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Original Article

Analysis of prognostic factors and the role of epilepsy in neurosurgical patients with brain metastases

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Received: 03 September 2023
Accepted: 01 February 2024
Published: 08 March 2024

DOI
10.25259/SNI_735_2023

Quick Response Code:

ABSTRACT

Background: Brain metastases (BMs) represent the most frequent brain tumors in adults. The identification of key prognostic factors is essential for choosing the therapeutic strategy tailored to each patient. Epilepsy can precede several months of other clinical presentations of BMs. This work aimed to study the impact of epilepsy and other prognostic factors on BMs patients' survival.

Methods: This retrospective study included 51 patients diagnosed with BMs and who underwent neurosurgery between 2010 and 2021. The impact of BM features and patient's clinical characteristics on the overall survival (OS) was analyzed through uni- and multivariate analysis.

Results: The average OS was 25.98 months and differed according to the histology of the primary tumor. The primary tumor localization and the presence of extracranial metastases had a statistically significant impact on the OS, and patients with single BM showed a superior OS to those with multifocal lesions. The localization of BMs in the temporal lobe correlated with the highest OS. The OS was significantly higher in patients who presented seizures in their clinical onset and in those who had better post-surgical Karnofsky performance status, no post-surgical complications, and who underwent post-surgical treatment.

Conclusion: Our study has highlighted prognostically favorable patient and tumor factors. Among those, a clinical onset with epileptic seizures can help identify brain metastasis hitherto silent. This could lead to immediate diagnostic-therapeutic interventions with more aggressive therapies after appropriate multidisciplinary evaluation.

Keywords: Brain metastases, Epilepsy, Overall survival, Prognostic factors

INTRODUCTION

Brain metastases (BMs) are adults' most common intracranial tumors, accounting for over half of brain tumors. BM incidence is rapidly increasing due to the more prolonged survival of patients with primary malignant tumors and the improvement of diagnostic tools that allow early diagnosis.[1] In cancer patients, BMs develop in 10–30% of cases, representing a significant cause of patient morbidity, diminished quality of life, and mortality.[9] Although about 30% of BMs are asymptomatic, the most common initial symptoms include headache (24–53%), focal

neurological deficits (16–43%), altered mental status (24–31%), epileptic seizures (15–16%), and ataxia (9–20%).[1,5,8,18,19] Seizures occur in approximately 20-35% of patients with BMs,[33] in whom they frequently represent the first sign allowing earlier identification of the disease.[1,28] On the other hand, the most common cause of seizures in patients with cancer is the development of solid BMs.[30] Tumor type and location are the most important factors associated with seizure risk in BMs. Among the most frequent types of cancer, the highest rate of seizures is reported in melanoma (15.6%), ovarian cancer (15.3%), lung cancer (12.5%), colorectal cancer (7.7%), hepatocellular (6.2%), and prostate cancers (4.9%).[1] The risk is most significant for patients with BMs involving or adjacent to regions of high epileptogenicity, such as the motor cortex and the temporal lobe.[33]

The current BM treatments include surgery, stereotactic radiosurgery, and/or whole-brain radiation therapy. Despite remarkable advances in systemic therapies, surgery remains an essential treatment modality, especially in patients with favorable functional status, a limited number of lesions, or neurological symptoms.[15,27] The definition of subgroups in relation to key prognostic factors is essential for choosing the therapeutic strategy tailored to each patient and could potentially improve patients' survival.[4] Early diagnosis certainly plays a leading role among prognostic factors; in this light, new-onset seizures may represent an early warning sign for the presence of a brain tumor and could count as a good prognostic factor for patients' survival. However, there is currently a paucity of data regarding which factor primarily predisposes patients to seizures at presentation[2] and affects survival in patients with BMs.[7] Moreover, to the best of our knowledge, seizures are not currently included in the more recent prognostic scores developed for patients who develop BMs.[26,29] We conducted a retrospective study to investigate clinical and tumoral characteristics that may serve as prognostic factors in BM patients and how they relate to the presence of epilepsy as an onset symptom.

MATERIALS AND METHODS

Study population

This retrospective study included patients with BMs who underwent neurosurgical treatment at the Clinics of Neurosurgery of the University Hospital, Ospedali Riuniti of Ancona, between 2010 and 2021. Patients' eligibility criteria were age >18 years old at the time of surgery, with a known primary cancer type, and with histologically confirmed BMs. Patients with leptomeningeal metastases and hematological malignancies were excluded from the study. The patient's clinical characteristics analyzed were gender, age, onset symptoms, presence or absence of epileptic seizures at clinical onset, presence of extracranial secondary disorders, the time interval between BMs and primary tumor diagnosis (metachronous vs. synchronous), pre-and post-surgical Karnofsky performance status (KPS), the time elapsed between the onset of symptoms and surgical treatment, post-surgical complications, and post-surgical treatment (chemotherapy, radiotherapy, etc.). Patients were divided into three groups according to the pre-surgical KPS (100–80, 70–50, and 40–10). BMs number, localization, volume and diameters, the degree of the midline shift, and the volume of perilesional edema were analyzed as well. The measurements were carried out using the picture archiving and communication system web system on pre-surgical magnetic resonance imaging (MRI) and computed tomography scans. Tumor volumes were calculated using the spheroid volume formula: $V = 4/3\pi \times AP/2 \times LL/2 \times CC/2$, where AP, LL, and CC were the maximum diameters in the axial (laterolateral), coronal (craniocaudal), and sagittal (anteroposterior) planes in T1-weighted MRI images after administration of gadopentetic acid (Gd-DTPA). Volume measurements were carried out in fluid-attenuated inversion recovery or T2-weighted MRI scans for the perilesional edema. Thenceforth, the edema volume (Ve) and edema index (EI) were calculated as follows: Ve = (V tumor + edema)−(V tumor); EI = (V tumor + edema)/(V tumor). The primary outcome was patients' overall survival (OS), defined as the time interval between BM diagnosis and death from any cause.

Statistical analysis

Relationships between categorical variables were analyzed using Fisher's exact test, whereas continuous variables were analyzed using Student's *t*-test for parametric and the Mann–Whitney U-test for non-parametric data. The correlations between patients' clinical and tumoral characteristics and the presence of seizures at onset were quantified using Spearman's correlation coefficient (r). The OS was analyzed according to Kaplan–Meier survival curves using the log-rank test to determine statistical significance between groups and Cox regression models to assess differences in continuous variables and determine independent predictors of OS. Variables that were significantly associated with OS based on univariate analysis were subjected to multivariate analysis. Differences were regarded as significant when the probability values were <0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) ver. 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Patients and tumour characteristics

Fifty-one patients fulfilled the inclusion criteria (33.3% of males and 66.7% of females). The average age was 60.33 years,

with 34/51 (67%) patients being younger than 65 years old. The follow-up available varied from a minimum of 1 month for those who died in the period immediately following surgery to a maximum of 75 months for long-term survivors. Regarding the pre-surgical KPS, 27/51 (52.9%) patients were included in the first group (100–80), 18 (35.3%) in the second (70–50), and 6 (11.8%) in the last one (40–10). A total of 25/51 (49%) patients presented nonseizure symptoms at the time of radiological diagnosis, and 17/51 (33.3%) showed seizures at the clinical onset. The primary tumors consisted of lung cancer in 18/51 (41.2%), breast cancer in 12/51 (27.5%), colorectal cancer in 10/51 (21.6%), and prostate cancer in 6/51 (11.8%) patients, whereas melanomas and renal tumors accounted for the remaining 5/51 (9.8%). Regarding their distribution, BMs were located in the frontal lobe in 18/51 (34.6%) patients, in 10/51 (30.8%) in the temporal lobe, in 8/51 (15.4%) in the occipital lobe, and 10/51 (19.2%) in the parietal lobe. Most patients showed a single BM (41/51, 80.4%), and extracranial metastases were found in 26/51 (51%) patients at the time of diagnosis. A total of 20 (39%) patients had metachronous BM from primary malignancy, whereas 31 (61%) patients had synchronous BM. The midline shift was present in 31/51 (61%) cases. The mean volume of BM was 22.68 mm^2, and the average volume of perilesional edema was 96.58 mm^2. All data are summarized in Table 1.

Table 1: Clinical and tumor characteristics of patients with BMs (n=51).

Variable	Classes	No. of patients	Percentage
Gender	Male	17	33.3
	Female	34	66.7
Age	<65 y	34	67
	>65 y	17	33
Pre-surgical KPS	80–100	27	52.9
	50–70	18	35.3
	10–40	6	11.8
Post-surgical KPS	80–100	27	52.9
	50–70	19	37.3
	10–40	5	9.8
Initial presentation with nonseizure symptoms	Yes	25	49
	No	9	17.6
Initial presentation with seizures	Yes	17	33.3
	No	34	66.7
Primary tumor	Lung	18	35.3
	Breast	12	23.5
	Colorectal	10	19.6
	Prostate	6	11.8
	Kidney and Melanoma	5	9.8
Localization	Frontal	18	35.3
	Parietal	10	19.6
	Temporal	15	29.4
	Occipital	8	15.7
Number of BMs	Single	41	80.4
	Multiple	10	19.6
Extracranial metastasis	Yes	26	51
	No	25	49
Time of occurrence of BM	Metachronous	20	39
	Synchronous	31	61
Midline Shift	Yes	31	61
	No	20	39
Surgical resection	Total	40	78.4
	Subtotal	6	11.8
	Partial	5	9.8
Post-surgical complications	Yes	6	11.8
	No	45	88.2
Post-surgical treatment	Yes	37	72.5
	No	14	27.5

KPS: Karnofsky performance status, BM: Brain metastases

Factors associated with seizures

A statistically significant correlation was found between BMs localization and the presence of epilepsy at the time of diagnosis (r = 0.284, P = 0.04). The proportion of patients with seizures at the clinical onset in relationship to BMs localization is shown in Table 2. The parietal lobe was the one that showed the highest proportion of seizure-free patients (27.5%), whereas the temporal lobe showed the highest proportion of patients with seizures (11.8%). Seizures at the clinical onset were observed in 14/31 (45%) patients with synchronous BMs, whereas only in 3/20 (15%) patients with metachronous BMs. Moreover, a statistically significant association was found between seizures and pre-surgical KPS (r = 0.350, P = 0.03). In the group with the highest pre-surgical KPS (100-80), 6/27 patients presented seizures at the time of diagnosis, whereas 21/27 did not. In the second group (KPS 70–50), 10/18 patients had seizures, whereas in the third group (KPS 40–10), only 1/6 [Table 2]. Patients were further categorized into two groups based on the presence/absence of seizures, and the distribution of primary tumors histotypes was studied within these two groups. Lung cancer was the most frequent primary tumor among patients without seizures, whereas breast and colorectal cancers were the most represented in the other group, as shown in Table 2. Finally, there was a statistically significant (P = 0.024) difference in terms of peritumoral edema, evaluated as EI: Patients with seizures at the time of diagnosis showed a higher peritumoral edema (EI = 7.09 ± 1.23) compared to those without seizures (EI = 3.49 ± 2.17).

Treatment and outcome

A total of 40/51 (78.4%) patients underwent complete surgical resection, whereas the resection was partial in 5/51 (9.8%) and subtotal in 6/51 (11.8%) patients. Post-surgical complications occurred only in 6/51 (11.8%) patients and included both

Table 2: Distribution of patients with and without seizures at the clinic onset according to different parameters.

Variable	Seizures	
	No (34)	Yes (17)
Localization		
Frontal	13	5
Parietal	9	1
Temporal	9	6
Occipital	3	5
Pre-surgical KPS		
80–100	21	6
50–70	8	10
10–40	5	1
Primary tumor		
Lung	12	3
Breast	8	5
Colorectal	2	5
Prostate	5	1
Kidney and Melanoma	7	3
Time of occurrence of BM		
Metachronous	17	3
Synchronous	17	14

KPS: Karnofsky performance status, BM: Brain metastases

local (epi/subdural hematomas, hemorrhages, and wound infections) and systemic ones (pulmonary embolism, systemic infection, and hemodynamic decompensation). According to the post-surgical KPS, 27/51 (52.9%) patients were included in the first group (100–80), 19 (35.3%) in the second (70–50), and 5 (11.8%) in the last one (40–10). There was an increase of only two percentage points (from 35.3% to 37.3%) among patients with a KPS between 50 and 70 and a two-point decrease (from 11.8% to 9.8%) among patients with lower KPS than the pre-surgical KPS. Moreover, 37/51 (72.5%) patients received post-surgical treatment, whereas the remaining did not. All data are summarized in Table 1.

Analysis of survival

The average OS was 25.98 months with a frequency distribution, as shown in Figure 1. The OS differed according to the histology of the primary tumor [Figure 2a]. Patients with BMs resulting from lung cancer showed a variable survival from 1 to 45 months with an average of 16.9 months. For BMs resulting from breast cancers, the mean OS was 28.2 months, whereas prostate cancer had the widest survival range, ranging from 15 to 75 months, with a mean survival of 35.8 months. Patients with BMs from colorectal carcinoma demonstrated the highest OS of 51.1 months. In the case of renal cancer, the median OS was 30.6 months, ranging from 2 to 67 months, and melanoma metastases resulted in a low OS of 19.2 months, with a trend ranging from 7 to 35 months.

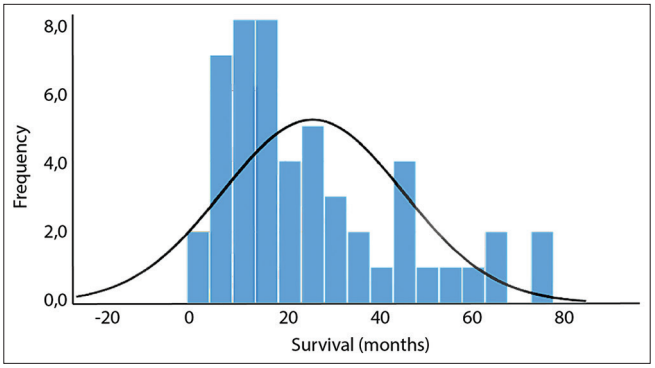

Figure 1: Frequency distribution of the overall survival of neurosurgical patients with brain metastases from our cohort.

Survival analysis with Kaplan–Meier curves showed that the presence of extracranial metastases had a statistically significant impact on the OS (P = 0.004) as it was related to an OS of 19.6 months compared to 37.2 months of patients without [Figure 2b]. Moreover, patients with single BMs showed a superior OS compared to those with multifocal lesions (P = 0.022) [Figure 2c]. The localization of BM in the occipital lobe correlated with the highest OS compared to other localizations, albeit not statistically significant (P = 0.581). The time of BM diagnosis (synchronous/metachronous) and the pre-surgical KPS had no statistically significant effect on the OS (P = 0.420 and P = 0.09, respectively), whereas a better post-surgical KPS corresponded to a higher OS (P = 0.015). In particular, patients with a KPS <50 showed an average survival of more than 30 months, whereas those with a KPS lower than 50 achieved an average survival of only 11 months [Figure 2d]. The absence of post-surgical complications also had a significant impact, as the median OS was doubled (30 vs. 15 months, P = 0.02) in patients with none of them [Figure 2e]. The OS was significantly higher in patients who underwent post-surgical treatment (34 vs. 15 months, P = 0.001) [Figure 2f] and who presented seizures at the time of diagnosis (P = 0.001) [Figure 2f].

Sex, age, maximum lesion diameter, midline shift, and time elapsed between diagnosis and surgery did not show a statistically significant impact on the OS.

DISCUSSION

After the creation of the Graded Prognostic Assessment as the first objective prognostic score for patients with BMs,[13,23,24,28] recent prognostic scores have been developed through the incorporation of more clinically relevant data in a process that tries to define a valuable tool in guiding clinical team decision-making.[11,14,20,21,22,25] In this study, we analyzed commonly adopted prognostic factors with a

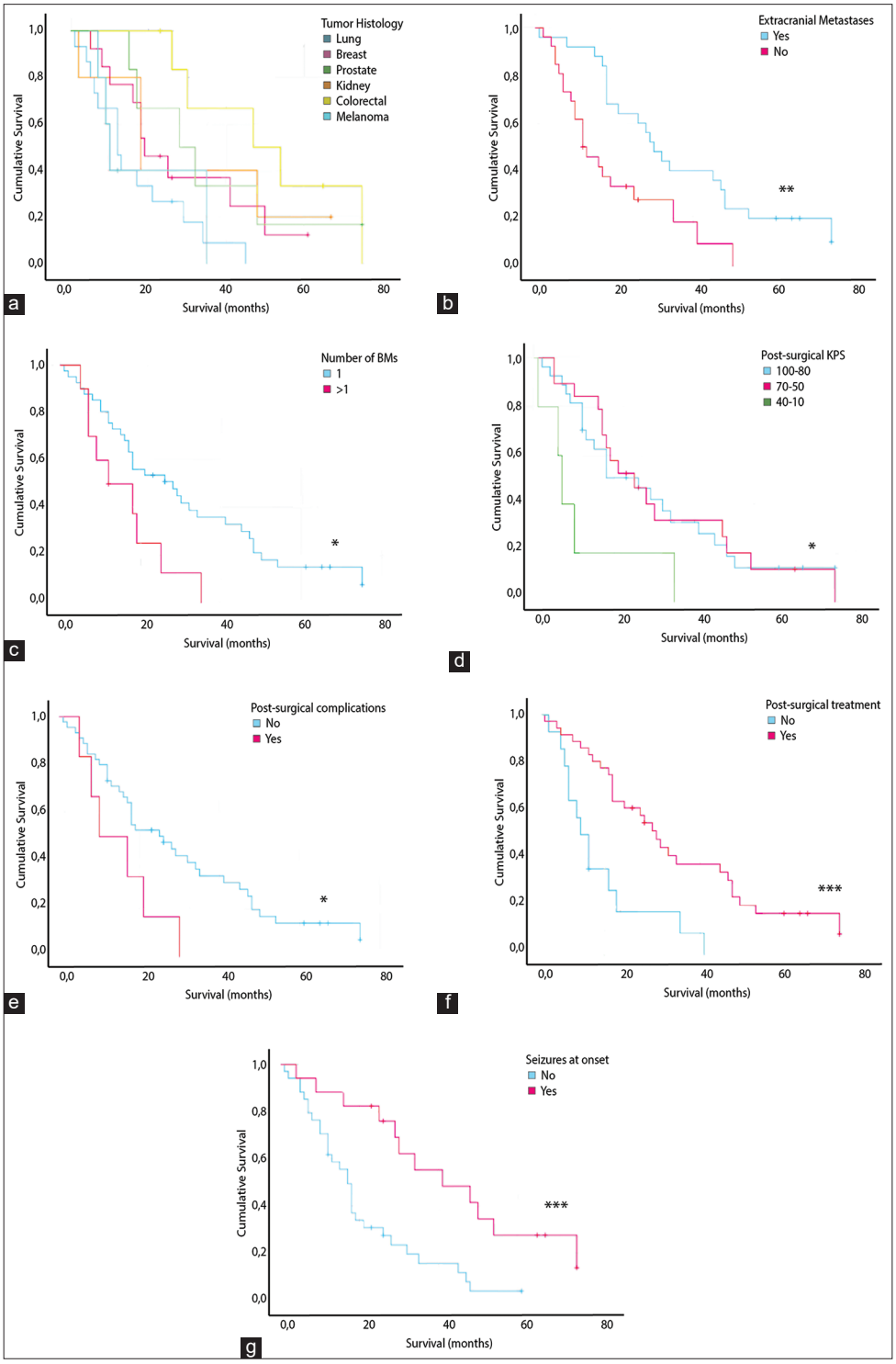

Figure 2: Kaplan–Meier curves with a statistically significant log-rank test of OS stratified by (a) primary histology, (b) presence of extracranial metastases (**), (c) number or BMs (*), (d) post-surgical KPS (*), (e) presence of post-surgical complications (*), (f) post-surgical treatment (***), (g) presence of seizures at the clinical onset (***).

particular focus on the role of seizures at the clinical onset. In our cohort, the absence of extracranial metastases, a single instead of multiple BMs, a higher postoperative KPS, the absence of postoperative complications, and

the administration of an adjuvant treatment positively affected patients' OS. While these results agree with the literature,[3,16,24,31] it was found that patients with colorectal cancer and prostate cancer were those with the longest OS differently from other studies. On the other hand, melanoma and lung cancer were confirmed as metastatic neoplasms with a very poor prognosis.[9,24]

Our study highlighted the prognostically favorable role of a clinical onset with epileptic seizures. This result can be interpreted as an epileptic seizure representing a striking clinical event that requires immediate diagnostic-therapeutic intervention, and therefore, it is capable of identifying BMs hitherto unknown and silent. The percentage of patients with onset seizures was 33.3%, higher than the mean percentage of 15% found in the literature.[1,12] This discrepancy can be explained by patients' selection as they were all surgically treated, and surgery is usually reserved for symptomatic patients, whereas those reported in the literature are predominantly patients diagnosed with BMs during oncological follow-up and in a relatively stable and symptomless clinical status. This is further supported by the high percentage of patients with synchronous BMs showing seizures as the clinical onset in our specimen. The timing of BM diagnosis did not affect patients' OS, possibly because, in the presence of BMs, primary tumor aggressiveness may be comparable between *de novo* tumors and those that had already been diagnosed and treated. However, the heterogeneous primary tumor landscape and the small sample size of the present study hinder drawing a firm conclusion.[17] It was also analyzed how the genesis of the epileptic seizures is influenced by BMs localization, and it was confirmed the well-documented data that the temporal localization correlates the most with the presence seizures at the clinical onset. Interestingly, the occipital localization was also highly correlated to seizures, as in a few other studies.[10,33] Other studies showed that, on one side, lung cancer produces the most epileptogenic BMs, whereas, on the other side, breast cancer produces the least epileptogenic BMs. In the present study, the primary tumor histology was not a factor related to the presence of epilepsy at clinical onset.[32] The lack of association between these two factors in our results is likely due to the small sample of patients examined. In this study, the pre-surgical KPS score showed a statistically significant association with epileptic seizures at onset, as reported in the scientific literature.[33] However, these data need further investigation with a larger series for a correct interpretation. Finally, the extent of peritumoral edema, expressed as the edema index, showed a statistically significant correlation to the development of preoperative epileptic seizures.[6] This could be explained by epilepsy pathogenesis secondary to BMs, which is known to be due to changes in the peritumoral microenvironment with alterations in the membrane flux of sodium and calcium, as well as in the metabolism of neurotransmitter amino acids with an imbalance between excitatory and inhibitory mediators.

CONCLUSION

The presence of BMs in the clinical history of an oncological patient usually represents a decisive moment for the patient's prognosis and implies an accurate multidisciplinary assessment for the choice of the best therapeutic path. In this regard, identifying key prognostic factors becomes essential for choosing the best therapeutic strategy personalized to each patient. Despite being a single-center experience with a relatively small sample size, our study confirms most of the positively related prognostic factors in BM patients reported in other series. Moreover, it shows a prognostically favorable role of seizures as they promoted an earlier BM diagnosis and timelier therapeutic management that resulted in longer OS in surgically treated patients. On one side, the time of BM diagnosis should not condition too much surgical decision-making in BM patients as it did not impact patients' OS. On the other side, it should be valued that BM resection may help in preventing seizure development or in their resolution with important improvements in patients' quality of life and help in the better definition of the systemic disease, which may result in different or additional therapeutic implications.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Ottaviani MM, Fasinella MR, Di Rienzo A, Gladi M, di Somma LGM, Iacoangeli M, *et al*. Analysis of prognostic factors and the role of epilepsy in neurosurgical patients with brain metastases. Surg Neurol Int. 2024;15:79. doi: 10.25259/SNI_735_2023