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SURVIVAL ANALYSIS IN PATIENTS WITH BRAIN METASTASES: A RETROSPECTIVE CASE SERIES

ANÁLISE DE SOBREVIDA EM PACIENTES COM METÁSTASES CEREBRAIS: UMA SÉRIE DE CASOS RETROSPECTIVA

ANÁLISIS DE SUPERVIVENCIA EN PACIENTES CON METÁSTASIS CEREBRALES: UNA SERIE DE CASOS RETROSPECTIVE

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ABSTRACT

Objective: The objective of this study was to analyze medical data from patients diagnosed with brain metastasis, to determine which factors influence patient survival.

Methods: The medical data used in this retrospective study ranges from 2018 to 2021. The medical records of patients diagnosed with brain metastasis were obtained from a reference hospital in the interior of São Paulo, Brazil. After data acquisition, survival analyses were performed, including the Log-Rank test, Kaplan-Meier survival curves, and Cox proportional hazards regression, using a significance level of 5%.

Results: Gender, age, primary tumor, number of brain metastases, size of brain metastases, location of brain metastases, extra-brain implantation site and treatment of brain metastasis were analyzed. Both univariate and multivariate analysis found significant variation in survival when correlating the number of brain metastases and whether patients underwent neurosurgery.

Conclusion: Patients with more than three brain metastases brain had shorter survival compared to those with three or fewer ($p = 0.018$), indicating a better prognosis for patients with a single metastasis or fewer lesions. Additionally, patients who underwent neurosurgery demonstrated longer survival compared to those who did not ($p = 0.037$) suggesting that surgical intervention is associated with improved prognosis in appropriately selected patients.

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Keywords: Brain Metastases. Treatment. Survival.

RESUMO

Objetivo: O objetivo deste estudo foi analisar dados médicos de pacientes diagnosticados com metástase cerebral, a fim de determinar quais fatores influenciam a sobrevida dos pacientes.

Métodos: Os dados médicos utilizados neste estudo retrospectivo abrangem o período de 2018 a 2021. Os prontuários de pacientes diagnosticados com metástase cerebral foram obtidos de um hospital de referência no interior de São Paulo, Brasil. Após a aquisição dos dados, foram realizadas análises de sobrevida, incluindo o teste de Log-Rank, curvas de sobrevida de Kaplan-Meier e regressão de riscos proporcionais de Cox, utilizando nível de significância de 5%.

Resultados: Foram analisados: sexo, idade, tumor primário, número de metástases cerebrais, tamanho das metástases cerebrais, localização das metástases cerebrais, local de implantação extracraniana e tratamento da metástase cerebral. Tanto a análise univariada quanto a multivariada identificaram variação significativa na sobrevida ao correlacionar o número de metástases cerebrais e a realização de neurocirurgia.

Conclusão: Pacientes com mais de três metástases cerebrais apresentaram menor sobrevida em comparação àqueles com três ou menos ($p = 0.018$), indicando melhor prognóstico para pacientes com metástase única ou menor número de lesões. Além disso, pacientes submetidos à neurocirurgia demonstraram maior sobrevida em comparação aos que não foram operados ($p = 0.037$), sugerindo que a intervenção cirúrgica está associada a melhor prognóstico em pacientes adequadamente selecionados.

Palavras-chave: Metástases Cerebrais. Tratamento. Sobrevida.

RESUMEN

Objetivo: El objetivo de este estudio fue analizar datos médicos de pacientes diagnosticados con metástasis cerebral, con el fin de determinar qué factores influyen en la supervivencia de los pacientes.

Métodos: Los datos médicos utilizados en este estudio retrospectivo abarcan el período de 2018 a 2021. Las historias clínicas de pacientes diagnosticados con metástasis cerebral se obtuvieron de un hospital de referencia en el interior de São Paulo, Brasil. Tras la recopilación de los datos, se realizaron análisis de supervivencia, incluyendo la prueba de Log-Rank, las curvas de supervivencia de Kaplan-Meier y la regresión de riesgos proporcionales de Cox, utilizando un nivel de significancia del 5%.

Resultados: Se analizaron el sexo, la edad, el tumor primario, el número de metástasis cerebrales, el tamaño de las metástasis cerebrales, la ubicación de las metástases cerebrales, el sitio de implantación extracraneal y el tratamiento de la metástasis cerebral. Tanto el análisis univariado como el multivariado identificaron variación significativa en la supervivencia al correlacionar el número de metástasis cerebrales y la realización de neurocirugía.

Conclusión: Los pacientes con más de tres metástasis cerebrales presentaron menor supervivencia en comparación con aquellos con tres o menos ($p = 0.018$), lo que indica un mejor pronóstico para pacientes con una sola metástasis o con menor número de lesiones. Además, los pacientes sometidos a neurocirugía demostraron mayor supervivencia en comparación con quienes no fueron operados ($p = 0.037$), lo que sugiere que la intervención quirúrgica se asocia con un pronóstico más favorable en pacientes adecuadamente seleccionados.

Palabras clave: Metástasis Cerebrales. Tratamiento. Supervivencia.

1 INTRODUCTION

Metastasis is a process characterized by the proliferation of cells from an initial cancer beyond its origin, resulting in their separation from the primary tumor. This dissemination occurs through the lymphatic and hematogenous systems1.

Brain metastases represent a significant clinical challenge. The incidence rate of brain metastases exceeds the combined incidence of all types of primary intracranial tumors2. Additionally, they are also responsible for 25% of deaths in individuals diagnosed with malignant neoplasms 3. The most common primary tumors associated with brain metastases include lung carcinoma (25-30%), breast carcinoma (22-25%), melanoma (11%), and renal carcinoma (<5%)4. Most diagnoses occur at an advanced stage, with 90% of cases identified based on the onset of neurological symptoms5.

Recent advances in the management of brain metastases have highlighted the importance of early diagnosis and intervention. Recent studies focused on brain metastases originating from endometrial cancer demonstrate that early diagnosis and treatment, involving surgical resection and whole-brain radiation, can significantly extend survival prognosis beyond 24 months6–8. Similarly, a German study showed that early diagnosis of brain metastases in women with primary breast carcinoma is associated with improved prognosis and prolonged survival 9.

Given the aggressive nature and clinical complexity of brain metastases, this study aims to evaluate how intrinsic patient factors — including age, primary tumor type, number of brain metastases, and others — influence patient survival. Furthermore, the study assesses the impact of different therapeutic strategies on clinical outcomes. By analyzing these variables, this research seeks to improve patient stratification and guide treatment decisions, ultimately enhancing survival predictions and optimizing therapeutic approaches.

2 METHODS

This is an observational, cross-sectional retrospective case series study. Data were collected from a reference heathcare facility located in the interior of São Paulo, Brazil following approval from the Ethics Committee of the University of Taubaté (UNITAU). Medical records from patients diagnosed with brain metastases between 2018 to 2021 were reviewed. No additional inclusion or exclusion criteria for patients included in the study. Data collection was conducted by research team between November 2021, December 2021 and January 2022.

The study included medical records of patients diagnosed with cancer in the lung, breast, unknown primary tumor, melanoma, kidney, endometrial, colon, ovarian, and womb, who had a confirmed diagnosis of brain metastases through histological and imaging findings, including computed tomography and magnetic resonance imaging.

Patients were evaluated for the following variables: (1) age, (2) gender, (3) primary tumor type, (4) location of brain metastases, (5) date of primary tumor diagnosis, (6) number of brain metastases, (7) size of brain metastasis, (8) date of brain metastasis diagnosis; (9) treatment of brain metastasis; (10) location of extracranial metastases and (11) date of death. The number of brain metastases corresponded to the number of metastatic lesions identified on imaging. Similarly, the location of brain metastases referred to the anatomical regions within the brain where the metastases were situated. The size of the brain metastases was extracted from the tomography reports available for consultation in the same electronic medical record system. Patients with substantial missing data — defined as having more than five out of the eleven variables unavailable — were excluded to ensure the reliability of the statistical analysis. It is acknowledged that this exclusion criterion may introduce selection bias, potentially excluding patients with more severe clinical conditions or distinct prognostic features.

The collected data were subjected to descriptive analysis and statistical analysis using Jamovi 2.3.28 and SPSS 25, with a significance level set at $\alpha = 0.05$. Descriptive statistics were used to summarize the characteristics of the sample. The Kaplan-Meier method was employed to estimate survival probabilities over time. The Log-Rank test was applied to compare survival distributions between groups, with p-values < 0.05 considered statistically significant. To evaluate the effect of multiple covariates on survival, a Cox proportional hazards regression model was performed to identify independent prognostic factors while adjusting for potential confounders.

3 RESULTS

Table 1 provides a descriptive analysis of the data collected for each study variable. For each variable, it is possible to observe the frequency of responses, the total number of valid responses, and the corresponding percentage.

Table 1

Descriptive Analysis of the Observed Variables

	Survival (months)	

Variables		Mean	Max	Min	Score	Total	%	
Age	<50	6,1	18	1	18	92	19.6	%
	>65	6,4	16	1	28	92	30.4	%
	50-65	7,4	24	1	46	92	50.0	%
Gender	Female	5,4	17	1	65	92	70.7	%
	Male	9,4	24	1	27	92	29.3	%
Type of primary tumor	Breast	5,0	17	1	33	92	35.9	%
	Lung	8,3	22	1	36	92	39.1	%
	Unknown primary tumor	2,2	4	1	7	92	7.6	%
	Others	8,8	17	1	16	92	17.4	%
Local of brain metastases	Supratentorial	7,2	24	1	50	82	61.0	%
	Supra and Infratentorial	7,0	17	1	24	82	29.3	%
	Infratentorial	2,5	4	1	8	82	9.8	%
Number of brain metastases	1	9,9	18	2	26	80	32.5	%

	2	7,3	22	1	28	80	35.0	%
	3	4,3	12	1	15	80	18.8	%
	4	4,0	9	1	5	80	6.3	%
	>5	2,0	3	1	6	80	7.5	%
Size of brain metastases	<30mm	8,7	18	1	27	41	65.9	%
	30-60mm	6,8	21	1	11	41	26.8	%
	>60mm	12,5	24	1	3	41	7.3	%
Implemented treatment	QT + RT + NS	7,5	18	1	35	83	42.2	%
	QT + RT	4,8	16	1	31	83	37.3	%
	RT + NS	13,8	24	1	14	83	16.9	%
	RT	4,0	7	2	3	83	3.6	%

QT: chemotherapy; RT: radiotherapy; NS: neurosurgery; "Others" represent a wide range of tumors, such as melanoma, ovarian, endometrial and kidney.

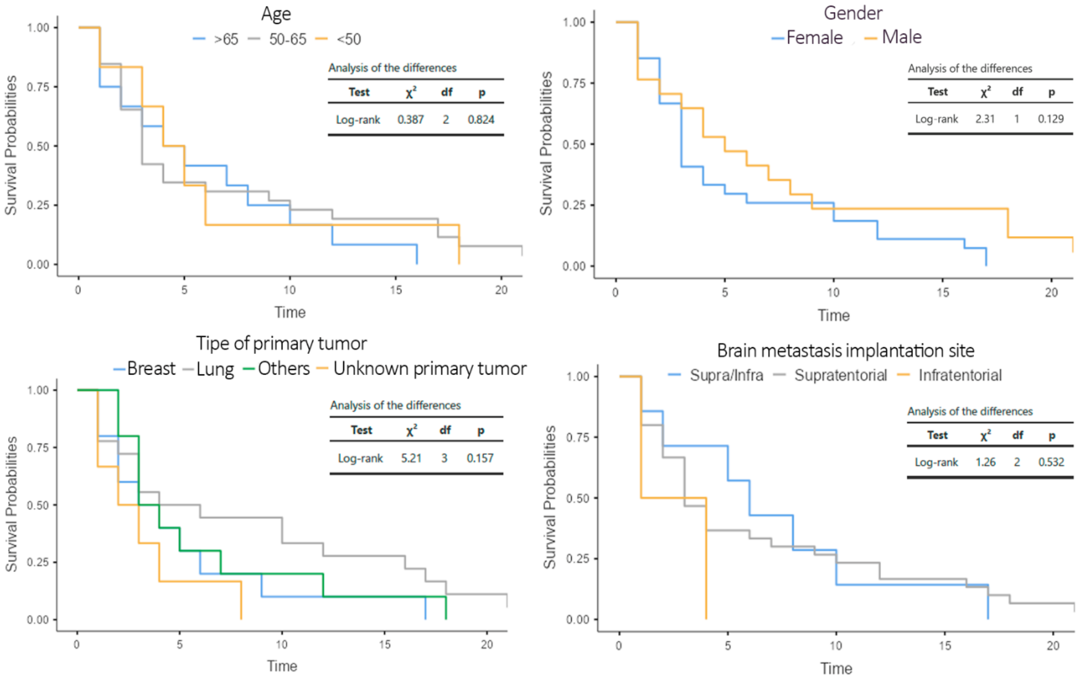
Figure 1 illustrates the overall survival curve, along with survival curves stratified by gender, number of implantations, number of brain metastases, presence of extracranial metastases, primary tumor type and location of brain metastases. The mean survival time was 6.34 months, with a 95% confidence interval (CI) ranging from 4.481 to 8.20 months. Due to the cross-sectional nature of the study, the date of death was not recorded for 48 out of the 92 patients included.

Using the Log-rank test and the Kaplan-Meier survival analysis — statistical methods that assess whether significant differences in survival exist between groups —the study found that the variables age (p=0.824), gender (p=0.129), type of primary tumor (p=0.157) and location of brain metastases (p=0.532), were not statistically significant predictors of survival (p > 0.05).

In contrast, both the number of brain implantations (p=0.018) and the treatment modality (p=0.037) were found to be statistically significant factors affecting survival.

Figure 1

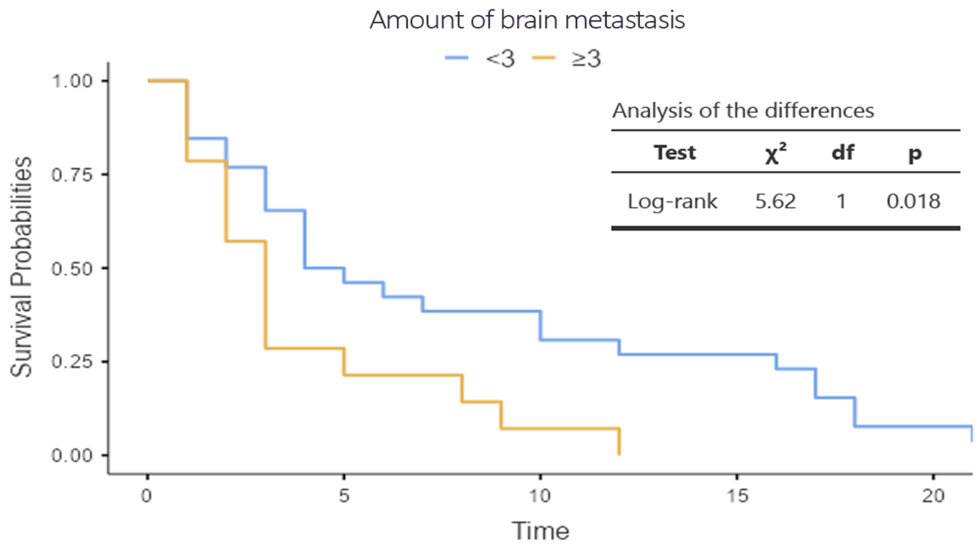
Survival Curves According to Non-significant Variables



The Kaplan-Meier curve presented in Figure 2 compares the survival probabilities between patients with fewer than three brain metastases (<3) and those with three or more metastases (≥3). The test resulted in a value of 0.018, indicating that the difference between the groups is statistically significant (p < 0.05). This finding suggests that patients with a higher number of brain metastases have a significantly shorter survival time.

Figure 2

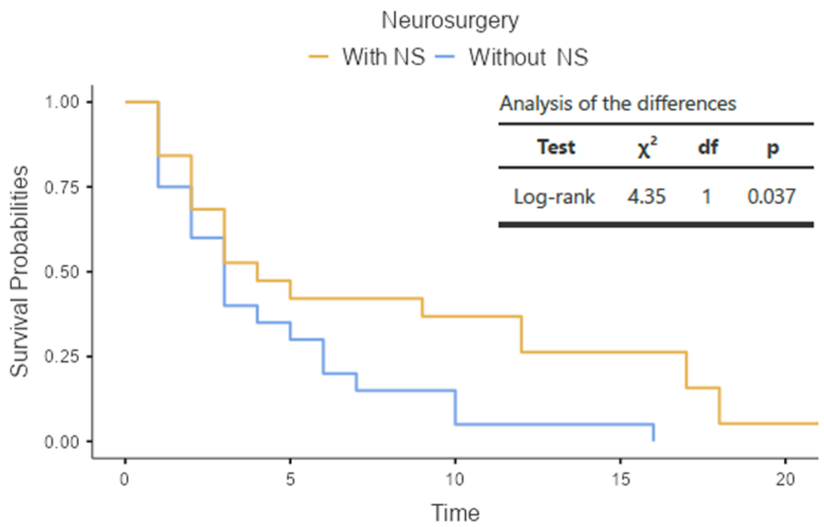
Correlation Between Survival Rate and Number of Brain Metastasis



Continuing the survival analysis, the curve shown in Figure 3 demonstrates that patients who underwent neurosurgery had a higher probability of survival over time. The Log-Rank test indicated a statistically significant difference between the groups ($p = 0.037$), suggesting that neurosurgery is associated with improved survival outcomes.

Figure 3

Relationship Between Implemented Treatment and Survival. "With NS" refers to neurosurgery combined with chemotherapy and/or radiotherapy, while "Without NS" refers to chemotherapy combined with radiotherapy or radiotherapy alone



The Cox regression analysis identified two variables that influenced patient survival. The number of brain metastases was independently associated with an increased risk of mortality (HR = 3.506, 95% CI [1.268 – 9.698], p = 0.016). Additionally, the treatment modality was significantly associated with a reduced risk of death (HR = 0.362, 95% CI [0.142 – 0.927], p = 0.034), indicating a protective effect. Other variables — including age, gender, primary tumor type, and location of brain metastases — did not show statistically significant associations with survival.

Table 2

Cox Regression Analysis Results

Variable	B (Coef.)	HR (Exp(B))	95% CI for HR	p-value
Age	-0.282	0.754	[0.432 – 1.318]	0.322
Gender	-0.064	0.938	[0.347 – 2.538]	0.900
Primary tumor	0.117	1.124	[0.624 – 2.026]	0.697
Local of brain metastasis	0.348	1.416	[0.611 – 3.281]	0.417
Number of brain metastasis	1.255	3.506	[1.268 – 9.698]	0.016
Treatment (Neurosurgery)	-1.016	0.362	[0.142 – 0.927]	0.034

4 DISCUSSION

Variables such as gender (p = 0.012), age (p = 0.082), location of brain metastases (p = 0.532), and lesion size (p = 0.15) did not show statistical significance in relation to survival in the present study. This may be attributed to methodological limitations, including a relatively small sample size and the unequal group distribution. In the case of gender, although the mean survival was higher among women, the female predominance may have reduced the power to detect real differences. Age, in turn, may not have independently influenced the prognosis in relation to more relevant clinical factors, such as the number of metastases and type of treatment. The impact of location may have been attenuated by the effects of effective therapeutic interventions, such as neurosurgery and radiotherapy, reducing its isolated prognostic value. Factors such as tumor volume, presence of edema, and clinical manifestations resulting from the location may have a more direct impact on the patient's clinical evolution than the isolated location of the lesion. The size of the lesions did not demonstrate statistical relevance, which can be explained, in part, by the small number of patients with metastases greater than 60 mm (7.3%), which makes comparison between groups difficult.

In the present study, mean survival was foinversely proportional to the number of brain metastases, ranging from 9.9 months for patients with a single implantation and 2 months for those with more than five lesions. Additionally, a statistically significant difference in survival was observed when comparing patients with fewer than three brain metastases to those with three or more (p = 0.037). These findings are consistent with previous studies, similarly, demonstrated that patients with single brain metastasis experience longer survival than those with multiple lesions. Shao et al. found significance for the number of implantations implying survival in the same number of implantations in the present study, with 3 or more implantations representing a worse prognosis compared to 1 or 2 implantations in both groups followed by the study (p = 0.0087 and 0.037)10. Knoll et al. found a median of 10.8 months for fewer than 4 implantations and 8.5 for 5 or more implantations11, demonstrating a longer survival time with fewer implantations. However, after adjusting for factors such as systemic disease status and clinical performance status, the number of metastases was not an independent predictor of survival. In the study by Rosati et al., it was seen that patients with single brain metastases had a median survival of 11.9 months, while those with more than three lesions had a median of 5.1 months (p = 0.001). However, this variable also did not remain significant in the multivariate analysis12. Although other studies have not found significance in the multivariate analysis, we believe that the number of metastatic implantations is a determining factor for survival. This occurs because multiple metastases have a greater ability to compress the brain, causing more complications to the patient13.

One possible explanation for the number of brain metastases being significant in the multivariate analysis of the study in question, but not in others, may be the way in which the variables were controlled. In this study, the number of metastases was not suppressed in the multivariate analysis. In other studies, the number of metastases often loses significance when adjusted for factors such as functional status, extracranial control, and total tumor burden, which are possibly more directly related to survival. As in our study, other studies also found multiple brain metastasis representing the majority of cases14,15. This observed survival difference between patients with a single lesion and those with multiple metastases highlights the importance of considering the number of brain metastases as a key criterion for prognostic stratification. This distinction may inform treatment decisions, favoring more aggressive interventions, such as surgical resection, in cases of solitary metastasis, whereas patients with multiple lesions may be better suited for palliative or systemic therapies.

Another aspect analyzed in our research concerns the impact of treatment on patient's outcomes. As shown in Figure 3, greater survival was found for patients who underwent neurosurgery compared to those who did not (p = 0.037). The findings of the present study align with the current literature, indicating that neurosurgical resection of brain metastases, particularly when combined with radiotherapy and chemotherapy, is associated with a significant increase in survival. The median survival of 12.5 months in patients treated with surgery, chemotherapy and radiotherapy exceeded that observed in the groups without surgical intervention (4.9 and 6.6 months). These results are consistent with previous studies, such as those by Niedermeyer et al. (12 months)[16] and Enders et al. (11.2 months)[17], which similarly identified survival benefits when surgery was combined with radiotherapy. The statistical analysis of this study confirmed the protective effect of neurosurgery (HR = 0.362; p = 0.034), corroborating findings from other studies that associate complete surgical resection and good functional status with improved prognosis. The variation in median survival times reported in different studies may be attributed to sample heterogeneity, including differences in baseline functional status (Karnofsky Performance Status — KPS), extracranial disease control. The present study attributes these survival benefits to the favorable prognosis typically observed in patients who are candidates for neurosurgery. These findings reinforce the central role of neurosurgery in the management of brain metastases, particularly when integrated into multimodal treatment strategies.

Few studies demonstrate opposition to the previously described benefits of neurosurgery. When filtering recent articles, it was seen that Kim et al. found a non-significant difference in overall survival between the groups undergoing or not undergoing neurosurgery (12.1 months vs. 10.2 months; p=0.550). However, in addition to the limited selection of patients (n=36), most surgical patients had multiple metastases (55%) and performance status (KPS) <70 (27%), which compromises the potential benefit of surgery[18].

The observed relationship between surgery and improved survival suggests that, when appropriately indicated, neurosurgery can significantly enhance prognosis. Neurosurgery intervention plays a critical role in the treatment of brain metastases, particularly in cases of single lesion[13,19]. In contrast, patients with multiple brain metastases are typically managed with chemotherapy and radiotherapy. In these situations, surgery is generally not feasible due to the limited accessibility of tumors and the generally poorer prognosis of these patients compared to those eligible for surgical intervention[13].

An essential step in the management of patients with brain metastases is a comprehensive prognostic evaluation to guide therapeutic decision-making, balancing clinical benefits with potential risks. Key prognostic factors that should be considered include patient age, the number of brain metastases, the status of extracranial disease, and functional status as measured by the Karnofsky Performance Scale (KPS); Among these, the present study was able to evaluate age and the presence of single versus multiple brain metastases. Patients with favorable prognostic indicators are likely to benefit from a wider range of therapeutic options, ultimately resulting in improved survival outcomes.

This study has several limitations that should be acknowledged. As a retrospective analysis, it is subject to inherent biases, including selection bias and potential confounding variables, despite attempts to adjust for them statistically. Furthermore, data were obtained from a single institution, which may limit the generalizability of the findings to other populations. Differences in clinical management protocols, treatment availability, and follow-up procedures across institutions may further impact the external validity of these results. Future prospective studies involving larger and more diverse patient populations are warranted to validate these findings and mitigate potential biases.

5 CONCLUSION

The data presented reinforce the correlation between the number of brain metastases and patient survival ($p = 0.018$). This finding aligns with previous studies that also demonstrated longer survival among patients with single brain metastases. Furthermore, patients who underwent neurosurgery exhibited improved survival over time compared to those who did not undergo the procedure ($p = 0.037$). Although some studies have not found any benefit with neurosurgery, the present study suggests that patients with fewer brain metastases and better operative status benefit from surgical interventions.

For future research, prospective clinical trials are recommended to validate these findings and mitigate potential selection biases. Additionally, further studies should investigate the benefits of neurosurgery across different patient subgroups. Exploration of other prognostic factors — beyond the number of brain metastases — such as molecular markers and the interplay between systemic and surgical treatments, may provide valuable insights for enhancing the clinical management of patients with brain metastases.

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