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Surgical treatment of multiple brain metastases

RAJESH K. BINDAL, B.A., RAYMOND SAWAYA, M.D., MILAM E. LEAVENS, M.D., AND J. JACK LEE, PH.D.

Departments of Neurosurgery and Biomathematics, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

✓ The authors conducted a retrospective review of the charts of 56 patients who underwent resection for multiple brain metastases. Of these, 30 had one or more lesions left unresected (Group A) and 26 underwent resection of all lesions (Group B). Twenty-six other patients with a single metastasis who underwent resection (Group C) were selected to match Group B by type of primary tumor, time from first diagnosis of cancer to diagnosis of brain metastases, and presence or absence of systemic cancer at the time of surgery. Statistical analysis indicated that Groups A and B were also homogeneous for these prognostic indicators. Median survival duration was 6 months for Group A, 14 months for Group B, and 14 months for Group C. There was a statistically significant difference in survival time between Groups A and B ($p = 0.003$) and Groups A and C ($p = 0.012$) but not between Groups B and C ($p > 0.5$). Brain metastasis recurred in 31% of patients in Group B and in 35% of those in Group C; this difference was not significant ($p > 0.5$). Symptoms improved after surgery in 65% of patients in Group A, 83% in Group B, and 84% in Group C. Symptoms worsened in 13% of patients in Group A, 6% in Group B, and 0% in Group C. Groups A, B, and C had complication rates per craniotomy of 8%, 9%, and 8%, and 30-day mortality rates of 3%, 4%, and 0%, respectively. Guidelines for management of patients with multiple brain metastases are discussed. The authors conclude that surgical removal of all lesions in selected patients with multiple brain metastases results in significantly increased survival time and gives a prognosis similar to that of patients undergoing surgery for a single metastasis.

KEY WORDS • **multiple brain metastases** • **brain neoplasm** • **multiple craniotomies**

BRAIN metastases occur in 20% to 30% of all patients with systemic cancer.[3,20,34] Each year, an estimated 82,000 patients in the United States develop brain metastases,[18] which are symptomatic in two-thirds of these patients.[2,9] The incidence of brain metastases is thought to be rising due to increased survival time of cancer patients resulting from improved therapy for systemic disease.

The development of brain metastases portends a poor prognosis. Without treatment, the median survival time is about 1 month.[26] Corticosteroid therapy alone can increase survival to 2 months.[30] With steroids and whole-brain radiation therapy, survival can be extended to 3 to 6 months.[8,23,29,31] For over 60 years, surgical excision has been performed in patients with a single brain metastasis. Currently, the median patient survival time after surgical excision of a single brain metastasis is 9 to 14 months, depending on such factors as the type of primary cancer, length of time between diagnosis of the primary tumor and diagnosis of brain metastasis, neurological performance status, and presence or absence of systemic disease.[6,19,29,31,32]

Patients with a single brain metastasis are offered surgery if they have an accessible lesion, limited or no systemic cancer, and a life expectancy greater than 2 months.[18,28,34,35] A recent randomized study by Patchell, *et al.*,[29] comparing the results of surgical excision followed by whole-brain radiation therapy to the results of whole-brain irradiation alone has shown that surgical excision is the therapy of choice for these selected patients.

Unfortunately, autopsy studies indicate that 60% to 85% of patients with brain metastasis have multiple lesions.[2,11,20,34] On contrast-enhanced computerized tomography (CT) scans, 50% of patients demonstrate multiple lesions.[14] With improved neuroimaging techniques such as contrast-enhanced magnetic resonance (MR) imaging, the presence of patients demonstrating multiple lesions is higher.[13,33] Accepted guidelines for the management of these patients is to not offer surgery except in rare situations such as the presence of a life-threatening lesion, the presence of two lesions that can be removed in a single craniotomy, or the need to establish a diagnosis.[28,35] For all other patients with multiple metastases, treatment is largely limited to steroids and whole-brain radiation therapy; life expectancy for these patients is 3 to 6 months. Although these represent the majority of patients with brain metastases,

no previous study has specifically attempted to determine the effectiveness of aggressive surgical treatment.

Clinical Material and Methods

The records of 56 patients with multiple brain metastases who underwent surgical resection of one or more lesions between January, 1984, and January, 1992, were retrospectively reviewed. The patients were divided into two groups: those who did not undergo resection of all known lesions (Group A, 40 lesions removed from 30 patients in 38 craniotomies) and those who had all lesions removed (Group B, 55 lesions removed from 26 patients in 44 craniotomies). In Group A, one lesion was removed from 22 patients, two lesions from six patients, and three lesions from two patients. Twenty-five Group A patients underwent one craniotomy, four patients underwent two craniotomies in a single operation, and one patient underwent three craniotomies in a single operation. In Group B, 23 patients had two lesions removed and three patients had three lesions removed. Ten Group B patients underwent a single craniotomy, 14 patients underwent two craniotomies in a single operation, while two patients underwent three craniotomies in a single operation. Prognostic indicators of Groups A and B were statistically compared and found to be homogeneous. Specific indicators compared and resulting p values are as follows: type of primary cancer ($p = 0.922$), length of time from first diagnosis of cancer to diagnosis of brain metastases (onset interval) ($p = 0.767$), Karnofsky Performance Score[22] (KPS) ($p = 0.934$), percentage of patients with systemic disease ($p = 0.831$), and patient age ($p = 0.58$).

The records of patients who underwent surgery for removal of a single metastatic lesion between January, 1986, and December, 1990, were also reviewed (Group C). Of 167 patients, 26 patients were selected who best matched the 26 patients in Group B in terms of type of primary cancer, onset interval, KPS, and presence or absence of systemic disease. These factors were matched because all are known prognostic indicators for survival of patients undergoing surgery for a single brain metastasis.[19,28,32] The characteristics for all three patient groups are shown in Table 1. Table 2 compares specific characteristics for Group B and C patients.

Survival time was measured from the date of surgery to the date of last follow-up evaluation or death. Cause of death was determined by the guidelines of Cairncross, *et al.*,[8] namely: deaths in patients with stable systemic disease and advancing neurological disease were considered neurological deaths; deaths in patients with stable neurological function and advancing systemic disease were considered systemic deaths; and deaths in patients with progressing neurological and systemic disease were considered combined deaths. Systemic and neurological survival data were calculated using the Kaplan-Meier survival method.[21] In calculating systemic survival, patient deaths from systemic or combined causes were used as endpoints whereas all other patients were censored at last follow-up evaluation or time of death. In calculating neurological survival, patient deaths from neurological or combined causes were used as endpoints; all other patients were censored at last follow-up evaluation or time of death.

The number of tumors present at the time of surgery, presence or absence of systemic disease, and time to recurrence of first brain metastasis were determined by contrast-enhanced CT or MR imaging. "Local tumor recurrence only" was defined as tumor recurrence at the site of previous resection with no other recurrence. "Distant recurrence only" was defined as tumor recurrence in a location other than the site of resection. "Local and distant recurrence" was defined as recurrence in both a site of resection and a location other than the site of resection. Because patients in Group A

TABLE 1

*Characteristics of patients with treatment of brain metastases**

Characteristic	Multiple Metastases	Group A	Group B	Group C
no. of cases	56	30	26	26
sex (M/F)	27/29	15/15	12/14	12/14
age (yrs)				
median	52	54	51	56
range	23–76	23–76	23–68	24–71
primary tumor				
melanoma	25	13	12	12
breast	11	6	5	5
lung	7	4	3	3
sarcoma	5	3	2	3
colon	3	1	2	2
renal	2	1	1	1
ovary	1	0	1	0
unknown	2	2	0	0
median time to metastasis† (mos)	23	24	20	21
Karnofsky score (mean ± SD)		77 ± 16	76 ± 19	79 ± 12
Percent with systemic cancer	59	57	62	62
no. of craniotomies	82	38	44	26
no. of lesions removed	95	40	55	26

* Group A = patients with multiple metastases who had one or more lesions unresected; Group B = patients with multiple metastases who had all lesions resected; and Group C = patients with a single metastasis who underwent surgery. SD = standard deviation.

† Median time from diagnosis of primary tumor to diagnosis of brain metastases.

TABLE 2

*Comparison of Group B and Group C patients**

Type of Primary Tumor	Median Time to Metastasis (mos)		No. With Systemic Disease	
	Group B	Group C	Group B	Group C
melanoma	17	18	7	7
breast	25	27	3	2
lung	9	6	2	2
sarcoma	37	60	2	2
colon	21	18	1	2
kidney	69	72	1	1
ovary	16	0	0	0
total	20	21	16	16

* For definition of patient groups see Table 1.

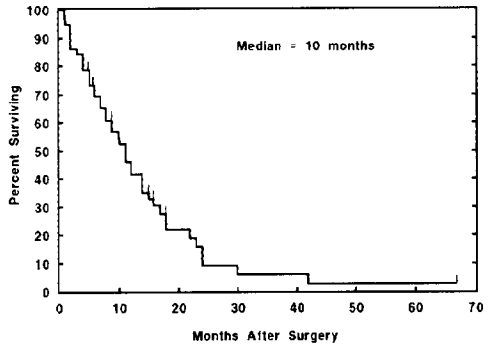

FIG. 1. Graph showing overall survival data for all patients with multiple brain metastases.

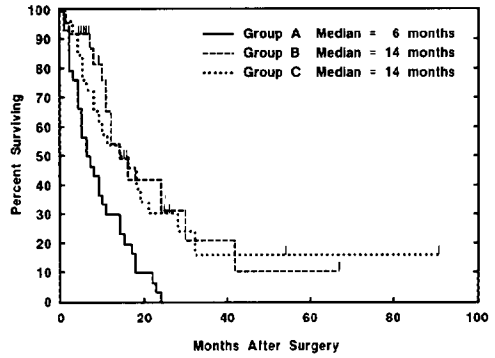

FIG. 2. Graph showing survival data by patient groups. Significance of difference for survival of Groups A versus B: $p = 0.003$; A versus C: $p = 0.012$; and B versus C: $p > 0.5$. For definition of patient groups see text and Table 1.

had unresected lesions present after surgery, recurrence data were not calculated for them.[8]

The goal of all surgical procedures was gross total excision. Postoperative CT scans or MR images were used to determine the completeness of tumor removal. Patients with immediate postoperative evidence of residual tumor were not considered to have local recurrence. Whole-brain radiation therapy for all patients consisted of 30 Gy in 10 fractions given over 2 weeks using parallel-opposed lateral ^{60}Co photon fields. In Group A, nine patients underwent preoperative treatment for brain metastases: eight underwent whole-brain radiation therapy, two with the addition of chemotherapy, and one underwent chemotherapy alone. Nine patients in Group B underwent previous treatment before having all lesions surgically removed: eight underwent whole-brain radiation treatment, two with chemotherapy, and one underwent chemotherapy alone. Two patients in Group C had treatment prior to surgery: whole-brain radiation therapy for one and chemotherapy for the other. Postoperative whole-brain irradiation was given to 17 patients (57%) in Group A, 13 patients (50%) in Group B, and 14 patients (54%) in Group C.

Response to surgery was determined by pre- and postoperative neurological examination. Patients were

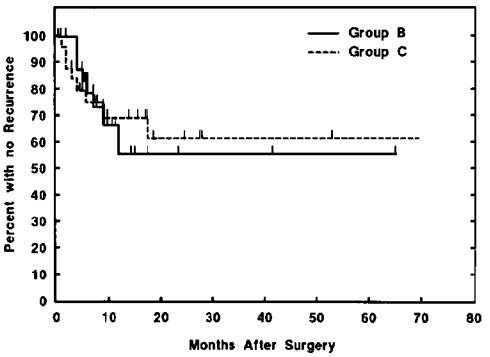

FIG. 3. Graph showing length of time to first recurrence of brain metastasis in Groups B and C. For definition of patient groups see text and Table 1.

considered to have improved if preoperative signs and symptoms had diminished or resolved; to have had no response if pre- and postoperative findings were the same; or to have become worse if any new deficit appeared or if any existing deficit became worse, regardless of the reduction of other symptoms.

Survival curves were drawn using the Kaplan-Meier product-limit method.[21] The log-rank test was applied to evaluate the differences between two or more survival curves. The Cox regression model[12] was used to study the effects of multiple covariates on patients' survival.

Results

Survival data for all patients with multiple brain metastases who underwent surgical treatment are shown in Fig. 1. Median survival for these patients was 10 months. Survival data for patients in Groups A, B, and C are shown in Fig. 2. The median postoperative life spans were 6 months for patients in Group A, 14 months for those in Group B, and 14 months for those in Group C. Survival rates for Group A, B, and C patients were 23%, 55%, and 50%, respectively, for 1 year and 0%, 32%, and 30%, respectively, for 2 years. Five-year survival rates for Groups B and C were 11% and 16%, respectively. Survival duration differed significantly between Groups A and B ($p = 0.003$) and Groups A and C ($p = 0.012$) but not between Groups B and C ($p > 0.5$).

Multivariate analysis was performed to determine what variables were significantly correlated with a difference in survival under the Cox regression model. The following variables were examined: lesion removal (Group A, B, or C), presence or absence of systemic disease, interval to metastasis, histological type of the primary tumor, and recurrence of brain metastasis. The results of these tests indicate that the only variables significantly affecting survival were the patient group and presence or absence of systemic disease ($p < 0.05$ for each variable). In Group A, patients with preoperative evidence of systemic disease had a median life span of 5 months, whereas those without any evidence of systemic disease survived 8 months. In Group B, patients with systemic disease survived 12 months and

TABLE 3

*Neurological or systemic cause of death**

Cause of Death†	Group A	Group B	Group C
neurological	11 (50%)	5 (42%)	5 (29%)
systemic	9 (41%)	5 (42%)	9 (53%)
combined	2 (9%)	2 (17%)	3 (18%)
unknown	8	2	3
alive	0	12	6

* Percentages are of evaluable deaths only. For definition of patient groups see Table 1.

† Groups are as described by Cairncross, *et al.*[8]

TABLE 4

*Patient survival by cause of death**

Cause of Death	Median Survival Time (mos)		
	Group A	Group B	Group C
systemic	11	18	19
neurological	9	16	> 21†

* For definition of patient groups see Table 1.

† The median survival time in patients with neurological disease was not reached. The survival rate was 55% at the last recorded death at 21 months.

TABLE 5

*Central nervous system disease relapse**

Location of Recurrence	Group B	Group C
local only†	4% (1/26)	8% (2/26)
distant only	23% (6/26)	19% (5/26)
local & distant	4% (1/26)	8% (2/26)
residual tumor (per resection)†	5% (3/55)	4% (1/26)

* For definition of patient groups see Table 1.

† At site of previous resection.

TABLE 6

*Complications and mortality related to patient group and multiple craniotomies**

Category	Group A	Group B	Group C	Multiple Craniotomies
complication per craniotomy	8% (3/38)	9% (4/44)	8% (2/26)	7% (3/45)
mortality	3% (1/30)	4% (1/26)	0% (0/26)	0% (0/21)

* For definition of patient groups see Table 1.

TABLE 7

*Response to surgery in symptomatic patients**

Neurological Response	Percent of Symptomatic Patients		
	Group A	Group B	Group C
improved	65	83	84
no change	22	11	16
worsened	13	6	0

* For definition of patient groups see Table 1.

those without survived 16 months. In Group C, patients with systemic disease survived 8 months, whereas those without systemic disease survived 26 months.

Duration of patient survival varied according to the tumor histological type, although not significantly ($p > 0.05$). Of patients with melanoma, those in Group A survived a mean of 5 months (13 cases); those in Group B, 16 months (12 cases); and those in Group C, 8 months (12 cases). Of patients with adenocarcinoma, those in Group A survived a mean of 9 months (13 cases); those in Group B, 11 months (10 cases); and those in Group C, 18 months (13 cases).

The cause of death is recorded in Table 3, and the median survival time related to cause of death is presented in Table 4. In Group C patients, the latest death associated with a neurological cause occurred 21 months after surgery, at which time the survival rate was still 55%. The log-rank test indicates that there is little difference in length of survival of patients with systemic disease among Groups A, B, and C ($p = 0.25$). As for patients surviving with neurological disease, Groups B and C have increased survival compared to Group A, although this difference is not quite significant ($p = 0.07$).

Recurrence of metastasis in the brain and extent of resection are detailed for Groups B and C in Table 5. Groups B and C had total recurrence rates of 31% and 35%, respectively. A Kaplan-Meier curve was drawn for Groups B and C using recurrence as an endpoint (Fig. 3). No significant difference in recurrence rate was detected ($p > 0.5$): Groups B and C had recurrence rates of 25% at 7 months and 6 months after surgery, respectively. By definition, patients in Group A already had one or more lesions remaining in the brain after surgery, therefore recurrence data were not deemed relevant. However, in this group residual tumor was noted in two (5%) of 40 tumor beds on postoperative scanning. Five patients (17%) in Group A, six (23%) in Group B, and one (4%) in Group C underwent one or more reoperations for recurrent or residual tumor.

Complication and mortality rates are presented in Table 6. There were three complications in Group A (one infection and two hematomas) and one death within 30 days. There were four complications in Group B patients (one infection, one pseudomeningocele requiring reoperation, and two hematomas) and one death within 30 days, attributed to the infection. The two complications in Group C were both infections; there were no deaths within 30 days. Three complications were noted in patients undergoing multiple craniotomies: one pseudomeningocele and two hematomas; there were no deaths within 30 days among these patients. The median hospital stay after craniotomy for all 82 patients in this study was 3 days.

Responses to surgery are shown in Table 7. In Group A, 65% of symptomatic patients improved postsurgically, 22% remained neurologically stable, 13% had progressive worsening of symptoms, and 8% were asymptomatic preoperatively and postoperatively. In Group B, 83% of patients improved, 11% were stable, 6% were worse, and 10% were asymptomatic preoperatively and postoperatively. In Group C, 84% improved, 16% stabilized, 0% worsened, and 0% were asymptomatic preoperatively. Comparison of improvement rates of patients in Group A with the corresponding rates in Groups B and C revealed a difference approaching but not reaching significance ($p = 0.09$).

Discussion

This study shows that the survival time of patients with multiple brain metastases who have all lesions removed is equivalent to that of similar patients undergoing surgery for a single metastasis and longer than that of patients who have one or more lesions remaining after surgery. Patients with multiple metastases undergoing surgical treatment live substantially longer than the 3 to 6 months reported by numerous investigators for patients with radiation treatment alone. In addition, patients having all lesions removed have rates of recurrence, mortality, complication per craniotomy, and neurological improvement similar to those of patients undergoing craniotomy for a single metastasis. Also, the necessity for multiple craniotomies during a single operation is not associated with an increase in risk of mortality or complication per craniotomy compared with those of a single craniotomy.

No previous study has analyzed in detail the results of surgery for multiple brain metastases. Isolated reports of surgical excision of multiple metastases have, however, appeared in the literature. Brega, *et al.*,[5] reported on eight patients undergoing surgery for multiple metastases from melanoma who survived from 6 to 18 months postoperatively. Fell, *et al.*,[15] presented four patients, each of whom had one of two metastases removed; these patients lived for 2, 6, 12, and 15 months. Fernandez, *et al.*,[16] described a patient with six lesions, two of which were removed with survival for 80 months. Oredsson, *et al.*,[27] reported on eight patients with multiple metastases who survived a median of 4 months; however, data on the number of lesions found and the number removed were not presented. These studies do not substantiate or refute the accepted guidelines for management of patients with multiple brain metastases. The present study is the first to critically analyze the issues involved in selection of surgical candidates among patients with multiple brain metastases.

Many other investigators have reported on the results of surgery for a single metastasis. Our finding of a 14-month median survival time for these patients is well within the range reported in the literature.[5–7,19,25,29,31,32] Our study's complication rate, mortality rate, and response to therapy are also all within the previously described range.[6,19,29,32] Additionally, the finding that patients with evidence of systemic disease survive for a shorter period than those with a solitary brain metastasis is consistent with previous reports.[19,32] These results mean that Group C patients, intended to be a standard for comparison with Group B, can be considered representative of patients who undergo surgery for a single metastasis.

The most common primary tumors associated with brain metastases are melanoma and lung, breast, kidney, and colon cancers.[28] Of these, melanoma and kidney and colon cancers are considered radioresistant.[18] Melanoma also has the highest frequency of presentation with multiple metastases of all primary tumors.[7,14,25,34] These facts explain why melanoma is highly overrepresented and lung cancer underrepresented in this surgical series compared with the expected distribution of primary cancers.

Because patients often die of their systemic disease, a more accurate way to examine the success of surgery for brain metastasis is to examine deaths from neurological causes separately from deaths due to systemic disease.[29] Group A patients with nonsystemic disease survived for shorter periods than did similar Group B or C patients. Although this difference was not quite significant, the lack of significance may be explained by the small sample sizes. This indicates that failure of treatment for nonsystemic disease occurred faster in Group A patients than in Group B or C patients. Patients in Group B dying of systemic and neurological causes survived for periods similar to those of patients in Group C. This provides added evidence that systemic disease was equally advanced in both of these patient groups and that treatment failure for neurological disease occurred at comparable rates.

Patients with multiple metastases often have lesions located too far apart to allow resection with a single craniotomy. Our data indicate that multiple craniotomies are not associated with increased complications per craniotomy or with increased 30-day mortality rates. It must be recognized that, since complication rates per craniotomy are similar, a patient undergoing multiple craniotomies has a higher cumulative probability of developing a complication. Even so, among all patients reviewed in this series, only one complication was fatal and only one required reoperation. Our data indicate that the need to perform multiple craniotomies should not dissuade a neurosurgeon from attempting to remove all accessible lesions.

Our guidelines for the management of patients with multiple brain metastases begin with an evaluation of the extent of systemic disease in the patient. Those patients not expected to survive for longer than 3 months due to their systemic cancer are not considered surgical candidates. Radiation therapy can palliate symptoms for this length of time and is, therefore, recommended for these patients. Patients with limited or controlled systemic cancer in whom resection of all lesions is possible are considered excellent surgical candidates. Even patients in whom all lesions cannot be removed are considered surgical candidates under certain circumstances. If one or two lesions are life-threatening or highly symptomatic, surgical removal may provide the patient an increased life span or an im-

proved quality of life beyond that achievable by radiation therapy alone. In general, the need for multiple craniotomies should not be an important deterrent to the decision to operate.

It is not our intent to endorse multiple craniotomies for multiple brain metastases under all circumstances. Only patients meeting the above criteria are considered surgical candidates. Using accepted guidelines for patient selection, which in most centers limit surgery to patients with a single metastasis, it has been estimated that up to 10% to 20% of patients with brain metastases are candidates for surgery.[18,28] By adding our guidelines for evaluating patients with multiple metastases, that number might be doubled.

The role of stereotactic radiosurgery in the palliation of patients with multiple metastases has been examined.[1,10,17,24] The physical nature of brain metastases makes them particularly well suited to this treatment. Encouraging results have been reported, but because of the developing nature of this treatment modality, data are relatively sparse, as are studies with adequate numbers of patients and follow-up times to determine effects of survival. Very little specific information is available regarding patients with multiple lesions treated with radiosurgery.

Conclusions

Patients with multiple brain metastases with limited systemic disease and in whom all lesions are accessible should have all lesions surgically removed, even if multiple craniotomies are required. This can significantly improve length and quality of life for those patients.

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Address reprint requests to: Raymond Sawaya, M.D., Department of Neurosurgery, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030.