ORIGINAL ARTICLE

Metastasis from glioblastoma multiforme: a meta-analysis

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SUMMARY

OBJECTIVE: *Extracranial metastases of glioblastoma multiforme (GBM) are rare due to the short survival experienced by the patients. Therefore, the natural history of GBM metastases remains elusive. The identification of clinical factors promoting GBM metastases may help elucidate the mechanisms of tumor cell invasion in the brain. The aims of this study were to perform a meta-analysis evaluating the survival, characteristics, prognostic factors, and predictors of treatment outcome in patients with metastatic GBM and describe a case of metastatic extracranial GBM.*

METHODS: *We report the case of a patient diagnosed with GBM metastatic to the lungs and the results of a meta-analysis of 114 other cases of metastatic GBM identified through a MEDLINE and BIREME search.*

RESULTS: *The mean age of the patients was 38.2±16.1 years and 70.4% were male. The time elapsed between the identification of the metastasis and death was significantly increased in patients undergoing surgery (p=0.019), whereas the time from the diagnosis of the primary tumor to death was significantly increased in patients receiving radiation therapy (p=0.050). The time elapsed from metastasis to death and diagnosis to death was significantly longer in patients receiving chemotherapy (p<0.001 and p=0.027, respectively). The liver was the metastatic site associated with the shortest time elapsed from diagnosis to death (p=0.024).*

CONCLUSIONS: *In GBM, surgical resection is important in reducing the risk of metastasis, and chemotherapy and radiation therapy help to prolong survival in metastatic GBM. Metastases to the liver are associated with shorter survival compared with metastases to other sites.*

KEYWORDS: *Glioblastoma. Neoplasm metastasis. Neurosurgery. Meta-analysis.*

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common primary malignant tumor of the central nervous system in adults, with an estimated incidence of 2–3 cases per 100,000 individuals in Europe and North America. Extracranial metastases of GBM are extremely rare, affecting 0.4–0.5% of all patients with GBM[1]. The rarity of this phenomenon is attributed to the very short survival experienced by the patients, in which not enough time is available for neoplastic cells to metastasize to extracranial organs.

Since the first case of GBM was reported in 1928 by Davis[2], the treatment of these extremely aggressive central nervous system (CNS) tumors has progressively improved. With the emergence of more

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aggressive neurosurgical therapies and ventricular peritoneal shunts, GBM metastases have been reported in association with hematogenous spreading of tumor cells or structural changes following surgery in the meningeal layers and skull. In a recent review[3], around 10% of the reported cases of extracranial GBM spread occurred without surgical intervention.

The natural history of extracranial GBM is unknown. The identification of clinical factors promoting extracranial metastases may help elucidate the mechanisms of invasion of tumor cells in the brain tissue. Based on these considerations, we report herein a case of GBM metastatic to the lungs, along with a meta-analysis evaluating the survival, characteristics, prognostic factors, and predictors of treatment outcome in patients with metastatic GBM.

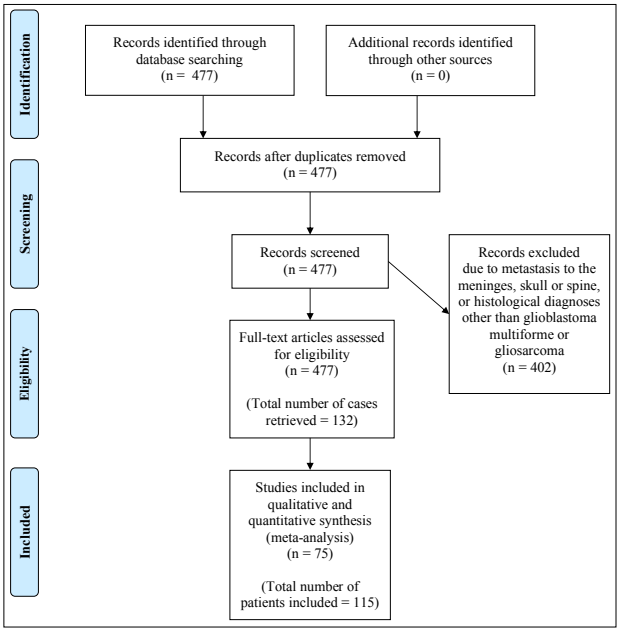
METHODS

The present article was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; www.prisma-statement.org) (see the supplemental Figure for the PRISMA checklist).

Selection of patients

We performed an electronic survey of the MEDLINE and BIREME database in search of cases of GBM with extracranial metastases published between January 1928 and September 2015. We identified 457 articles retrieved from MEDLINE using the keywords "Neoplasm Metastasis" [MeSH] AND "Glioblastoma" [MeSH]. In the BIREME platform, 20 other publications not identified in the MEDLINE search were retrieved with the search terms "Neoplasm Metastasis" AND "Glioblastoma." Publications in languages other than English were included if abstracts were available in this language. Cases with suspected radiological diagnosis of GBM metastases but without corroborative histology were excluded. The selected cases include primary and secondary GBM and gliosarcoma, which subsequently progressed with extracranial metastases confirmed by surgery or autopsy. Cases with metastasis to the meninges, skull, or spine were included. All histological diagnoses other than GBM or gliosarcoma were excluded. After an individual analysis of 477 abstracts, 75 publications comprising cases or described series of metastatic GBM were selected (Figure 1).

FIGURE 1. PRISMA 2009 FLOW DIAGRAM OF SEARCH STRATEGY



Case report

The present case report is described in accordance with the ethical standards of our institution.

In addition to the cases selected from the literature, we added the case of a 43-year-old female patient who had undergone surgery at another institution for resection of a left frontal glial mass lesion with dimensions of 3.8 x 2.7 x 3.2 cm on magnetic resonance imaging (MRI). The lesion was diagnosed after the patient complained of headache that had progressively worsened over 3 months. No images are available from that period. After partial resection of the lesion (motor area), a diagnosis of GBM was established, and the patient underwent conformal radiotherapy (total 60 Gy) and chemotherapy, according to the protocol recommended by Stupp et al.[4]. At 23 months after the initial surgery, the patient was admitted to our hospital due to seizures and right hemiparesis that had developed 10 days earlier. A new brain MRI showed a solid-cystic lesion in the left frontoparietal region measuring 5.8 x 4. 7 x 5.4 cm in the largest diameter (Figure 2).

The patient underwent subtotal resection of the tumor due to the eloquence of the location. A pathological diagnosis was consistent with GBM, and the patient received chemotherapy with irinotecan. At 36 months after the diagnosis of the tumor, the patient was admitted to the emergency department for dyspnea lasting over 3 days. A chest computed tomography (CT) showed expansive lesions in the lung parenchyma and bilateral pleural effusion (Figure 3).

FIGURE 2. CEREBRAL AXIAL (LEFT) AND SAGITTAL (RIGHT) T1 MAGNETIC-RESONANCE IMAGING WITH CONTRAST SHOWING A SOLID-CYSTIC LEFT FRONTOPARIETAL LESION

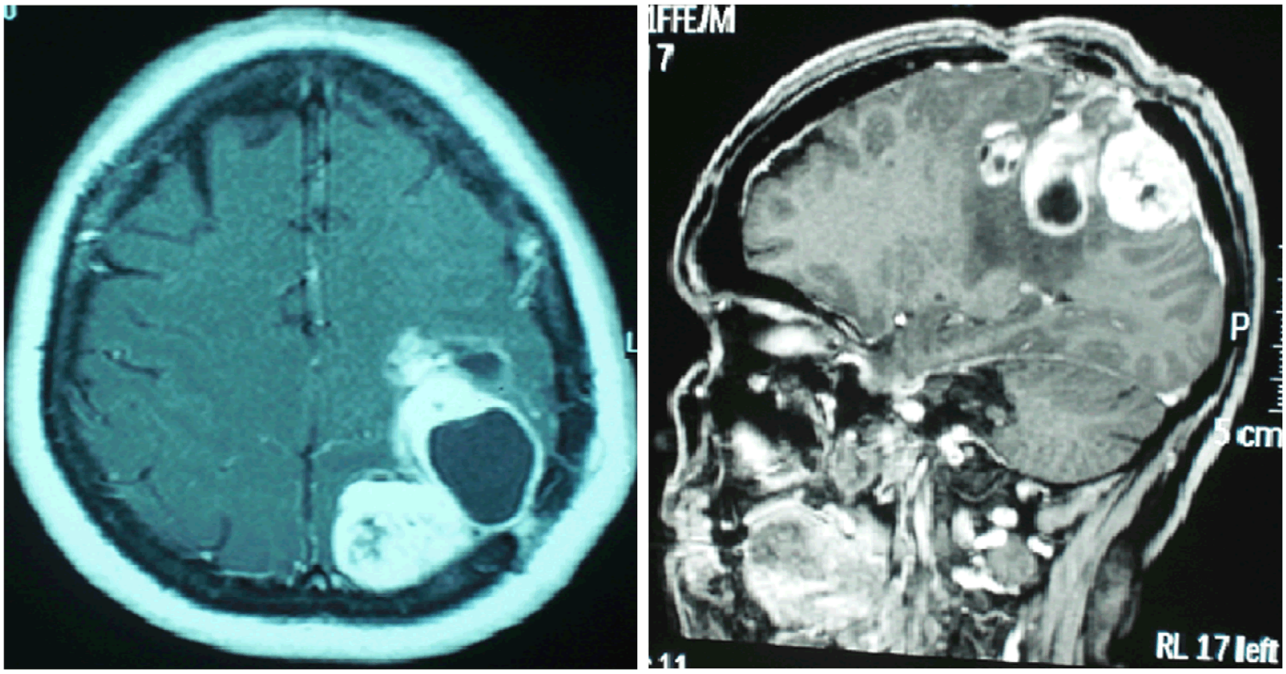
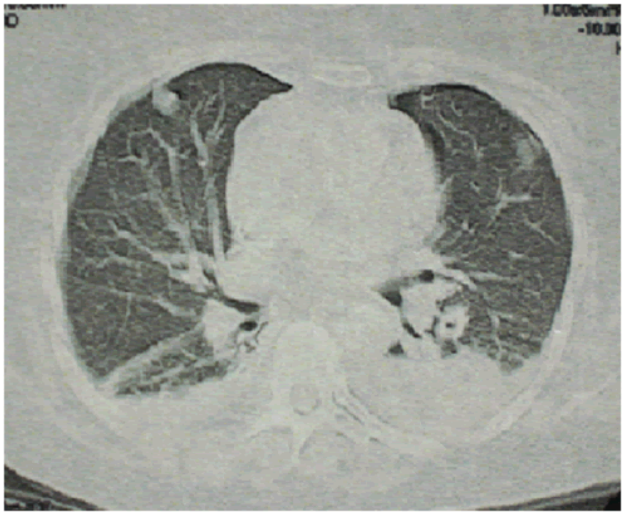


FIGURE 3. CONTRAST COMPUTED TOMOGRAPHY OF THE CHEST SHOWING BILATERAL PLEURAL EFFUSION, MORE PRONOUNCED ON THE LEFT, AND NODULES WITH WELL-DELINEATED MARGINS, SUGGESTIVE OF SECONDARY IMPLANTATION



A pathological diagnosis of pulmonary metastatic GBM was established by fiberoptic bronchoscopy. The patient died 2 months after the lesion was histologically confirmed to be metastatic GBM.

Data Collection

Our survey retrieved 132 cases of GBM with extracranial metastasis, of which 18 were excluded for not meeting the inclusion criteria. With the addition of our case, a total of 115 cases were included in the meta-analysis.

The data collected were organized in a spreadsheet and included the following:

- Survival time, divided into four stages: (A) from symptom onset to diagnosis of GBM; (B) from diagnosis of GBM to detection of extracranial metastases; (C) from the detection of extracranial metastasis to death, and (D) from the diagnosis of GBM to death;
- Year of publication, categorized from the 1950s until 2010 (cases published before 1950 were categorized in the same group);
- Patients' age, divided into decades: below 20 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, and above 60 years;
- Patients' described gender;
- Neuroimaging method used to diagnose the metastases, categorized as CT, MRI, both, or neither;
- GBM anatomical site, categorized as frontal, parietal, temporal, occipital, parietal + temporal, parietal + occipital, frontal + parietal, temporal + occipital , frontal + temporal, cerebellum, and brainstem;
- Location of the metastasis, categorized as systemic, bone, liver, lung, lymph nodes, and neck;
- Treatment performed, categorized as no therapy or a combination of tumor resection, radiation, chemotherapy, and/or ventriculoperitoneal shunt (VPS).

We excluded from the analysis the patients' neurological performance and extension of the surgical resection since these data were scarce in the reviewed literature.

When the GBM was located in three or more lobes or parts of the brain in a given patient, we considered the tumor to affect the entire hemisphere. We used the same criteria in regards to the metastatic site, grouping under the category "systemic" those metastases affecting organs not included in the five most prevalent groups described above. We considered to be the "metastatic site" the area other than the brain where the initial tumor cell growth was recorded and confirmed by biopsy.

Statistical analysis

The interval of time elapsed between variables of interest were evaluated with summary measures (mean, standard deviation, median, minimum, and maximum values). Comparisons of the time elapsed between the categories of characteristics were evaluated using the Kruskal-Wallis test followed by Dunn's multiple comparison or Mann-Whitney tests, as appropriate.

The tests were performed with a significance level of 5% and the software used for the analysis was SPSS 20.0 [5,6].

RESULTS

A total of 115 cases of GBM with extracranial metastases (110 cited as GBM and 5 as gliosarcoma) published between 1928 and 2015 were selected for the analysis. Table 1 shows the general characteristics of the study population and the time elapsed between events. The individual characteristics of each patient included in the meta-analysis are shown in the Supplemental Table.

We observed that the time elapsed between the emergence of symptoms and the diagnosis of the pri-

TABLE 1. GENERAL CHARACTERISTICS OF THE STUDY POPULATION

Variable	Values
Age (years)	
Mean (SD)	38.2 (16.1)
Median (min.– max.)	39.5 (6–68)
Sex, n (%)	
Female	34 (29.6)
Male	81 (70.4)
GBM site, n (%)	
Frontal	21 (18.6)
Temporal	25 (22.1)
Parietal	6 (5.3)
Occipital	9 (8)
Hemispheric	12 (8.8)
Parietal + Temporal	6 (5.3)
Parietal + Occipital	11 (9.7)
Frontal +Parietal	15 (13.3)
Temporal + Occipital	5 (4.4)
Frontal + Temporal	3 (2.7)
Cerebellum	1 (0.9)
Brain stem	1 (0.9)
CT/MRI, n (%)	
None	54 (47)
CT	16 (13.9)
MRI	11 (9.6)
Both	34 (29.6)
Surgery, n (%)	
No	12 (10.5)
Yes	102 (89.5)
Radiation, n (%)	
No	18 (16.8)
Yes	89 (83.2)
Chemotherapy, n (%)	
No	75 (66.4)
Yes	38 (33.6)
Shunt, n (%)	
No	102 (88.7)
Yes	13 (11.3)
Extracranial GBM site, n (%)	
Bone	28 (24.3)
Liver	10 (8.7)
Lung	25 (21.7)
Lymph nodes	14 (12.2)
Neck	10 (8.7)
Systemic	28 (24.3)
Time from symptoms to diagnosis (months)	
Mean (SD)	7.5 (14.2)
Median (min. – max.)	2.5 (0–75)
Time from diagnosis to metastasis (months)	
Mean (SD)	11.7 (11.9)
Median (min.– max.)	7.5 (0–62)
Time from metastasis to death (months)	
Mean (SD)	4.6 (9.3)
Median (min.– max.)	2.3 (0–78)
Time from diagnosis to death (months)	
Mean (SD)	15 (14.4)
Median (min.– max.)	10 (1–90)

Abbreviations: min. – minimum; max. – maximal; n – number; CT – computed tomography; MR – magnetic resonance.

mary tumor and between the detection of the metastasis and death differed significantly across decades, as shown in Table 2. The time elapsed between the diagnosis of the primary GBM tumor and the patients' death increased by 1.68 months per decade (p = 0.034), and the time elapsed between the detection of the metastasis until death increased by 0.87 months per decade (p = 0.024).

Given that CT and MRI can provide an earlier detection of the tumor, we analyzed whether the use of these imaging modalities affected the survival of patients with extracranial GBM. As shown in Table 3, the time elapsed between the detection of the metastases and death increased significantly with the use of CT, MRI, or both when compared with the absence of use of these imaging methods.

We also analyzed the effect of the delivered treatment on the patients' survival. As shown in Table 3, the time elapsed between the detection of the metastases and the patients' death was significantly longer in patients who had undergone surgical resection of the primary tumor. Similarly, the time between the diagnosis of the primary tumor and death was significantly longer in patients who had received radiation therapy, while the time between the detection of the metastasis and death and between diagnosis of the primary tumor and death were significantly longer in patients who received chemotherapy. The use of VPS had no influence on survival in the overall cohort.

As also shown in Table 3, the time elapsed between the diagnosis of the primary tumor and death was affected by the location of the metastases. On multiple comparison analysis, the time elapsed between the diagnosis of the primary tumor and death was longer in patients with neck metastases and lung metastases, and shortest in patients with liver metastases.

The GBM location in the brain or the patients' age and gender were not significantly associated with the development of metastases.

DISCUSSION

The small number of reported cases of patients with extracranial metastases of GBM prevents the development of prospective studies focused on this issue. Thus, the understanding of the impact of GBM metastases relies on meta-analyses of existing cases in the literature, such as the one reported in this

TABLE 2. TIME ELAPSED BETWEEN IMPORTANT EVENTS ACROSS DECADES IN PATIENTS WITH GLIOBLASTOMA MULTIFORME

Year	Time S-Dx (months)	Time Dx-M (months)	Time M-D (months)	Time Dx-D (months)
Up to 1950 Mean (SD) Median (min. – max.)	4.5 (3) 3 (2.5 – 8)	6 (6) (4 – 8)	2 (2) 2 (0 – 4)	8 (3.5) 6 (6 – 12)
1950 to 1959 Mean (SD) Median (min. – max.)	24.4 (26.6) 10.5 (2 – 75)	8.1 (5.1) 7.8 (0 – 17)	1.3 (1. 9) 0.3 (0 – 5)	8.5 (5) 9 (1 – 18)
1960 to 1969 Mean (SD) Median (min. – max.)	5.4 (3.6) 5 (1 – 11)	12.7 (10.3) 8 (3 – 32)	3.1 (3.2) 1.5 (1 – 9)	15.6 (13.3) 10.5 (1 – 60)
1970 to 1979 Mean(SD) Median (min. – max.)	10.8 (21) 1 (0.3 – 60)	6.1 (4.4) 6.5 (0 – 13)	0.9 (1.3) 0 (0 – 4)	6.6 (3.9) 7.5 (1 – 13)
1980 to 1989 Mean (SD) Median (min. – max.)	4.1 (4) 2 (0.5 – 12)	9.6 (9.3) 7.5 (1 – 31)	1.8 (2.1) 1 (0 – 7)	10.5 (9.7) 7.8 (1 – 32)
1990 to 1999 Mean (SD) Median (min. – max.)	4.8 (4.5) 3 (1 – 13.5)	12.8 (12) 10 (0 – 35)	6.2 (5.6) 3 (1 – 15)	18 (14.4) 15 (1 – 46)
2000 to 2009 Mean (SD) Median (min. – max.)	1.3 (1.2) 1 (0 – 4)	12 (9.6) 7.8 (3 – 34)	4.3 (3.6) 3 (1 – 13)	14.4 (9.3) 10 (3 – 36)
After 2010 Mean (SD) Median (min. – max.)	3.5 (3.7) 3 (0 – 12)	16.1 (17.7) 9 (1 – 62)	8.9 (16.7) 3 (1 – 78)	22.3 (22.3) 18 (1 – 90)
P	0.011	0.719	0.002	0.122

Kruskal-Wallis test. Abbreviations: S-Dx – symptoms to diagnosis; Dx-M – diagnosis to metastasis; M-D – metastasis to death; Dx-D – diagnosis to death; SD – standard deviation; min.: minimum; max.: maximum.

study. The current need for clinical elements to contribute to improving survival and the understanding of prognostic factors in patients with GBM was the rationale for this analysis.

Tumor dissemination generally occurs via lymphatic, vascular, or direct spreading. The occurrence of lymph node metastases from GBM suggests the participation of meningeal lymphatics in the process. This hypothesis is likely in patients undergoing surgery, but difficult to explain in patients with lymph node metastases who had not undergone surgery[7]. The brain lacks a true lymphatic system, thus limiting the lymphatic spread of tumor cells. The unique and characteristic vascular intracerebral glioblastoma network is notorious; the neoplastic vessels have thick walls with several layers of endothelial cells

TABLE 3. IMPACT OF (A) THE APPLICATION OF COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING COMPARED WITH THE ABSENCE OF USE OF BOTH METHODS, (B) THE DELIVERED TREATMENT, AND (C) THE LOCATION OF THE EXTRACRANIAL METASTASIS ON TIME ELAPSED BETWEEN IMPORTANT EVENTS IN PATIENTS WITH GLIOBLASTOMA MULTIFORME

(A) CT/MR	Time S-Dx (months)	Time Dx-M (months)	Time M-D (months)	Time Dx-D (months)
None Mean (SD) Median (min. – max.)	13.2 (19.7) 5 (0.3 – 75)	9.3 (7.3) 7 (0 – 32)	1.7 (2.2) 1 (0 – 9)	12.8 (11.3) 9 (1 – 60)
CT Mean (SD) Median (min. – max.)	3.3 (3.6) 2 (0 – 12)	9.2 (10.5) 6 (0 – 35)	3.5 (4.4) 1.8 (0 – 15)	12.1 (12.5) 8 (1 – 46)
MR Mean (SD) Median (min. – max.)	1.2 (0.8) 1 (0.5 – 2)	14.1 (8.8) 15 (2 – 30)	4.5 (3.8) 3 (1 – 13)	18 (10.6) 18.8 (2 – 36)
Both Mean (SD) Median (min. – max.)	3.2 (3.2) 1.5 (0 – 12)	14.1 (15.9) 7.8 (0 – 62)	7.7 (14.4) 3 (1 – 78)	19.1 (19.7) 11.5 (1 – 90)
P	0.040	0.362	0.002	0.215

(B) Surgery	Time S-Dx (months)	Time Dx-M (months)	Time M-D (months)	Time Dx-D (months)
No Mean (SD) Median (min. – max.)	8.8 (15.8) 2 (0.3 – 50)	6.6 (6.3) 6 (0 – 17)	1.3 (1.7) 0.9 (0 – 5)	8.4 (4.8) 9 (2 – 18)
Yes Mean (SD) Median (min. – max.)	7.2 (14) 2.8 (0 – 75)	12.4 (12.3) 8 (0 – 62)	5.1 (9.9) 2.5 (0 – 78)	15.9 (15) 10 (1 – 90)
p	0.919	0.125	0.019	0.122
Chemoterapy				
No Mean (SD) Median (min. – max.)	9.8 (16.7) 3 (0 – 75)	10.3 (9.3) 7 (0 – 36)	2.2 (2.6) 1 (0 – 10)	13.1 (12) 9 (1 – 60)
Yes Mean (SD) Median (min. – max.)	2.8 (3) 2 (0 – 12)	14.2 (14.6) 8.5 (0 – 62)	8.1 (13.7) 3.3 (0 – 78)	19.5 (18) 13 (3 – 90)
p	0.093	0.203	<0.001	0.027
Radiation				
No Mean (SD) Median (min. – max.)	7.7 (9.7) 6 (1 – 36)	8.6 (11.2) 5 (1 – 36)	2.2 (2.7) 1.3 (0 – 10)	10.5 (12) 7 (1 – 46)
Yes Mean (SD) Median (min. – max.)	7.6 (15.2) 2 (0 – 75)	12.4 (12) 8 (0 – 62)	5.1 (10.2) 2.5 (0 – 78)	15.5 (14.5) 10 (1 – 90)
p	0.083	0.065	0.121	0.050
Shunt				
No Mean (SD) Median (min. – max.)	7.8(14.7) 2.5 (0 – 75)	11.8 (12) 7.5 (0 – 62)	4.7 (9.7) 2 (0 – 78)	15.5 (14.8) 10 (1 – 90)
Yes Mean (SD) Median (min. – max.)	3.5 (3.2) 4 (0 – 7)	10.4 (11.5) 8 (0 – 34)	3.1 (2.2) 3 (0 – 7)	9.6 (7.5) 8 (3 – 25)
p	0.683	0.605	0.694	0.188

(C) Local extracranial metastasis	Time S-Dx (months)	Time Dx-M (months)	Time M-D (months)	Time Dx-D (months)
Bone Mean (SD) Median (min. – max.)	3 (3) 2 (0.3 – 12)	10.8 (8.3) 8 (0 – 31)	8.5 (17) 3.3 (0 – 78)	18.3 (18.1) 12.5 (1 – 90)
Liver Mean (SD) Median (min. – max.)	11.1 (16.9) 4 (0.3 – 36)	6 (4.2) 4 (3 – 13)	1.5 (1.7) 1 (0 – 4)	7.1 (2.9) 6.5 (3 – 13)
Lung Mean (SD) Median (min. – max.)	3.5 (3.1) 2.8 (0 – 10)	12.1 (10.8) 8 (1 – 36)	2.2 (2.7) 2 (0 – 10)	16.9 (16) 10.5 (1 – 60)
Lymph node Mean (SD) Median (min. – max.)	19.4 (30.4) 2.5 (0.3 – 75)	9.9 (10) 9 (0 – 32)	3.5 (4.2) 1.5 (0 – 10)	13.9 (10) 11.8 (2 – 33)
Neck Mean (SD) Median (min. – max.)	5 (5.5) 3 (0.5 – 13.5)	17 (18.4) 8 (2 – 60)	5.5 (5.3) 2.8 (2 – 18)	22.4 (18.5) 17.3 (2 – 63)
Systemic Mean (SD) Median (min. – max.)	10.1 (15.9) 6 (0 – 60)	11.9 (14) 7 (0 – 62)	3.3 (4) 2 (0 – 15)	10.9 (9.4) 8 (1 – 35)
p	0.887	0.695	0.079	0.024

Kruskal-Wallis test. Abbreviations: S-Dx – symptoms to diagnosis; Dx-M – diagnosis to metastasis; M-D – metastasis to death; Dx-D – diagnosis to death; SD – standard deviation; min. – minimum; max. – maximum.

forming irregular interconnected glomerular structures arranged chaotically. Circulatory disorders, local hypoxia at low pH, and increased permeability of the tumor blood vessel wall occur as a result. Vascular proliferation is stimulated by the tumor itself, which produces growth factors and cytokines. Vascular endothelial growth factor (VEGF) is the most common among them, and its concentration is up to 50 times greater in the CNS of patients with GBM compared with healthy ones[8]. Unlike other malignant systemic diseases, glial cells do not spread through blood vessels, making hematogenous spread highly unusual.

Despite the notable progress in the quality of surgery, chemotherapy, and radiotherapy that has occurred over the decades evaluated in this study, survival has failed to increase in the same proportion. Overall, 70% of the patients with GBM die within 2 years from the diagnosis[4]. Molecular genetics has an intrinsic relationship with survival in individuals with GBM. Patients with epigenetic silencing of the O[6]-methylguanine-DNA methyltransferase (*MGMT*) gene have an estimated average survival of 48.9% at 2 years and 13.8% at 5 years when compared with those with unmethylated *MGMT*, whose corresponding average survival rates were reported to be around 14.8% and 8.3%, respectively[8]. The present study did not evaluate the methylation status of the *MGMT* gene due to the scarcity of this information in the retrieved cases, even in recently published ones. Our work also showed an increased survival of the patients over the decades, probably associated with improvement and agility in diagnostic imaging, as well as the benefit of combination therapies including surgery, radiotherapy, and chemotherapy. Currently, the molecular determinants that may predispose to the occurrence of GBM metastasis are unknown, and no molecular characteristics have been correlated with increased survival.

The paradoxical observation of a low (0.4%) incidence of metastases[1] in GBM combined with its highly invasive nature led Sullivan et al.[9] to search for circulating tumor cells (CTCs) in peripheral blood. The authors analyzed with immunofluorescence markers (especially EGFR) peripheral blood of 33 patients diagnosed with GBM. CTCs were present in 13 cases (39%), which is a much higher rate than the recorded rate of GBM metastases. Interestingly, the authors found that these GBM CTCs predominantly expressed genes associated with mesenchymal differentiation. This finding may be related to their greater phenotypic aggression, which may justify their ability to invade the cerebral blood flow and spread. Following the same line of reasoning, Müller et al.[10] used the glial fibrillary acidic protein (GFAP; mainly expressed in astrocytes and glial tumors) as a marker to isolate GBM cells in peripheral blood. Of the 141 patients included in the study, CTCs were identified in 29 cases (20.6%). Importantly, the analysis in both studies was performed preoperatively, indicating that the presence of CTCs was not the result of disruption of the blood brain barrier due to surgery. Another issue to be discussed is the fact that the studies used different methodologies to isolate CTCs based on different markers, raising questions regarding the

best method to detect CTCs. The molecular diversity of GBM must also be considered, and some tumor cells may not express GFAP markers and vice versa. In addition, CTCs expressing different markers may coexist and fluctuate over time. Thus, new technologies and more accurate identification of CTCs of GBM need to be developed to clarify these questions.

The patients in our study group had a mean age of 38.2 years, which is lower than that of typical adults with GBM, and a median survival of 15 months. This finding was also shown in a review by Lun et al.[11], which reported a mean age of 38 years and median survival of 10.5 months in 88 cases of GBM. In contrast, a review of 94 cases conducted by Anghileri et al.[12] found a mean age of 41.1 years and median survival of 12 months. Both studies found a mean time from the initial diagnosis of GBM to the emergence of metastases of 8.5 months, which is lower than that found in our analysis (11.7 months). It is possible that the occurrence of metastases from low-grade gliomas occur before these tumors undergo malignant transformation, enabling the ability of tumor cells to settle in metastatic sites. However, this hypothesis lacks proof [12].

In our analysis, the metastatic site influenced survival, considering the time from the diagnosis of the primary tumor to death. This fact was also evidenced in a previously published series, which showed a better prognosis of GBM metastatic to the neck and a worse prognosis for GBM metastatic to the lung[10]. Our study demonstrated that patients with metastases to the neck also showed a longer time from diagnosis of the primary tumor to death (22.4 ± 18.5 months). Patients with metastasis to the liver – and not to the lungs – had the lowest survival time from diagnosis to death (7.1 ± 2.9 months). This difference was statistically significant and may be explained by cellular and molecular heterogeneity, which was clearly demonstrated in a study by Fidler and Kripke[13] using B16 melanoma cells. Certain tumor clones had a predilection for specific organs such as the lung or liver. Thus, it is possible that GBM clones migrating to the neck are less aggressive than those migrating to the liver.

Despite GBM being the most common CNS tumor, the number of patients with metastatic GBM is very low. The explanation for this discrepancy is unclear but may involve the short survival experienced by the patients and a possible absence of a suitable environment for multiplication of metastatic cells. Rubenstein et al.[14] have reported that GBM cells may have preferential adhesion to the neural stroma. With disease progression, tumor cells can violate the existing cerebral vasculature, achieving a greater capacity to spread to the CNS via a hematogenous route. With prolonged survival of young patients with GBM, the possibility of GBM cells spreading to the bloodstream may increase, which will also increase the odds of distant metastasis[15]. There have been reports of the occurrence of extracranial GBM in recipients of liver and kidney grafts from donors with GBM. Additionally, immunosuppression for prevention of organ rejection may have a potentiating action on the development of tumors in recipients[16].

The development of extracranial GBM indicates that systemic spread occurs early in the disease[10]. The immune system appears to be a link in the understanding of this kind of behavior towards CTCs of GBM. As suggested by Seoane & de Mattos-Arruda[17], existing CTCs would require time to learn how to escape immune surveillance, which is not feasible considering the short survival experienced by these patients. GBM cells in the circulation may provide an opportunity for gene detection and analysis of the incipient intracranial GBM disease. These "liquid biopsy" are potentially powerful tools for characterization of patients with GBM. CTCs can represent materials derived from tumor sources and be regarded as tissue barcodes of brain tumor, with the advantage of being a minimally invasive procedure. Thus, these biomarkers can be molecularly categorized to reveal a repertoire of momentaneous somatic genomic aberrations and yield a longitudinal overview of the molecular characteristics of the tumor.

The "liquid biopsy" still needs further studies for validation. Some of its advantages include the discrimination of tumoral pseudoprogression, selecting specific therapies and monitoring mechanisms of resistance to cytotoxicity and therapeutic targets. In our view, the genomic changes "written" in the blood should be one of the most valuable tools to guide treatment and assist in the understanding of GBM and its molecular variants, given the scarcity of reported cases of extracranial GBM with the paradoxically higher incidence of GBM and amount of CTCs investigated in previous studies.

A potential limitation of our study was the small number of patients included in the analysis, retrieved from a period spanning almost a century. As mentioned earlier, this limitation is due to the

scarcity of cases of metastatic GBM described in the literature.

A meta-analysis of cases with extracranial metastatic GBM showed that over the past seven decades, patients affected with this disease experienced a decrease in the time elapsed between the onset of symptoms and the diagnosis of the primary tumor in addition to an increase in the time elapsed from the detection of metastasis to death. The increasing use of neuroimaging methods (CT and MRI) over time decreased the time elapsed between the development of symptoms and the diagnosis of GBM and prolonged the survival from the diagnosis of the metastasis until death. Surgery for treatment of the primary GBM tumor was associated with an increased time elapsed from the detection of the metastasis until death, while radiation increased the time elapsed between the diagnosis of the primary tumor and death. The time elapsed between the metastasis and death and between the diagnosis and death was significantly longer in patients who received chemotherapy. Hepatic metastasis of GBM was associated with the worst prognosis when compared with other metastatic sites.

The limited number of patients with GBMs presenting extracerebral metastases prevents the development of prospective studies. Improvements in molecular testing and immune response evaluation may help elucidate the occurrence of low metastatic rates in GBM. Perhaps this reversal path (investigation of the metastatic site) may shed new perspectives for the understanding of the adherence of CTCs into metastatic sites in patients with GBM.

CONCLUSIONS

The results of our study, spanning almost a decade and including patients with metastatic GBM, confirm the benefits of surgical resection as an important step in reducing the risk of metastasis, as well as those of chemotherapy and radiation therapy in prolonging survival in patients with metastatic GBM. Compared with other metastatic sites, the liver was the site associated with the shortest survival.

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RESUMO

OBJETIVO: *Metástases extracranianas do glioblastoma multiforme (GBM) são raras devido à baixa sobrevida dos pacientes. Portanto, a história natural das metástases do GBM permanece incerta. A identificação de fatores clínicos que promovem metástases no GBM pode ajudar a elucidar os mecanismos de invasão das células tumorais no cérebro. O objetivo deste estudo foi realizar uma meta-análise avaliando a sobrevida, características, fatores prognósticos e preditores de desfechos do tratamento em pacientes com GBM metastático e descrever um caso de GBM extracraniano metastático.*

MÉTODOS: *Relatamos o caso de uma paciente diagnosticada com GBM metastático para os pulmões e os resultados de uma meta-análise de 114 outros casos de GBM metastático identificados por meio de uma pesquisa no Medline e Bireme.*

RESULTADOS: *A média de idade dos pacientes foi de 38,2±16,1 anos e 70,4% eram do sexo masculino. O tempo decorrido entre a identificação da metástase e o óbito foi significativamente maior em pacientes submetidos à cirurgia (p = 0,019), enquanto que o tempo do diagnóstico do tumor primário até o óbito aumentou significativamente em pacientes submetidos à radioterapia (p = 0,050). O tempo decorrido da metástase até o óbito e do diagnóstico até o óbito foi significativamente maior nos pacientes que receberam quimioterapia (p < 0,001 e p = 0,027, respectivamente). O fígado foi o local metastático associado ao menor tempo decorrido do diagnóstico até a morte (p = 0,024).*

CONCLUSÕES: *No GBM, a ressecção cirúrgica é importante para redução do risco de metástase, e a quimioterapia e a radioterapia ajudam a prolongar a sobrevida no GBM metastático. Metástases para o fígado estão associadas a uma sobrevida mais curta quando comparadas a metástases para outros locais.*

PALAVRAS-CHAVE: *Glioblastoma. Metástase neoplásica. Neurocirurgia. Meta-análise.*

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