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Multiplicity does not significantly affect outcomes in brain metastasis patients treated with surgery

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Abstract

Background. Brain metastasis quantity may be a negative prognostic factor for patients requiring resection of at least one lesion.

Methods. We retrospectively reviewed patients who underwent surgical resection of brain metastases from July 2018 to June 2019 at our institution, and examined outcomes including overall survival (OS), progression free survival (PFS), and rates of local failure (LF). Patients were grouped according to the number of metastases at the time of surgery (single vs multiple).

Results. We identified 130 patients who underwent surgical resection as the initial treatment modality. At the time of surgery, 87 patients had only one lesion (control) and 43 had multiple (>1). Two-year OS for the entire cohort was 46%, with equal rates in both the multiple metastases group and the control group ($P = .335$). 2-year PFS was 27%; 21% in the multiple metastases group and 31% in the control group ($P = .766$). The rate of LF at 2 years was 32%, with equal rates in both the multiple lesion group and control group ($P = .889$). On univariate analysis, multiplicity was not significantly correlated to OS (HR = 0.80, 95% CI: 0.51–1.26, $P = .336$), PFS (HR = 1.06, 95% CI: 0.71–1.59, $P = .766$) or LF (HR = 1.06, 95% CI: 0.57–1.97, $P = .840$). Multivariate analysis revealed preoperative tumor volume of the resected lesion to be the single correlate for OS ($P = .0032$) and PFS ($P = .0081$).

Conclusions. Having more than one metastasis does not negatively impact outcomes in patients treated with surgery. In carefully selected patients, especially those with large tumors, surgery should be considered regardless of the total number of lesions.

Key Points

- Multiplicity does not affect survival time or local failure.
- High postoperative functional status correlates with prolonged survival.
- Preoperative volume of the resected lesion influences patient survival.

Brain metastases are the most common adult intracranial neoplasm, comprising more than 30% of all brain tumors.[1] They occur in 10–30% of cancer patients,[2] with an increasing incidence in recent decades due to advances in cancer treatment and more widespread brain imaging. Most brain metastases develop from lung cancer, breast cancer and colorectal cancer,

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Importance of the Study

Multiplicity is considered a negative prognostic factor for patients with brain metastases. There is no consensus regarding surgical management of patients with more than one intracranial metastasis. We retrospectively reviewed our single-center experience and discovered that multiplicity at the time of surgical intervention did not affect overall survival, progression free survival, or the rate of local failure. On the other hand, higher postoperative functional status correlated with longer survival, highlighting the importance of neurological function preservation. A survival benefit was identified in patients who underwent resection of large intracranial metastases. We advocate for resection of large intracranial metastases in carefully selected patients, regardless of the total number of lesions discovered at the time of diagnosis.

melanoma and renal cell carcinoma, with more than 5% of cases being secondary to a primary tumor of unknown origin.[2] Patients may present with symptoms of elevated intracranial pressure including headache, nausea, and vomiting, or neurological deficits including paresis, seizures, or cognitive changes which may significantly affect quality of life.[3]

Brain metastases are associated with a limited life expectancy,[4,5] with almost half of these patients dying from advanced systemic cancer.[6,7]The primary goal of treatment is to control both local and widespread metastatic disease progression, while maintaining or improving quality of life. This may be achieved via a combination of multiple treatment modalities including surgery, radiation therapy, chemotherapy, and more recently targeted and immune therapies. Recent advances in targeted systemic therapies and immunotherapy, combined with a more aggressive multidisciplinary management strategy, have allowed better symptom control and increased OS for patients with brain metastases.[8,9]

Among the available treatment modalities for brain metastasis, surgery offers several unique advantages. It provides histological diagnosis when needed, alleviates intracranial mass effect, facilitates seizure control and recovery of neurologic deficits, and reduces the necessity for long-term steroid use. Surgical resection is the cornerstone treatment for patients with a single, accessible brain metastasis, with proven survival benefits.[10–12] However, 80% of the patients with metastatic disease in the brain have more than one tumor at diagnosis and up to 50% have three or more brain metastases.[3] After resection, the median survival time of patients with a single brain metastasis averages about 1 year, whereas for patients with multiple lesions it is approximately 6–12 months.[3,13–15] The presence of multiple metastases is considered a negative prognostic factor,[16,17] and operating on patients with multiple metastases is therefore rare, and often considered palliative for patients with lesions that are immediately threatening due to their size, location, or associated symptoms. To date, there is no consensus with regard to the role for surgery for patients with multiple brain metastases.[18,19] We retrospectively reviewed our experience with surgical management for patients with brain metastases with the goal of examining the impact of multiplicity (>1), at the time of surgical intervention, on patient outcomes, including survival time and local failure.

Methods

We retrospectively identified all brain metastasis patients who underwent surgical resection of one or more lesions at our center from July 1, 2018 to Jun 30, 2019, from a prospectively-collected registry database. Ethical approval was obtained from the institutional review board. All cases were discussed at our multidisciplinary brain metastasis clinic with representatives from neurosurgery and radiation oncology. Postoperatively, all patients underwent adjuvant stereotactic radiation surgery (SRS), either single-fraction SRS (SF-SRS) or fractionated SRS (F-SRS) using a Gamma Knife Radiosurgery Unit (Elekta AB). Generally, adjuvant SRS was performed 2–4 weeks after surgery to the cavity with 1–3 fractions. Dose and fractionation were determined according to our institutional policies and at the discretion of the treating radiation oncologist for SF-SRS $\leq$ 4 cc: 21Gy, 4–10 cc: 18 Gy, >10 cc: 15 Gy. F-SRS was delivered utilizing the ICON frameless system, with the following dosing: 4–8 cc: 27 Gy/3, 8–22 cc: 24 Gy/3, 22–60 cc: 21 Gy/3. Every treatment was prescribed to a median isodose line of 50% (range 40–60) with a tumor volume coverage >98%. Each SRS plan was reviewed and approved by a radiation oncologist, a neurosurgeon, and two physicists.

Patients who underwent radiation therapy without surgical intervention were excluded. All patients underwent postoperative magnetic resonance imaging (MRI) of the brain every three months to monitor disease progression during the course of follow up, or at the time of suspected disease progression or neurological deterioration. All patients were followed till death, last follow up, or Apr 15, 2021 for those still alive.

The following variables were collected: age, gender, histology of the primary tumor, time interval between the diagnosis of primary tumor and the development of cerebral lesions, control of systemic disease, number and location of brain metastases, adjuvant radiation therapy, preoperative volume of the resected lesion, and the largest diameter of the resected tumor. Preoperative tumor dimensions were obtained in millimeters and then calculated in cubic centimeters. We collected quality of life measures including the preoperative and postoperative Karnofsky performance status (KPS) score and postoperative Eastern Cooperative Oncology Group (ECOG) performance status

prior to receiving adjuvant radiation therapy. Graded Prognostic Assessment (GPA) score[20] was also collected.

Our outcome measures included overall survival (OS), progression free survival (PFS), and rate of local failure (LF). For each, the time was calculated in years from the date of surgery. OS was calculated to the date of death or last follow up. PFS represented the time to radiographic progression at original site of operation or with occurrence or progression of distant intracranial metastases, clinical deterioration secondary to neurological decline, death, or last follow up. Local failure was defined as radiographic recurrence or progression at the site of original operation, and calculated based on MRI dates, last follow up, or death.

For data analysis, the number of brain metastases at the time of surgical intervention was dichotomized (single vs multiple). Survival (OS and PFS) analysis was done using the Kaplan–Meier method and the difference between the groups was tested using the Cox proportional hazards model. The rate of local failure was calculated using the cumulative incidence method and the difference between groups was tested using the Fine-Gray competing risk model. Multivariate survival analysis was also used to assess independent predictors of outcome (OS, PFS, and LF). Throughout the analysis, we took $P < .05$ to represent statistical significance.

Results

We identified 130 patients who underwent surgical resection as the initial treatment modality of at least one brain metastasis. The median age at the time of surgery was 61.5 years. There were 71 female patients (55%), and 59 male patients (45%). The most common primary tumors of origin were lung (39%), melanoma (18%), breast (12%), and gastrointestinal (GI) (12%) (Table 1).

Patients were dichotomized by the number of brain metastases for the purpose of comparative analysis: those with multiple (>1) lesions ($n = 43$) lesions and those with a single lesion ($n = 87$) for comparison. 90% of our patients underwent resection of a brain metastasis >2 cm, with 53% undergoing resection of a lesion >3 cm. All patients underwent resection of a dominant lesion, with the exception of one patient who underwent resection of two lesions at the time of intervention. Gross total resection was achieved in all cases. The majority of patients had high functional status preoperatively, with a median KPS of 90 (range: 20–100) in both the multiple metastases group and the control group ($P = .84$). Our patient cohort maintained a high functional status postoperatively, prior to receiving adjuvant radiotherapy, with a median KPS of 90 (range: 20–100) for the entire cohort, the multiple metastases group, and the control group ($P = .35$). In addition, there was no significant difference in the makeup of primary tumors for the two groups ($P = .99$) (Table 1).

All patients received adjuvant radiation therapy to the surgical cavity and were followed with MRI of the brain at least every three months for surveillance for distant recurrences and local failures. The median preoperative tumor volume was 22.5 cm^3 (range: 1.7–132). The median treatment volume at the surgical cavity was 15.1 cm^3 (range: 4–54). The median prescription dose was 18 Gy (range: 10–27), with 93 patients receiving single fraction and 37 receiving three fractions. The median follow up duration is 1.52 years for all patients and 1.9 years for surviving patients (Table 1).

Median OS for patients with multiple metastases was 1.96 years, compared to 1.66 years for those with a single metastasis. One-year OS was 71%; 67% in patients with multiple brain metastases and 74% in the control group. Two-year OS for the entire cohort was 46%, with equal rates in both groups ($P = .335$, Figure 1A). OS correlated with postoperative ($P = .035$, Figure 1B) but not preoperative KPS ($P = .273$).

One-year PFS was 51%; one-year PFS in the multiple lesions group was 51%, compared to 52% in controls. Two-year PFS for the entire cohort was 27%; 21% and 31% in the multiple lesion and control group respectively ($P = .766$, Figure 2A). PFS correlated to postoperative ($P = .018$; Figure 2B) but not preoperative KPS ($P = .159$).

The 1-year rate of LF was 19%; 16% in the multiple metastases group compared to 20% in the control group. The 2-year rate of LF was 32%, and was equal in both groups ($P = .889$; Figure 3A). Neither pre nor postoperative KPS correlated with the rate of LF ($P = .700$, Figure 3B). Considering that the modality of SRS may also influence rates of local failure, we have further stratified our data based on the number of treatment sessions. The number of metastases at the time of surgical intervention had no effect on rates of local failure in those who received single-fraction SRS ($P = .396$, Supplemental Figure 1A), or fractionated SRS ($P = .564$, Supplemental Figure 1B).

On univariate analysis, multiplicity was not significantly correlated to OS (HR = 0.80, 95% CI: 0.51–1.26, $P = .336$; Figure 1A), PFS (HR =1.06, 95% CI: 0.71–1.59, $P = .766$; Figure 2A) or LF (HR = 1.06, 95% CI: 0.57–1.97, $P = .840$; Figure 3A). Multivariate survival analysis examining tumor number, resected tumor volume, location (supratentorial vs infratentorial), pre and postoperative KPS, GPA score, and prescription dose indicated that resected tumor volume alone correlated to OS ($P = .0032$, Table 2), and PFS ($P = .0081$, Table 3), but not LF ($P = .93$, Supplemental Table 1). Importantly, multiplicity was not a significant predictor of these outcome measures (Tables 2 and 3). GPA score,[20] which classifies patients based on age, KPS, number of brain metastases, and presence of extracranial metastases, was not predictive of OS ($P = .61$) in our multivariate analysis model (Table 2).

There was no perioperative mortality. Neurological morbidity occurred in 4 out 130 patients (3.08%). Three patients had postoperative infection, requiring a washout procedure at two months. One patient experienced delayed hemiparesis and dysphasia.

Discussion

The role for surgery in patients with multiple brain metastases is controversial. We retrospectively reviewed our single-center experience with surgically treated brain metastases in 130 patients who had varying numbers of brain metastases in addition to the lesion that required

Table 1. Patient Demographics of the Studied Cohort

Covariate	*n* = 130
Age at the time of surgery	
Mean (SD)	60.9 (12.4)
Median (Min, Max)	61.5 (23,90)
Gender	
Female	71 (55)
Male	59 (45)
Primary tumor type	
Breast	16 (12)
Gastrointestinal	15 (12)
Genitourinary	11 (8)
Gynecologic	7 (5)
Head and Neck	2 (2)
Lung	51 (39)
Melanoma	24 (18)
Other	1 (1)
Sarcoma	3 (2)
Number of lesions at the time of surgery	
1	87 (67)
2	19 (15)
3	11 (8)
4	8 (6)
5	3 (2)
7	1 (1)
10	1 (1)
Preoperative KPS	
20	2 (2)
50	3 (2)
60	1 (1)
70	22 (17)
80	14 (11)
90	71 (55)
100	17 (13)
Postoperative KPS	
20	2 (2)
50	3 (2)
70	34 (26)
90	65 (50)
100	26 (20)
Postoperative ECOG	
1	66 (51)
2	34 (26)
3	3 (2)
4	2 (2)
Postoperative morbidity	
Nil	126 (97)
Abscess/infection at 2 months	3 (2)
Delayed hemiparesis/dysphasia	1 (1)

Table 1. Continued

Covariate	*n* = 130			
Location of the resected lesion				
Supratentorial	103 (79)			
Infratentorial	27 (21)			
Largest diameter of resected lesion				
1–2 cm	13 (10)			
2–3 cm	48 (37)			
3–4 cm	38 (29)			
4–5 cm	27 (21)			
>5 cm	4 (3)			
Preoperative volume of the resected lesion (cm^3)				
Mean (SD)	33.5 (29.4)			
Median (Min, Max)	22.5 (1.7,132)			
Treatment volume (cm^3)				
Mean (SD)	17 (9.5)			
Median (Min, Max)	15.1 (4,54)			
Total GPA score				
Mean (SD)	2.5 (0.8)			
Median (Min, Max)	2.5 (0,4)			
Prescription dose (Gy)				
Mean (SD)	18.2 (3.6)			
Median (Min, Max)	18 (10,27)			
Fractions				
1	93 (72)			
3	37 (28)			
Length of follow up (years)				
Median (Min, Max)	1.52 (0.1,6.1)			
Covariate	Full Sample (*n* = 130)	1 (*n* = 87)	>1 (*n* = 43)	*P*-value
KPS				.35
Mean (SD)	84.8 (14.5)	85.4 (14.3)	83.5 (15.1)	
Median (Min,Max)	90 (20,100)	90 (20,100)	90 (20,100)	
Preop KPS				.84
Mean (SD)	84.6 (13.5)	84.3 (13.8)	85.3 (13.2)	
Median (Min,Max)	90 (20,100)	90 (20,100)	90 (20,100)	
General tumor type				.99
Breast	16 (12)	12 (14)	4 (9)	
GI	15 (12)	10 (11)	5 (12)	
GU	11 (8)	8 (9)	3 (7)	
Gynecologic	7 (5)	5 (6)	2 (5)	
Head and Neck	2 (2)	1 (1)	1 (2)	
Lung	51 (39)	32 (37)	19 (44)	
Melanoma	24 (18)	16 (18)	8 (19)	
Other	1 (1)	1 (1)	0 (0)	
Sarcoma	3 (2)	2 (2)	1 (2)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GPA, Graded Prognostic Assessment; Gy, Gray; KPS, Karnofsky performance status; SD, standard deviation.

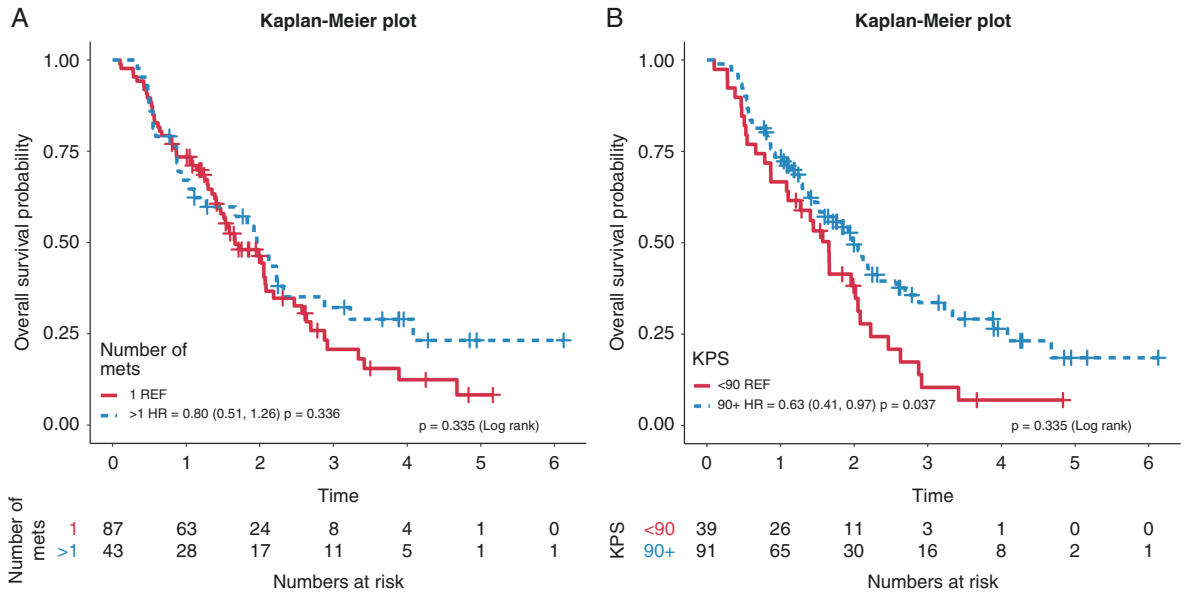

Figure 1. Multiplicity does not reduce overall survival. (A). Multiplicity was not significantly correlated to OS (HR = 0.80, 95% CI: 0.51–1.26, *P* = .336). (B) OS correlated with postoperative (HR = 0.63, 95% CI: 0.41–0.97, *P* = .037, B) KPS.

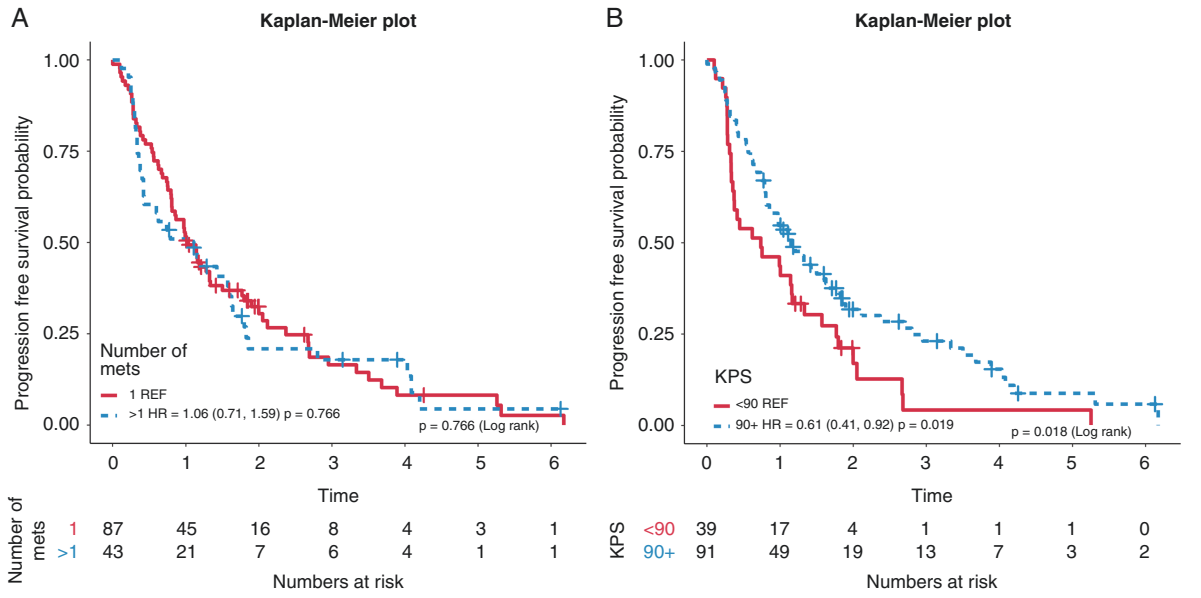

Figure 2. Multiplicity does not reduce progression free survival. (A) multiplicity was not significantly correlated to PFS (HR = 1.06, 95% CI: 0.71–1.59, *P* = .766). (B) PFS correlated to postoperative KPS. (HR = 0.61, 95% CI: 0.41–0.92, *P* = .019).

resection. We did not detect a statistical difference in rates of OS, PFS, or LF when comparing patients with single versus multiple brain metastases. However, higher postoperative functional status (KPS of 90–100) was associated with improved OS and PFS, reflecting the importance of neurologic function preservation following surgical intervention. Finally, our multivariate survival analysis revealed preoperative tumor volume of the resected lesion to be the only independent predictor of patient survival.

Several factors influence prognosis in patients with brain metastases, including age, systemic disease control, time interval between diagnosis of the primary tumor and the development of the brain metastases, number of brain metastases, and KPS score.[21] Surgical resection and SRS

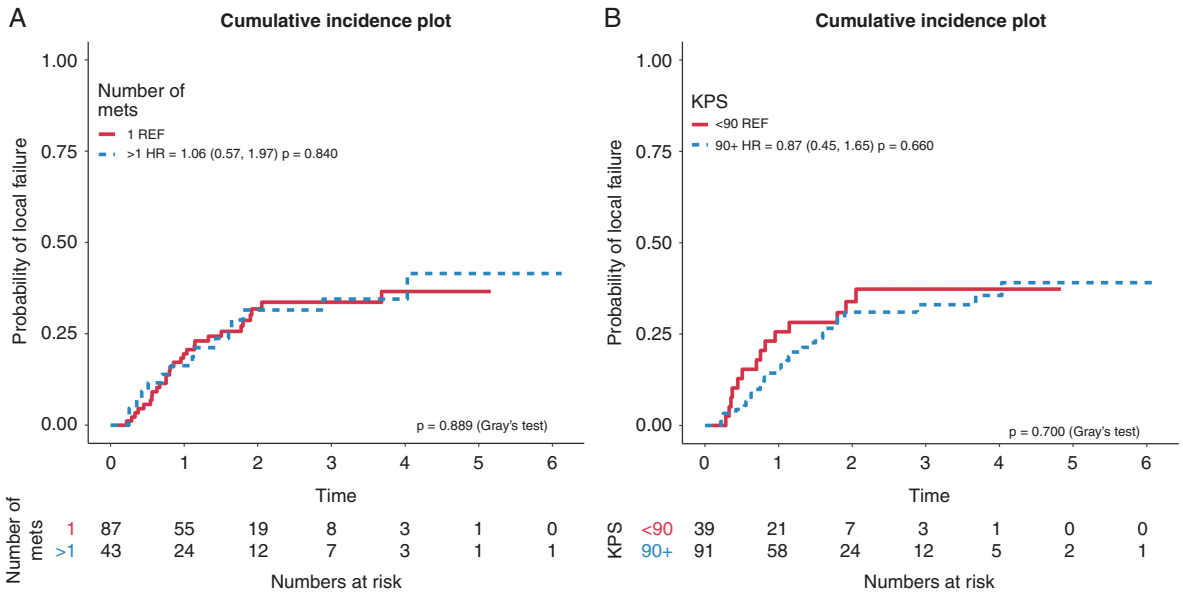

Figure 3. Multiplicity does not affect local failure. LF did not correlate with multiplicity (A, HR = 1.06, 95% CI: 0.57–1.97, *P* = .840) or postoperative KPS (B, HR = 0.87, 95% CI: 0.45–1.65, *P* = .66).

Table 2. Overall Survival by Multivariate Survival Analysis

Covariate	HR (95%CI)	*P*-value
Number of metastases		.11
1	reference	
>1	0.65 (0.39,1.10)	
Location		.56
Infratentorial	Reference	
Supratentorial	0.84 (0.46,1.52)	
KPS	0.99 (0.96,1.02)	.49
Preoperative KPS	1.01 (0.98,1.04)	.67
ECOG status		.083
0/1/2	Reference	
3/4	3.87 (0.84,17.84)	
Total GPA score	0.91 (0.63,1.32)	.61
Prescription Dose (Gy)	0.99 (0.92,1.06)	.73
Preoperative volume of the resected lesion	1.01 (1.00,1.02)	**.0032**

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GPA, Graded Prognostic Assessment; KPS, Karnofsky performance status.

Table 3. Progression Free Survival by Multivariate Survival Analysis

Covariate	HR (95%CI)	*P*-value
Number of metastases		.74
1	Reference	
>1	0.93 (0.58,1.47)	
Location		.36
Infratentorial	Reference	
Supratentorial	0.77 (0.45,1.33)	
KPS	0.98 (0.96,1.01)	.23
Preoperative KPS	1.01 (0.98,1.04)	.56
ECOG status		.17
0/1/2	Reference	
3/4	2.74 (0.65,11.62)	
Total GPA score	0.93 (0.67,1.29)	.65
Prescription Dose (Gy)	1.00 (0.94,1.06)	1
Preoperative volume of the resected lesion	1.01 (1.00,1.02)	**.0081**

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GPA, Graded Prognostic Assessment; KPS, Karnofsky performance status.

provide a survival benefit in only a subset of the patients, especially those with a high functional status (KPS score > 70), a younger age, a controlled systemic disease, the absence of extracranial metastases, and the presence of a single brain metastasis.[6,22] Similar to our study, the survival benefit with higher KPS score (70 or greater) has been well recognized.[3,23,24]

The importance of the number of brain metastases has been examined in previous studies and several have identified multiplicity to be a negative prognostic factor for these patients.[16,17] In our patient cohort, multiplicity did not significantly influence patient outcomes including overall survival, progression free survival, or time to local failure. Similarly, Schacket *et al.* retrospectively reviewed 104 patients who underwent surgical resection of brain

metastases and reported equivalent rates of OS among patients with a single metastasis compared to those with more than one lesion.[25] Paek *et al.* reported that surgical resection of a dominant lesion in patients with two or three metastases followed by whole brain radiotherapy resulted in similar survival rates to those undergoing resection of a single lesion.[26] Bindal *et al.* retrospectively evaluated 56 patients who underwent surgical resection of up to 3 brain metastases. Patients who underwent resection of all lesions had a median survival time of 14 months, which was equivalent to that of a matched cohort who underwent resection of a single metastasis, with similar morbidity and mortality profile.[13] Wronski *et al.* reported equivalent rates of OS among 12 patients who underwent resection of a single metastasis to 16 who underwent resection of more than one lesion.[27] Finally, Iwadate *et al.* reviewed the outcomes of 138 patients who underwent resection of brain metastases followed by adjuvant radiotherapy. Median OS for those with a single metastasis was 8.7 compared to 9.2 months for patients with multiple lesions. They recommended consideration of surgical resection for multiple brain metastases in selected patients, especially those greater than 2 cm, to improve neurological quality of life and prolong survival.[28]

Our cohort demonstrated improved OS following surgery compared to prior literature, with 71% surviving at 1 year and 49% surviving at 2 years. For patients with multiple metastases, 67% were alive at 1 year and 46% at 2 years. This may reflect advances in systemic therapy for extracranial disease, including tyrosine kinase inhibitors, the use of immunotherapy, advances in adjuvant radiation therapy, or patient selection, given our median preoperative KPS of 90.

While the number of brain metastases did not significantly influence patient outcome in out cohort, we discovered a significant correlation between the resected tumor volume and OS and PFS. Tumor volume is known to significantly influence survival and local control in brain metastasis, especially in those treated with radiosurgery.[29–31] Although it is rational and intuitive to operate on large space-occupying lesions associated with high intracranial pressure, the influence of tumor volume is less well understood in surgically treated patients. In our cohort, resecting larger preoperative tumor demonstrated both overall and progression free survival benefits, highlighting the survival benefits of upfront resection of large cerebral metastases.

Overall postoperative complication rates range from ≤5% to 40% in patients who undergo surgical resection for brain metastases,[32] with an average 30-day major neurological morbidity rate of 6%.[33] The use of intraoperative navigation and mapping has improved safety and minimized morbidity, especially for tumors located in eloquent brain areas.[32,34] Our overall rate of perioperative morbidity was 3.08%; 3 patients required wound washout at 2 months and 1 experienced delayed neurological deficits. Importantly, this demonstrates that in appropriately selected patients, surgical morbidity can be very low, including for patients with several brain metastases.

Our study is limited by its retrospective nature and the associated selection bias. We examined our cohort of patients who received surgery and adjuvant radiation therapy but did not compare outcomes to patients who underwent radiation therapy alone. Surgery was performed primarily for patients with one large lesion (>3 cm), therefore results may not generalize to patients with multiple smaller lesions. Importantly, the numbers of patients with more than one metastasis were much smaller than that with one lesion, indicating some selection bias in the clinical decision-making process and limiting statistical power. Several factors may have contributed to the decision-making favoring nonsurgical management for patients with multiple metastases. The size of the lesions may have been amenable to radiosurgery. The type of primary tumor, based on molecular profile, may respond well to immunotherapy or radiotherapy. Patients may have declined surgical intervention or been deemed unsuitable for surgery due to poor functional status or multiple medical comorbidities. Additional treatment modalities including chemotherapy, targeted immunotherapy, the heterogeneity of primary malignancy and tumor biology, and the spectrum of radiation therapy also invariably influences patient outcomes but were outside the scope of the current study.

Conclusions

Our study examined the effect of multiplicity in patients undergoing surgical resection of brain metastases and did not reveal any adverse outcomes associated with having more than one lesion. We advocate that surgery should be an important consideration in appropriately selected patients regardless of the number of brain lesions.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

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