

CURRENT TREATMENT APPROACHES TO SURGERY FOR BRAIN METASTASES

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THE ROLE FOR surgical treatment of brain metastases continues to evolve. Data have demonstrated survival and quality-of-life benefits for surgical treatment of appropriate lesions in selected patients. With improvements in surgical technique, along with therapeutic improvements in the management of systemic cancers, more patients are now eligible for surgical resection. Selection of patients for surgical treatment depends on performance status, size, location, and number of brain lesions, as well as the status of systemic disease. Although surgery has traditionally been performed for patients with a single brain metastasis, an increasing number of patients with multiple brain metastases may also be treated surgically. Surgical techniques, such as image guidance, intraoperative ultrasound, functional neuronavigation, cortical mapping, and awake craniotomies, have expanded the scope of lesions that can be removed safely to optimize outcomes. Seizures, peritumoral edema, and venous thromboembolic disease all contribute significantly to surgical morbidity and mortality and thus require aggressive treatment around the time of the surgical procedure to improve the quality of life and maximize survival time.

KEY WORDS: Brain metastases, Neuronavigation, Radiosurgery, Recursive partitioning analysis, Whole-brain radiotherapy

Neurosurgery 57:S4-24-S4-32, 2005

DOI: 10.1227/01.NEU.0000182763.16246.60

www.neurosurgery-online.com

It is estimated that up to 170,000 new cases of brain metastases occur each year in the United States (23, 45). Some of these patients will be treated with craniotomy. As potential candidates for resection are considered, it is impossible to determine exactly who will benefit from surgical resection and postresection treatment because of the limited survival time associated with metastatic brain tumors. However, maturation of outcomes data has progressed sufficiently that predictions can be made with greater confidence. Surgical technique has improved to the extent that only a small part of patient prognosis is based on purely surgical considerations, per se. These improvements have led to approaches to treatment that are more aggressive. With advances in surgical techniques, more lesions are considered accessible, and have fewer complications from surgical procedures and less postsurgery morbidity. Modern imaging techniques are now able to locate and define smaller metastases that can be operated on earlier in their development, with a greater likelihood of being resected. Studies have demonstrated the benefit of surgical resection for controlling brain metastases, particularly when used in combination with whole-brain radiotherapy (41, 42). Most patients will succumb to extracranial disease rather than recurrence of brain metastases.

ROLE OF SURGERY IN THE TREATMENT OF BRAIN METASTASES

For many decades, whole-brain radiotherapy (WBRT) has been the standard approach for patients with cranial metastases. The benefit of surgery in the treatment of brain metastases has been validated by data from randomized trials (42, 56). In 1990, Patchell et al. (42) demonstrated the usefulness of craniotomy in a comparison of WBRT with and without surgery for patients with a single brain metastasis. This randomized study showed that the addition of surgery improved patient outcome. Median survival was significantly longer in the surgery-plus-WBRT group compared with the WBRT-alone group (40 wk versus 15 wk; $P < 0.01$), and patients who underwent surgery experienced longer functional independence (38 wk versus 8 wk; $P < 0.005$). These data later were confirmed by Vecht et al. (56), who randomized a group of 63 patients with brain metastases. Median survival in this study was 10 months for patients treated with surgery plus WBRT versus 6 months for patients treated with WBRT alone ($P = 0.04$). Another randomized trial in 84 patients failed to show a treatment benefit with the addition of surgery to WBRT (33). However, many patients in this study had factors that are associated

TABLE 3.1. Comparison of median survival times among patients with metastatic brain disease, according to type of treatment^a

	Series (ref. no.)		
	Fife et al., 2004 (15)	Sampson et al., 1998 (49)	Lagerwaard et al., 1999 (28)
No. of patients	1137	702	1292
Primary tumor type	Melanoma	Melanoma	Lung, breast, and melanoma
Supportive care (mo)	2.1	—	1.3
Radiation therapy (mo)	3.4	4.0	3.6
Surgery (mo)	8.7	6.5	—
Surgery + radiation therapy (mo)	8.9	8.9	8.9

^a From Fife KM, Colman MH, Stevens GN, Firth IC, Moon D, Shannon KF, Harman R, Petersen-Schaefer K, Zacest AC, Besser M, Milton GW, McCarthy WH, Thompson JF: Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol* 22: 1293-1300, 2004 (15).

with poor prognosis for surgical treatment, such as a low Karnofsky Performance Scale (KPS) score and disseminated systemic disease.

A subsequent study by Patchell et al. (41) in 1998 assessed the benefit of adding WBRT to surgery by randomizing 95 patients with brain metastases to surgery with or without WBRT. Although a difference in survival was not observed between the treatments arms, recurrence and neurological death were less likely in patients treated with surgery plus WBRT versus surgery alone. These data lend support to the use of WBRT with surgery, but it should be noted that adjunct WBRT remains a controversial topic (40).

Recent Progress in the Treatment of Brain Metastases

Although the prognosis for many patients with brain metastases remains poor, much progress has been made during the past 3 decades. Table 3.1 shows median survival for patients with metastatic brain tumors, comparing supportive care to radiation therapy alone and to surgery alone in three recent retrospective analyses, totaling 3131 patients. Two studies (15, 49) included patients with suspected melanoma, and the third study (28) included cerebral metastases arising mainly from primary tumors of the lung and breast. Regardless of the primary tumor type, median survival in patients who received supportive care was only 1 to 2 months. With surgery, the median survival time increased, ranging from 7 to 9 months, and the median survival time also was extended to approximately 9 months with surgery plus radiation therapy. These retrospective studies reveal that patient survival was significantly prolonged in treatment protocols that used surgery alone or in combination with radiotherapy compared with nonsurgical treatments.

It is of interest that the 1137 patients with brain metastases from melanoma evaluated in Fife et al. (15) were divided into two

groups based on the dates of the patient treatments: one cohort consisted of patients treated from 1952 to 1984 (n = 451) and a second cohort consisted of patients treated between 1985 and 2000 (n = 686). Both groups received supportive care, surgery, or radiation therapy, or a combination of surgery and radiotherapy. Despite advances in surgery and radiation therapy, the median survival was essentially the same in both cohorts. What did change was the percentage of patients who received more aggressive treatment: supportive care in the pre-1984 group was 74%, compared with 32% after 1984. In addition, the percentage of

patients receiving surgery alone was approximately the same, but surgery plus radiation therapy increased from 3% to 24%.

Selecting Patients for Surgical Treatment of Metastatic Brain Tumors: Who Will Survive Long Enough to Benefit from Treatment?

It is important to recognize that not all patients will benefit from the surgical removal of brain metastases, and a number of factors should be carefully considered in developing a treatment plan. Traditional criteria for selecting patients who will benefit from surgery include good physical function as assessed by KPS score, a single and surgically accessible metastasis, and stable or absent extracranial metastases. The KPS ranks patients on their ability to carry out activities of daily life, with scores of 70 or above having the best outcome after surgery (50). More recently, the Radiation Therapy Oncology Group has developed the recursive partitioning analysis (RPA) class, a statistical method of classifying patients that includes KPS score, patient age, and the status and extent of extracranial disease (16). Patients in RPA Class 1 are the best candidates for craniotomy. These patients are characterized by an age of 65 years or less, a KPS score of 70 or higher, and the absence of extracranial metastases, with good control of their systemic disease. The RPA Class 2 patients have a KPS score of 70 or higher but may also have age greater than 65 years, and have uncontrolled systemic disease and other systemic metastases. Selection of these patients for surgical treatment requires careful consideration of their likely duration of survival and their operative risks. Patients in RPA Class 3 are those patients with a KPS of less than 70; these patients have the poorest prognosis and are usually not chosen for surgery (1).

In addition to considering these RPA class prognostic factors, it is also important to consider tumor histology. Ad-

