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# Reoperation for recurrent metastatic brain tumors

**RAJESH K. BINDAL, M.D., RAYMOND SAWAYA, M.D., MILAM E. LEAVENS, M.D., KENNETH R. HESS, PH.D., AND SARAH H. TAYLOR, M.P.H.**

*Departments of Neurosurgery and Patient Studies, M. D. Anderson Cancer Center, Houston, Texas*

Results of reoperation in 48 patients who developed recurrent brain metastases between January 1984 and April 1993 are presented. Median time from first craniotomy to diagnosis of recurrence (time to recurrence) was 6.7 months. Median Karnofsky performance scale (KPS) score prior to reoperation was 80. Recurrence was local in 30 patients, distant in 16 patients, and both local and distant in two patients. Median survival time after reoperation was 11.5 months. There were no operative mortalities. Multivariate analysis revealed that presence of systemic disease ($p = 0.008$), KPS scores less than or equal to 70 ($p = 0.008$), time to recurrence of less than 4 months ($p = 0.008$), age greater than or equal to 40 years ($p = 0.51$), and primary tumor type of breast or melanoma ($p = 0.028$) negatively affected patient survival time. These five factors were used to develop a grading system (Grades I–IV). Patients categorized in Grade I had a 5-year survival rate of 57%, whereas the median survival time of patients in Grades II, III, and IV was 13.4, 6.8, and 3.4 months, respectively ($p < 0.0001$).

Overall, 26 patients developed a second recurrence after reoperation. Seventeen patients underwent a second reoperation, whereas nine did not. Patients undergoing a second reoperation survived a median of 8.6 additional months versus 2.8 months for those who did not ($p < 0.0001$).

This study concludes that reoperation for recurrent brain metastasis can prolong survival and improve quality of life. A second reoperation can also increase survival. Five factors influence survival: status of systemic disease, KPS score, time to recurrence, age, and type of primary tumor. The grading system using these five factors correlates with survival time. Reoperation should be approached with caution in Grade IV patients because of their poor prognosis.

**KEY WORDS • brain metastasis • grading system • recurrent brain neoplasm • reoperation**

BRAIN metastases occur in 15% to 20% of all patients with systemic cancer.[11,16] Each year, an estimated 97,800 patients in the United States develop brain metastases,[11] and in two-thirds of these patients, the tumors are symptomatic.[6] Many patients develop brain metastasis in the setting of widespread systemic disease. Their life expectancy is limited, and treatment with whole-brain radiation therapy (WBRT) alone for short-term palliation is adequate. Patients receiving WBRT alone survive 3 to 6 months, with negligible long-term survival.[11] However, up to 50% to 62% of patients develop brain metastasis in the setting of limited or stable systemic disease.[3,10] In these patients, the brain metastasis is likely to be the limiting factor in survival, and aggressive treatment of the brain lesions can improve both the length and the quality of life. Two randomized studies[12,17] have demonstrated that in those patients with a single brain metastasis and a good Karnofsky performance scale (KPS)[8] score, surgical resection followed by WBRT is superior to WBRT alone and increases both the length and the quality of survival. Recently, we showed that selected patients with multiple brain metastases should also be treated with surgery.[1] Unfortunately, 31% to 48% of surgically treated patients will develop recurrence in the brain.[1,4,12,14] Little is known about the prognosis and results after reoperation for such patients.[15]

## Clinical Material and Methods

We present 48 patients who underwent reoperation for recurrent brain metastases at M. D. Anderson Cancer Center between January 1984 and April 1993. Only patients who initially underwent surgical removal of all lesions in the brain and who received treatment for all recurrent lesions are included.

The goal of all surgical procedures was gross total resection. Local recurrence was defined as tumor recurrence at the site of previous resection. Distant recurrence was defined as tumor recurrence in the brain in a location other than the site of resection.

Patients were determined to have improved, stabilized, or suffered morbidity by comparing KPS scores at prereoperative evaluation and at 30 days after reoperation.[9] We emphasize that prereoperative KPS scores were evaluated after steroid administration to minimize the impact of peritumoral edema. Complications included wound infection, dehiscence, or the development of any new neurological deficit after surgery that could be attributed to the procedure. Operative mortality was defined as death from any cause within 30 days of reoperation. Cause of death was determined to be neurological in patients who died with stable systemic disease and advancing neurological disease, systemic in patients who died with stable neuro-

TABLE 1

*Primary tumor type leading to brain metastasis*

| Type of Primary Tumor | No. Cases (%) |
|---|---|
| melanoma | 14 (29.2) |
| lung | 11 (22.9) |
| breast | 10 (20.8) |
| kidney | 4 (8.3) |
| colon | 4 (8.3) |
| sarcoma | 1 (2.1) |
| germ cell | 1 (2.1) |
| unknown | 3 (6.3) |

logical function and advancing systemic disease, and combined in patients who died with progressing neurological and systemic disease.

Survival curves were estimated using the Kaplan–Meier product-limit method.[7] Median survival times were computed from the Kaplan–Meier estimates. Confidence intervals (CI 95%) were computed for survival probabilities and medians to quantify the statistical uncertainty. The log-rank test was applied to evaluate the differences between two or more survival curves. The Cox[5] regression model was used to study the effects of multiple covariates on patients' survival.

## Results

### *Patient Characteristics*

The types of primary tumors are detailed in Table 1. Median patient age was 47.5 (range 17–68 years). There were 24 men and 24 women. The median interval from initial diagnosis of cancer to initial craniotomy for brain metastasis was 11.5 months (range 0–109 months). Five patients (10.4%) had two lesions removed at the time of initial craniotomy; all others had only a single lesion. Whole-brain radiation therapy after craniotomy was given to 31 patients (64.5%).

The median interval from initial craniotomy to diagnosis of recurrence in the brain was 6.7 months (range 1.2–28.8 months). At the time of recurrence, six patients (12.5%) had two lesions; all others had a single lesion. Five of the six patients with two tumors required two craniotomies to allow resection of both lesions. Recurrence was local in 30 (62.5%), distant in 16 (33.3%), and both local and distant in two patients (4.2%). Median preoperative KPS score was 80 (range 40–100). Systemic disease was present at the time of reoperation in 23 patients (47.9%) and absent in 25 (52.1%).

### *Results of Reoperation*

Four patients were asymptomatic before and after reoperation. As determined by KPS score evaluation at the time of reoperation and 30 days later, 33 (75.0%) of the 44 symptomatic patients improved after reoperation and 11 (25.0%) stabilized. There was no morbidity or operative mortality. No patient suffered wound infection, dehiscence, or cerebrospinal fluid leaks after reoperation. As determined by neurological examination, five patients

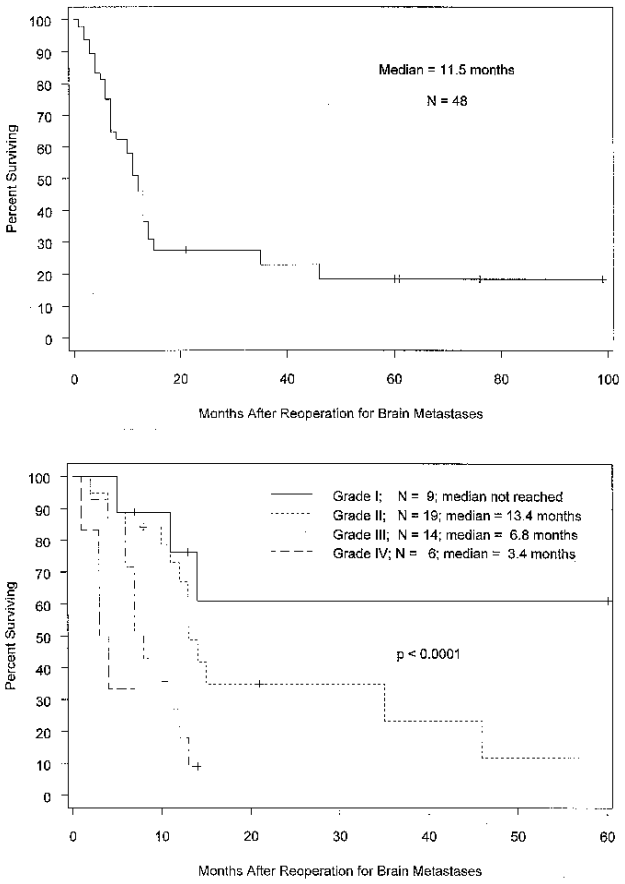


FIG. 1. Graphs depicting survival times. *Upper:* Overall patient survival time after reoperation. *Lower:* Survival of patients by grade. See text for explanation of how to determine grade.

(10.4%) developed new or increased neurological deficits after surgery. In three of these patients, the deficits completely resolved within 30 days of surgery. Median hospital stay after surgery for all patients was 5 days (range 2–32). Six patients (12.2%) received WBRT after reoperation.

### *Survival Results*

Median survival time after initial craniotomy was 21.9 months; survival rates at 2 and 5 years after initial craniotomy were 40% and 21%, respectively. Median survival after reoperation with a 95% CI was 11.5 months (95% CI 7.8, 14.0 months) (Fig. 1 *upper*). Survival rates at 2 and 3 years after reoperation were 26% and 22%, respectively. The 5-year survival rate was 17% (95% CI 5%, 39%).

Univariate analysis (log-rank test) was performed to determine which variables correlated with survival time. Status of systemic disease ($p = 0.012$), KPS score ($p < 0.0001$), and time to recurrence ($p = 0.0037$) significantly affected survival, whereas the patient's age, type of primary tumor, and location of recurrence (local vs. distant) did not ($p > 0.05$).

Multivariate analysis was also performed using the same six variables. Status of systemic disease ($p = 0.008$),

TABLE 2

*Risk factors predicting survival time: results of multivariate analysis**

| Variable | Contrast | Relative Risk of Death | 95% CI | p Value |
|---|---|---|---|---|
| systemic disease | yes vs no | 2.85 | 1.22–6.67 | 0.015 |
| prereoperative KPS score | ≤70 vs >70 | 3.70 | 1.47–9.09 | 0.006 |
| time to recurrence | <4 mos vs ≥4 mos | 2.86 | 1.23–6.67 | 0.014 |
| age | ≥40 vs <40 | 2.43 | 0.95–6.20 | 0.055 |
| type of primary tumor | lung or other vs breast or melanoma | 2.79 | 1.22–6.39 | 0.014 |

* CI = confidence interval; KPS = Karnofsky performance scale.[9]

KPS score (p = 0.008), time to recurrence (p = 0.008), age (p = 0.051), and type of primary tumor (p = 0.028) significantly influenced survival time. Five of the six variables substantially affected survival as measured by both p values and assessment of the relative risk of death (Table 2). The location of recurrence had no significant impact on survival (relative risk 0.85, p = 0.73).

### *Grading for Prognosis*

A model was developed to predict patient survival time using the five prognostic factors determined by multivariate analysis. In this system, a patient was first assigned a score by adding the number of negative prognostic indicators as presented in Table 3. This score was then converted to a grade. For example, a 60-year-old patient who presents with a recurrent brain metastasis from breast cancer, who underwent initial craniotomy 7 months ago, with no evidence of systemic disease, and with a KPS score of 90 has a score of 2 and is therefore in Grade II. Nine patients were in Grade I, 19 in Grade II, 14 in Grade III, and six in Grade IV. Figure 1 *lower* presents survival time as a function of grade. Median survival time for patients in Grade I was not reached. Patients in Grades II, III, and IV survived a median of 13.4 (95% CI 12.3, 14.9), 6.8 (6.0, 10.2), and 3.4 (2.9, 4.4) months, respectively

TABLE 3

*Scoring system to determine patient's grade**

| Factor Evaluated | Score |
|---|---|
| status of systemic disease | |
| present | 1 |
| absent | 0 |
| prereoperative KPS score | |
| ≤70 | 1 |
| >70 | 0 |
| time to recurrence | |
| <4 mos | 1 |
| ≥4 mos | 0 |
| age | |
| ≥40 yrs | 1 |
| <40 yrs | 0 |
| type of primary tumor | |
| melanoma or breast | 1 |
| lung or other | 0 |

* KPS = Karnofsky performance scale.[9]

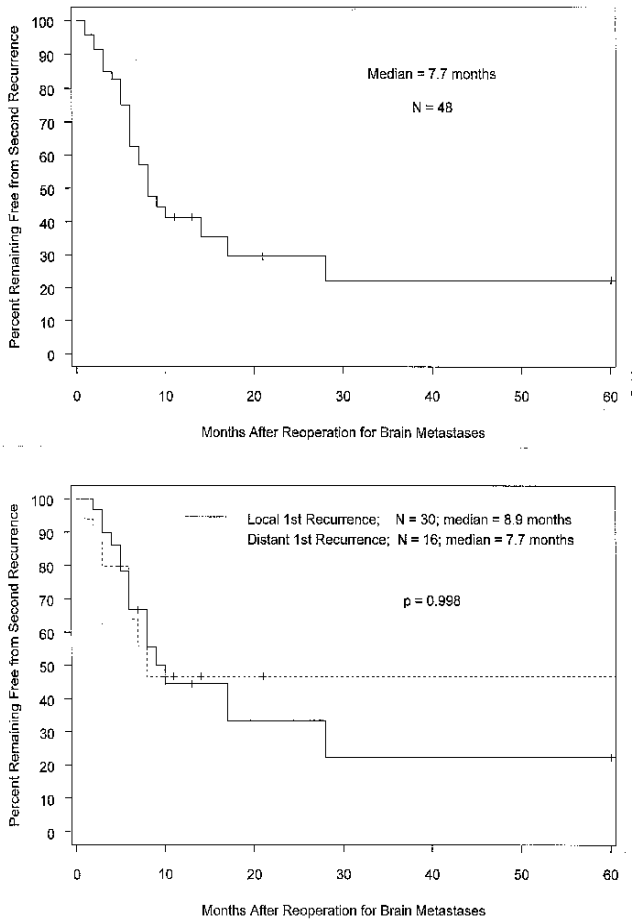


FIG. 2. Graphs showing freedom from recurrence. *Upper:* Patient freedom from second recurrence in the brain after reoperation. *Lower:* Freedom from local second recurrence for patients who underwent reoperation for local recurrence versus those who underwent reoperation for a distant recurrence.

(p < 0.0001). Patients in Grade I had a 5-year survival rate of 57%. Patients in Grade II had 3- and 5-year survival rates of 23% and 11%, respectively. Patients in Grades III and IV had 1-year survival rates of 17% and 0%, respectively.

### *Second Recurrence*

Figure 2 *upper* shows a Kaplan–Meier curve evaluating disease-free survival from brain metastasis. Overall, 26 patients developed a second recurrence in the brain. The median interval between reoperation and diagnosis of a second recurrence was 7.7 months (95% CI 6.1, 13.5 months). Eighteen patients (69.2%) developed a second local recurrence, that is, in a previous site of resection, three (11.5%) in a distant site, and five (19.2%) in both. Table 4 shows the number of brain metastases at the time of diagnosis of second recurrence.

Patients receiving a first reoperation for local recurrence had a median time to second recurrence of 8.9 months versus 7.3 months for those undergoing first reoperation for a distant recurrence (p = 0.42). Additionally,

TABLE 4

*Number of brain metastases at second recurrence*

| No. of Tumors | No. of Cases (%) |
|---|---|
| 1 | 18 (69.2) |
| 2 | 4 (15.4) |
| 3 | 1 (3.8) |
| 4+ | 3 (11.5) |

patients who underwent first reoperation for a local recurrence did not have a significantly increased risk for developing a second local recurrence compared with patients who underwent a first reoperation for a distant recurrence ($p = 0.998$) (Fig. 2 *lower*). The risk of a second local recurrence increased in patients with a first local recurrence at more than 12 months after reoperation, but not significantly.

Of the 26 patients who developed a second recurrence, 17 (65.3%) underwent a second reoperation. Three of these patients had two lesions removed and 14 had one lesion removed. Patients who underwent a second reoperation survived a median of 8.6 additional months (95% CI 7.8, 26.9 months) after diagnosis of the second recurrence. Survival rates at 2 and 3 years for patients who underwent a second reoperation were 40% and 13%, respectively. Patients who did not undergo a second reoperation survived a median of only 2.8 months (95% CI 2.0, 2.9 months) after second recurrence, with a 0% 1-year survival. The difference in survival after second recurrence between those who underwent a second reoperation and those who did not was significant. ($p < 0.0001$) (Fig. 3).

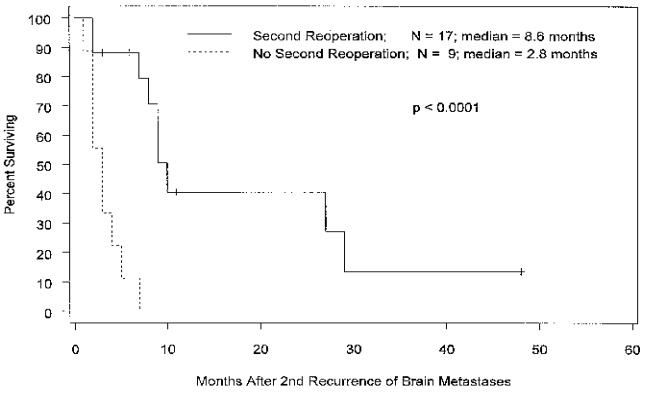


FIG. 3. Graph showing survival time after the second recurrence for patients who underwent a second reoperation versus those who did not.

*Cause of Death*

Of all 48 patients, 14 were alive at last follow-up contact. The cause of death was unknown in nine. Of the remaining 25, 12 (48%) died of neurological causes, three (12%) of combined causes, and 10 (40%) of systemic causes.

## Discussion

Our study demonstrates that reoperation is effective in treating patients with recurrent brain metastases. Furthermore, we present five prognostic indicators that influence survival time and a grading system that integrates these factors.

*Grading System*

Our system was useful in dividing patients into four well-differentiated prognostic categories. In our category of patients who fared best, patients had a greater than 50% chance of surviving more than 5 years, whereas in the worst category, no patient survived for even 1 year.

We use five factors in our grading system: status of systemic disease, KPS score, time to recurrence, age, and type of primary tumor. Numerous studies in patients undergoing initial craniotomy have shown that the status of systemic disease and performance status are important factors influencing survival, as determined by both univariate and multivariate analyses.[1,4,11–14,17] Age and histological composition of the tumor have also been shown by multivariate analysis to influence survival.[11,12] Time to recurrence may represent a measure of the biological aggressiveness of the tumor.

Our grading system is not valid for patients with advanced systemic disease who are expected to die within 4 months; it is valid for patients with multiple brain metastases only if all lesions in the brain are removed. We previously showed that patients with multiple brain metastases who undergo removal of all lesions had a median survival of 14 months, which was significantly greater than the 6-month survival time for patients having one or more lesions unresected.[1] Additionally, patients with multiple brain metastases undergoing surgical treatment of all lesions have a similar prognosis to patients with a single lesion undergoing surgery.[1]

*Second Recurrence*

Our data indicate that patients who suffer a relapse after reoperation very often have a limited number of brain metastases. Thus, the number of brain lesions is not usually a deterrent to second reoperation. Most patients who develop a second recurrence are candidates for a second reoperation. A second reoperation significantly prolongs the patient's life.

*Guidelines for Management.* Reoperation must be strongly considered in all patients who have recurrent brain metastases and limited systemic disease. In our experience, approximately half of all patients with recurrent brain metastases are candidates for reoperation. Patients with advanced systemic disease (expected survival time $< 4$ months) should not be offered reoperation, with few exceptions. In patients with limited systemic disease, the number and location of brain metastases are then evaluated. Ideally, all lesions should be resectable; multiple craniotomies can be safely performed to achieve this goal.[1] If all lesions are not resected or resectable, survival is worse. Radiosurgery may be useful in treating patients with one or two inaccessible lesions if other lesions can be surgically resected. Patients in whom all lesions can be resected are graded according to our system. Reoperation should be approached with caution in patients with Grade IV disease due to their poor prognosis and should not be

offered except in circumstances in which a lesion is immediately life-threatening. Reoperation may also be indicated in Grade IV patients if there is a question about diagnosis, such as whether there is recurrent brain metastasis or radiation necrosis or infection. However, there was no surprise diagnosis in any patient in our series thought to have recurrent brain metastasis.

Whether the recurrence is local or distant is of no importance in determining whether a patient is a surgical candidate; however, location is important in surgical planning. If the recurrence is local and if on computerized tomography or magnetic resonance imaging the lesion appears to be invasive or to have recurred from the entire surgical bed, then excision of both the lesion and a surrounding rim of brain parenchyma should be performed whenever possible to minimize the risk of subsequent local recurrence. In our series, there was no significantly increased risk of a second local recurrence in patients undergoing reoperation for a first local recurrence. We believe this is due to our surgical technique in treating such lesions. Even so, after 1 year of follow up, patients with a local first recurrence appear to have an increased risk of a second local recurrence. This may be due to an intrinsically increased invasiveness of such lesions.

*Literature Review*

We found no other report in the literature evaluating prognostic indicators for patients undergoing reoperation for recurrent brain metastases. The only previous study to evaluate the results of reoperation for brain metastasis, by Sundaresan, *et al.*,[14] consisted of 21 patients. The median survival time was 9 months after reoperation. No prognostic indicators were presented. Interestingly, three of the 21 patients were found to have radiation necrosis at the time of reoperation.

Our 11.5-month median survival time for patients after reoperation is similar to the 9- to 15-month median survival time after initial craniotomy for patients in recent series in the literature, suggesting that prognosis after reoperation is similar to prognosis after initial resection.[1,4,12,14,17] Minimal data exist in the literature regarding the survival of patients who develop recurrent disease after initial surgery but who do not undergo reoperation. However, we recently reported on five such patients who survived only 2.5 months after recurrence.[2] Additionally, the nine patients in this report suffering from a second recurrence who did not undergo reoperation survived only a median of 2.8 months. Therefore, survival time is improved with reoperation.

The data on morbidity, mortality, and complications in our series are also comparable to those data on patients undergoing initial craniotomy.[1,11,12,14] Reoperation for recurrent brain metastasis can be performed without any increased risk of wound complication. This is in contrast to reoperation for malignant glioma. This may be because of the fact that not all patients in our series received radiation therapy prior to reoperation, and the radiation doses generally used for brain metastases, 30 Gy in 10 fractions, are lower than those used for malignant glioma.

## Conclusions

We conclude that reoperation for recurrent brain metastases can prolong survival and improve quality of life. A second reoperation can also increase survival. Five factors influence survival: status of systemic disease, KPS score, time to recurrence, age, and type of primary tumor. Our grading system using these five factors correlates with survival time. Finally, reoperation should be approached with caution in Grade IV patients because of their poor prognosis.

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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, Box 64, Houston, Texas 77030.