Other[2]	5 (3%)
WHO Grade 2	
Atypical (%)	61 (38%)
Clear Cell	2 (1%)
Chordoid	1 (1%)
WHO Grade 3	
Anaplastic (%)	29 (18%)
Papillary	5 (3%)
Rhabdoid	4 (3%)
Other[3]	1 (1%)

SD Standard Deviation, *SSS* Superior Sagittal Sinus, *WHO* World Health Organization.

[1]Includes 2 skull base not otherwise specified, 2 extracalvarial, 2 spinal, 2 nasal cavity, 1 olfactory groove, 1 petrous dural sinus.

[2]Includes 3 atypical meningothelial, 1 atypical fibroblastic, 1 meningothelial and fibroblastic.

[3]Includes 1 anaplastic papillary.

Table 3 Summary of metastasis characteristics. The number of patients for which values are reported are denoted in parenthesis (n = # of patients, t = # of tumors)

Characteristics	Value
Intracranial Recurrence (n = 265)	
Yes (%)	210 (79%)
Number of Intracranial Recurrences (n = 223)	
Mean ± SD, range (No.)	1.7 ± 1.5, 0 – 8
Time to Metastases	
Primary – M1 Mean ± SD, range (months), (n = 224)	95 ± 88, 0 – 450
M1—M2 Mean ± SD, range (months), (n = 18)	18 ± 27, 2 – 120
M2—M3 Mean ± SD, range (months), (n = 5)	41 ± 52, 5 – 132
M3—M4 Mean ± SD, range (months), (n = 2)	7.0 ± 7.1, 2 – 12
M4—M5 (months), (n = 1)	12
Location of Metastasis	
M1 (n = 282, t = 378)	
Lungs	164 (43%)
Bone[1]	90 (24%)
Liver	48 (13%)
Skin and Soft Tissue	18 (5%)
Cervical Lymph Nodes	16 (4%)
Thorax[2]	9 (2%)
Parotid Gland	8 (2%)
Kidney	8 (2%)
Abdomen	4 (1%)
Adrenal Glands	2 (0.5%)
Gastrointestinal	2 (0.5%)
Orbit	2 (0.5%)
Other[3]	7 (2%)
M2 (n = 37, t = 48)	
Bone	14 (29%)
Lungs	10 (21%)
Skin and Soft Tissue	8 (17%)
Liver	6 (13%)
Thyroid	2 (4%)
Adrenal Glands	2 (4%)
Other[4]	6 (13%)
M3 (n = 7, t = 8)	
Lungs	4 (50%)
Bone	3 (38%)
Skin & Soft Tissue	1 (12%)
M4 (n = 3, t = 3)	
Skin and Soft Tissue	1 (33%)
Bone	1 (33%)
Kidney	1 (33%)
M5 (n = 1, t = 1)	
Bone	1 (100%)
Histologic Evolution (n = 161)	
No (%)	104 (65%)
Evolution of Histological Grade from Primary to Metastasis (n = 132)	
No change in grade (%)	86 (65%)
1 to 1	38 (44%)
2 to 2	21 (24%)
3 to 3	27 (31%)
Metastasis had a higher histologic grade (%)	44 (33%)

Table 3 (continued)

Characteristics	Value
1 to 2	15 (34%)
1 to 3	9 (20%)
2 to 3	20 (45%)
Metastasis had a lower histologic grade (%)	2 (2%)
2 to 1	1 (50%)
3 to 2	1 (50%)
Evolution of Histological Type from Primary to Metastasis (n = 89)	
No change in grade (%)	64 (72%)
1 to 1	
Meningothelial to meningothelial	10 (16%)
Transitional to transitional	3 (5%)
Fibrous to fibrous	3 (5%)
Psammomatous to psammomatous	2 (3%)
Transitional to meningothelial	2 (3%)
Meningothelial to transitional	1 (2%)
Microcystic to meningothelial	1 (2%)
2 to 2	
Atypical to atypical	19 (30%)
Clear cell to clear cell	2 (3%)
3 to 3	
Anaplastic to anaplastic	16 (25%)
Rhabdoid to rhabdoid	2 (3%)
Papillary to papillary	1 (2%)
Anaplastic to papillary or vice versa	2 (3%)
Metastasis had a higher histologic grade (%)	24 (27%)
1 to 2	
Meningothelial to atypical	4 (17%)
Transitional to atypical	1 (4%)
Meningothelial to clear cell	1 (4%)
1 to 3	
Fibrous to anaplastic	2 (8%)
Meningothelial to anaplastic	1 (4%)
2 to 3	
Atypical to anaplastic	14 (58%)
Atypical to rhabdoid	1 (4%)
Metastasis had a lower histologic grade (%)	1 (1%)
3 to 2	
Anaplastic to atypical	1

M1-X 1st metastasis, 2nd metastasis…etc., *SD* Standard Deviation.

[1]59 (66%) cases of bony metastases included the spine (vertebrae).

[2]Includes 4 mediastinal lymph nodes, 3 thorax, and 2 mediastinum locations.

[3]Includes 1 each of retroperitoneum, stomach, heart, thyroid, uterus, pancreas, and multiple lymph nodes.

[4]Includes 1 each of the orbit, occipital lymph nodes, thorax, gastrointestinal system, cervical lymph nodes, and spleen.

Discussion

Metastatic meningioma cells can potentially migrate to other sites via neighboring blood vessels, venous sinuses, cerebrospinal fluid, and the more recently discovered meningeal lymphatic system. Hematogenous dissemination is perhaps more likely to occur near fenestrated blood vessels that lack tight junctions, such as those present in the dura and choroid plexus [10]. Although the location distribution of the meningioma primary among our metastatic cases resembled that of

Table 4 Summary of management and outcomes. The number of patients for which values are reported are denoted in parenthesis (n = # of patients)

Characteristics	Value
Treatment of Primary (n = 254)	
Surgery (%)	183 (72%)
Surgery + Radiotherapy (%)	56 (22%)
Surgery + Radiotherapy + Chemotherapy (%)	10 (4%)
Radiotherapy (%)	3 (1%)
Surgery + Chemotherapy (%)	1 (0.4%)
None	1 (0.4%)
Extent of Surgical Resection of Primary (n = 121)	
GTR (%)	88 (73%)
STR (%)	23 (19%)
PR (%)	10 (8%)
Treatment of Initial Metastasis (n = 206)	
Surgery (%)	88 (43%)
Chemotherapy (%)	42 (20%)
None/Palliative (%)	28 (14%)
Surgery + Radiotherapy (%)	17 (8%)
Radiotherapy + Chemotherapy (%)	10 (5%)
Radiotherapy (%)	9 (4%)
Surgery + Radiotherapy + Chemotherapy (%)	8 (4%)
Status (n = 210)	
Alive (%)	106 (50%)
Follow-Up	
Mean After Primary ± SD, range (months) (n = 91)	131 ± 99, 2 – 468
Mean After Metastasis ± SD, range (months) (n = 77)	37 ± 50, 1 – 294
Survival from Primary	
Mean After Primary ± SD, range (months) (n = 81)	106 ± 96, 4 – 384
Mean After Metastasis ± SD, range (months) (n = 73)	17 ± 26, 0.5—168

GTR Gross Total Resection, *PR* Partial Resection, *SD* Standard Deviation, *STR* Subtotal Resection.

general meningioma series with convexity, parasagittal, falx, and middle fossa locations being among the most common [11], we observed a high proportion of ventricular meningiomas (3%) in comparison to larger series reports of less than 1% [11, 12], possibly due to their proximity to such vessels. Additionally, our relatively high proportion of cervical lymph node and parotid gland sites for metastasis suggests that lymphatic vessels are implicated in meningioma spread.

The path of meningeal lymphatic vessels can be traced in parallel to the dural sinuses, increasing in network at the base of the skull [13, 14], then directly draining into cervical lymph nodes [15]. Among 24 cases of lymph node involvement reported in the metastatic event of an intracranial meningioma primary, 16 (67%) were found in the cervical region. Additionally, the parotid gland, while a more common site for metastasis arising from skin cancers of the head and neck [16] but rare for metastases in general [17], was the 7th most common location for metastasis identified in our series. Although the lymphatic vessel network appears to be more concentrated at the skull base in comparison to more superior areas [13], most metastatic meningioma cases in our review appeared to have a non-skull base primary. This is in alignment with the fact that higher grade meningiomas are more often found at the convexity or other non-skull base sites [18]. Besides neoplastic migration via the lymphatic vessels, metastatic meningioma cells travel through venous channels and deposit in commonly known sites of metastasis for all types of cancers, such as the lung, liver, and bone [17, 19].

Meningioma characteristics

Meningiomas are remarkably diverse, with 15 subtypes described in the 2021 World Health Organization (WHO) classification [20]. Most are benign WHO grade 1 neoplasms (80%), with the minority assigned the more aggressive grade 2 (18%) or grade 3 (2%) [21]. The higher the grade, the worse the overall survival and recurrence rate [22]. While intuitively we might expect that cases of metastatic meningioma would predominantly consist of high-grade meningioma primaries, our dataset was comprised of mostly grade 1 (38%), followed by grade 2 (36%), and grade

3 (26%) tumors. The relatively high frequency of low-grade meningioma primaries in our dataset is likely influenced by the substantial number of patients affected by benign grade 1 neoplasms, compared to the much fewer occurrences of grade 2 and 3 types.

However, implication of a benign appearing primary in a later metastatic event could also be due to intratumoral heterogeneity. Aggressive or highly vascularized cellular subpopulations [23–25] may be missed during tissue biopsy and perhaps underestimate tumor grade. Additionally, faster local cellular replication may favor asymmetric growth and increase the likelihood of microscopic remnants after a seemingly complete surgical resection. In our dataset, most primary tumors exhibited an intracranial recurrence (79%). This may attest to the aggressiveness of at least some portion of the meningioma primary, but several other reasons may contribute to the possible link between recurrence and metastasis. Vascular endothelial growth factor expression has been associated with meningioma recurrence [26] and thus neovascularization, and consequently an increased number of possible connections to the systemic vasculature, may increase the likelihood of metastasis. Another contributing factor could be the nature of extended follow-up, increasing the chance of observing a clinically relevant metastatic event with a recurrence rate of as high as 40% at 10 years for resected benign meningiomas [27–32]. Finally, surgical treatment for a recurrence and thus violation of innate physical defenses at the site of the tumor along with potential iatrogenic seeding may also pose risks for metastatic development.

If an aggressive cellular subpopulation becomes the predominant cell type in the metastatic meningioma, one might anticipate an evolution in histologic grade. However, most of our cases reported no change in WHO grade (65%) and raises questions as to whether genetic alterations that involve transport mechanisms more so than replication rates contribute to metastatic spread. In contrast, however, the atypical histological type was the most common in our dataset (38%) and is associated with higher recurrence rates than other subtypes [33]. It is perhaps a combination of both that may foster metastatic transformation. Although many aspects of meningioma metastasis remain unclear, it is apparent that existing classification schemes, though generally effective in capturing essential information for prognosis, still fall short of conveying the complete biological behavior of meningiomas.

Disease course

The median overall survival after metastasis of approximately 36 months for meningioma appears to be more favorable than the 3 to 11 months reported for other primary brain tumors with extraneural metastasis [34–36]. Perhaps the most striking finding was the difference in survival time following metastasis when comparing grade 1 versus grade 2 or 3 primary meningiomas, with low-grade meningiomas exhibiting a median survival duration of nearly 11 times longer than their higher-grade counterparts. However, this is likely skewed by several outliers with more than 20 years of survival. Despite relatively long survival times, the clinical course is not completely benign. In the subgroup of patients with at least 10 years of survival after the diagnosis of metastasis [2, 3, 37–41], most underwent treatment for multiple intracranial recurrences and extraneural metastases. While no survival benefit was noted between treatment and non-treatment groups, this analysis was limited by small patient sizes particularly in the no treatment group, and future studies will be needed to discern the risk and benefit ratio of treatment. The relatively positive prognosis for patients with metastatic meningioma arising from a grade 1 primary has important implications in patient counseling.

Our systematic review bears resemblance to other reviews performed on the topic of extraneural meningioma metastasis, but also adds new findings. In 1963, Glasauer and Yuan noted a similar male predominance (65%), and primary meningioma and metastases location distribution [6]. The adults survived an average of 7 years and 9 months from onset of symptoms or diagnosis, which is slightly lower than the average of 9 years obtained in our study. Our extended survival time is possibly due to advances in treatment for both primary and metastatic disease. In 2013, Surov and colleagues presented 115 metastatic meningioma cases and remarked on a similarly high proportion of grade 1 WHO meningiomas (34%). However, no survival analysis was performed [42]. In 2022, Montgomery et al. presented a systematic review focused on elucidating incidence and risk factors, and thus included studies reporting metastatic meningioma in larger series of WHO grade 2 and 3 meningiomas [43]. Consequently, only 23 patients with metastatic meningioma were included. Most recently, Himic and colleagues performed a PRISMA systematic review in 2023 with studies primarily from the MEDLINE database. They included 155 cases of metastatic meningioma, but did not provide details on histologic evolution, time to subsequent metastasis, or survival trends. Our review is thus the most comprehensive, including the largest number of metastatic meningioma cases to date, and uniquely adds details on the histologic evolutionary trends from the primary to metastatic meningioma, survival analysis from both diagnosis of primary and metastasis, and management.

Limitations

This review is limited to case reports and series, and thus results are skewed towards data that is reported and patient populations are heterogeneous. Results must be interpreted

cautiously and with knowledge of the number of patients that data was made available, as indicated in our tables. We did not employ the Weiss criteria [44] in our inclusion criteria, which would have provided a more strict confirmation of metastatic meningioma. Despite limitations of this systematic review, the extreme rarity of this event renders it unlikely to be amenable to other forms of study. Additionally, although case reports and series cannot be a true representation of population distribution, it is probably the closest approximation we can obtain to understanding such frequencies.

Conclusion

Metastatic meningioma appears to be associated with more positive prognosis than other brain tumor types with extraneural metastasis or metastasis in general. Cases arising from a WHO grade 1 meningioma are associated with longer survival times than higher-grade primaries. Despite long survival times, the clinical course is not completely benign and recurrence or multiple metastatic events are relatively common.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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