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Surgery versus radiosurgery in the treatment of brain metastasis

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Surgery and radiosurgery are effective treatment modalities for brain metastasis. To compare the results of these treatment modalities, the authors followed 31 patients treated by radiosurgery and 62 patients treated by surgery who were retrospectively matched. Patients were matched according to the following criteria: histological characteristics of the primary tumor, extent of systemic disease, preoperative Karnofsky Performance Scale score, time to brain metastasis, number of brain metastases, and patient age and sex. For patients treated by radiosurgery, the median size of the treated lesion was 1.96 cm^3 (range 0.41–8.25 cm^3) and the median dose was 20 Gy (range 12–22 Gy). The median survival was 7.5 months for patients treated by radiosurgery and 16.4 months for those treated by surgery; this difference was found to be statistically significant using both univariate ($p = 0.0018$) and multivariate ($p = 0.0009$) analyses. The difference in survival was due to a higher rate of mortality from brain metastasis in the radiosurgery group than in the surgery group ($p < 0.0001$) and not due to a difference in the rate of death from systemic disease ($p = 0.28$). Log-rank analysis showed that the higher mortality rate found in the radiosurgery group was due to a greater progression rate of the radiosurgically treated lesions ($p = 0.0001$) and not due to the development of new brain metastasis ($p = 0.75$).

On the basis of their data, the authors conclude that surgery is superior to radiosurgery in the treatment of brain metastasis. Patients who undergo surgical treatment survive longer and have a better local control. The data lead the authors to suggest that the indications for radiosurgery should be limited to surgically inaccessible metastatic tumors or patients in poor medical condition. Surgery should remain the treatment of choice whenever possible.

Key Words • **brain metastasis** • **radiosurgery** • **surgery** • **outcome**

Brain metastasis is the most common type of intracranial tumor, with an estimated annual incidence of over 100,000 cases.[20] For patients with limited or absent systemic disease, brain metastasis reduces survival; hence, aggressive treatment is indicated. Surgical resection prolongs the survival of patients with limited systemic disease and single[17,18] or multiple[2] brain metastases. Recent data have indicated that radiosurgery is effective in the treatment of brain metastasis.[1,6,8,10,11,14–16,22,23,25] Even though survival results for radiosurgical series are not as impressive as those for surgery, some authors have suggested that radiosurgery is as effective as, or superior to, surgery.[14,16,25] However, to date no study has ever compared these two treatment modalities in a meaningful way.

Clinical Material and Methods

Radiosurgery Patients

Thirty-one consecutive patients with new brain metastasis who were treated with radiosurgery at the M. D. Anderson Cancer Center from August 1991 to March 1994 were followed and analyzed. The eligibility criteria for radiosurgical treatment were similar to those for surgical treatment: all patients had limited systemic disease and good Karnofsky Performance Scale[13] (KPS) scores. Additional selection criteria for radiosurgical treatment included small (< 3 cm in maximum diameter) spherical well-circumscribed lesions and patient preference.

Follow-up neuroimaging was performed at intervals of 1, 3, 6, 12, and 18 months until last follow-up examination or death. The size of each lesion treated was determined by computerized volumetric analysis at each follow-up visit. Progression of disease was defined as an increase in lesion size that was greater than 25% compared to the previous image. The median size of the lesions treated was 1.96 cm^3 (range 0.41–8.25 cm^3). The median radiation dose at the isocenter was 20 Gy (range 12–22 Gy). The median radiation dose at the tumor margin was 18.7 Gy (range 17–22 Gy). In all instances, only one isocenter was used. The mean cone size was 2.27 cm (range 1.5–3.25 cm).

Volumetric Measurements

An imaging software program (Image 1.52, supplied at no charge by the National Technical Information Service, Springfield, VA) was used to obtain volumetric measurements.

Matching of Patients

Each patient who underwent radiosurgery was matched to two patients from a pool of over 500 who underwent surgery for brain metastasis over a similar time period. The large number of surgically treated patients allowed us to select 62 well-matched patients, thereby increasing the statistical power of the study. Patients were matched according to the following criteria: histological characteristics of the primary tumor, extent of systemic disease, preoperative KPS score, time to brain metastasis, number of brain metastases, and patient age and sex. All of these are known or potential prognostic indicators.[20] The characteristics of both patient groups and the results of a statistical comparison are presented in Table 1.

Location of Tumor

The hypothetical surgical morbidity of resection of the lesions in the radiosurgery group was similar to that of the surgery group. Retrospective analysis of the tumors treated with radiosurgery demonstrated that 80.5% were surgically resectable with minimal or no morbidity.

Whole-Brain Radiation Therapy

Treatment with whole-brain radiation therapy (WBRT) was similar in both groups of patients. Of the 22 patients in the radiosurgery group receiving WBRT, 16 received preradiosurgery WBRT and six received periradiosurgery WBRT. None of the radiosurgically treated patients had WBRT withheld until recurrence. Two patients in the surgically treated group had WBRT at the time of recurrence. This difference was not statistically significant ($p > 0.05$).

Cause-of-Death Analysis

Cause of death was defined as "neurological" in patients who died with stable systemic disease and advancing brain metastasis or radiation effect; as "systemic" in patients who died with stable brain metastasis and advancing systemic disease; and as "combined" in patients who died with progressive neurological and systemic disease. Systemic and neurological survival periods were calculated using the Kaplan–Meier[12] survival method. In calculating systemic survival periods, patient deaths from systemic or combined causes were used as the endpoints, whereas all other patients were censored at last follow-up examination or at time of death. In calculating neurological survival periods, patient deaths from neurological or combined causes were used as the end points, whereas all other patients were censored at last follow-up examination or at time of death.

Recurrence of Tumor

"Local recurrence" was defined as failure of the treatment to control the treated lesion as exhibited on follow-up magnetic resonance (MR) imaging. Growth of a radiosurgically treated lesion that was greater than 25% or radiographic recurrence of a surgically treated lesion was labeled a local recurrence. We prefer to use the term "progression of disease" for the radiosurgery group because radiographic growth of a lesion does not distinguish between tumor growth, radiation necrosis, or tumor hemorrhage. "Distant recurrence" was defined as development of a new brain metastasis elsewhere in the brain. Reoperation was considered for patients in both groups who developed recurrence in the brain and had limited systemic disease.

TABLE 1

*Characteristics of 62 surgically treated patients and 31 radiosurgically treated patients with brain metastasis**

Variable	No. of Patients (%) Surgery	Radiosurgery	p Value
sex			0.30
male	29 (47)	18 (58)	
female	33 (53)	13 (42)	
site of primary tumor			1.0
lung	16 (26)	8 (26)	
melanoma	14 (23)	7 (23)	
breast	10 (16)	5 (16)	
kidney	10 (16)	5 (16)	
colon	6 (10)	3 (10)	
other	2 (3)	1 (3)	
none found	4 (6)	2 (6)	
multiple lesions			0.73
yes	16 (26)	7 (23)	
no	46 (74)	24 (77)	
whole-brain radiation therapy			0.64
yes	41 (66)	22 (71)	
no	21 (34)	9 (29)	
chemotherapy			0.026
yes	21 (34)	18 (58)	
no	41 (66)	13 (42)	
systemic disease			0.38
yes	32 (52)	13 (42)	
no	30 (48)	18 (58)	
median age (yrs)	54.5	58.0	0.15
median preop KPS score	80	80	0.58
median time to metastasis (mos)	11.5	11.0	0.89

* KPS = Karnofsky Performance Scale.

Statistical Analysis

Survival curves were drawn using the Kaplan–Meier product-limit method.[12] The log-rank test and univariate Cox proportional hazards regression analyses were applied to evaluate the differences between survival curves.[7] The Cox regression model was used to study the effects of multiple covariates on patient survival periods.[7] The following covariates were used in the Cox regression model: surgical or radiosurgical treatment, site of the primary tumor, extent of systemic disease, preoperative KPS score, patient age, presence of multiple lesions, use of WBRT, and use of chemotherapy. Where indicated, 95% confidence intervals (CIs) and relative risks (RRs) are given.

Results

Survival Analysis

Figure 1 displays a comparison of survival curves in the surgical and radiosurgical groups. The median survival

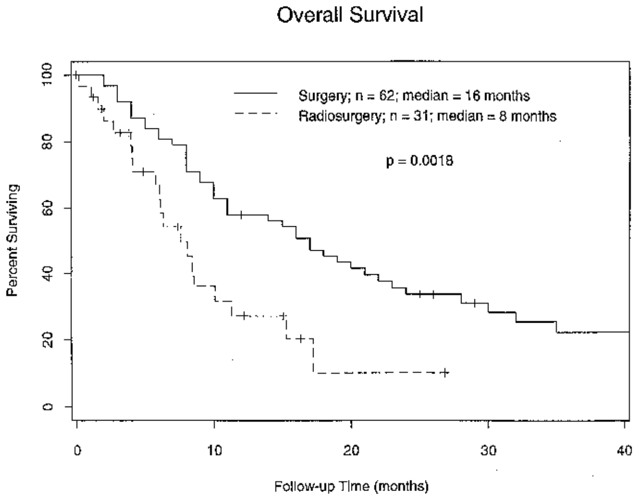


FIG. 1. Graph depicting a comparison of survival periods in surgically and radiosurgically treated patients. Radiosurgically treated patients had a shorter overall survival period according to both univariate and multivariate analyses. n = number of patients.

period in the surgical group was 16.4 months, whereas that in the radiosurgical group was 7.5 months. The 1-year survival rates for the surgical and radiosurgical groups were 58% (95% CI 44%–71%) and 27% (95% CI 11%–50%), respectively. This difference was statistically significant according to both univariate ($p = 0.0041$, RR = 2.36) and multivariate ($p = 0.0009$, RR = 3.17) analyses.

Cause-of-Death Analysis

Causes of death are shown in Table 2. Causes of death differed significantly between the two groups ($p = 0.037$, Pearson Chi-square test). Neurological causes accounted for 50% of deaths in the radiosurgical group but only 19% of deaths in the surgical group.

Figure 2 *left* displays a comparison of systemic survival periods in the surgical and radiosurgical groups. The median systemic survival period in the surgical group was 25 months; the median was not reached in the radiosurgical group. The rates of 6-month freedom from systemic death were 84% for the surgical group (95% CI 72%–92%) and 79% for the radiosurgical group (95% CI 55%–94%). There was no statistically significant difference in systemic survival periods ($p = 0.28$, RR = 1.53) between the two groups.

TABLE 2

Causes of death in patients treated by surgery or radiosurgery

Cause of Death	Surgical Group (43 patients)	Radiosurgical Group (20 patients)
neurological	8 (19%)	10 (50%)
systemic	23 (53%)	5 (25%)
combined	6 (14%)	4 (20%)
unknown	6 (14%)	1 (5%)

Figure 2 *right* shows a comparison of neurological survival periods in the surgical and radiosurgical groups. The median neurological survival for the surgical group was not reached; this period was 9 months in the radiosurgical group. The rates of 6-month freedom from neurological death were 95% for the surgical group (95% CI 86%–99%) and 79% for the radiosurgical group (95% CI 56%–94%). The 1-year freedom from neurological death was 83% for the surgical group (95% CI 67%–93%) and 40% for the radiosurgical group (95% CI 16%–68%). Radiosurgically treated patients had significantly shorter neurological survival periods according to both univariate ($p < 0.0001$, RR = 5.12) and multivariate ($p = 0.05$) analyses.

Recurrence of Tumor

In the surgical group, five patients (8.1%) suffered a local recurrence, 13 (21.0%) a distant recurrence, and three (4.8%) both local and distant recurrences. In the radiosurgical group, 12 patients (38.7%) suffered a local progression of disease, three (9.7%) a distant recurrence, and none (0%) both local and distant recurrences. The median time from the last MR image to death or last follow-up examination was 2 months each. Figure 3 *left* dis-

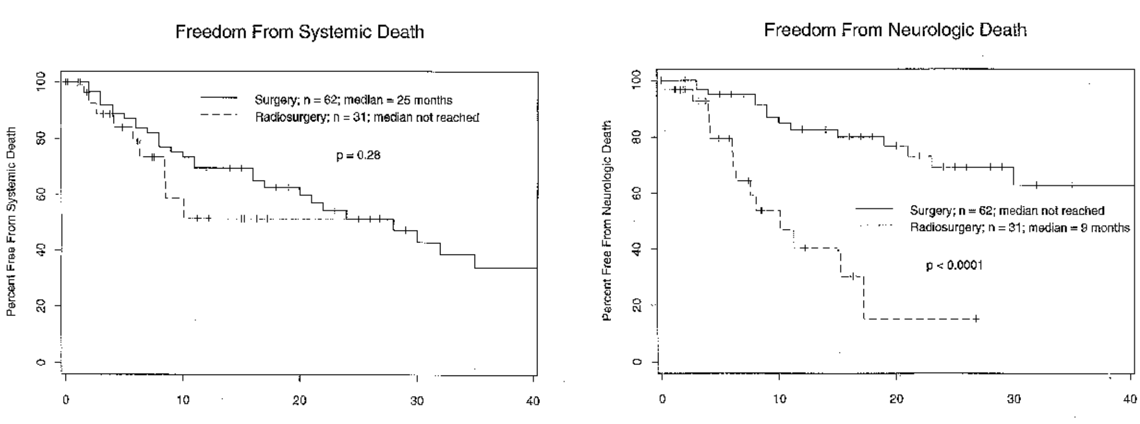
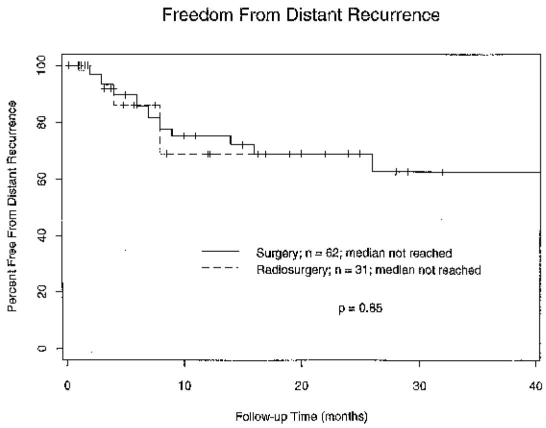


FIG. 2. Graphs showing comparisons of systemic *(left)* and neurological *(right)* survival in the surgical and radiosurgical groups. There was no difference in systemic survival. Radiosurgically treated patients exhibited shorter neurological survival periods according to both univariate and multivariate analyses. n = number of patients.



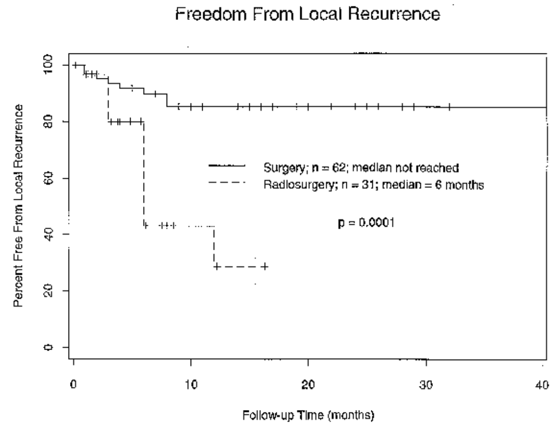


FIG. 3. Graphs displaying comparisons between the surgical and radiosurgical groups for freedom from both distant *(left)* and local *(right)* recurrence of disease. There was no difference in distant recurrence rates between the two groups. Radiosurgery yielded significantly poorer local tumor control than surgery according to both univariate and multivariate analyses. n = number of patients.

plays a comparison of freedom from distant recurrence in the brain in the surgical and radiosurgical groups. The rate of 6-month freedom from distant recurrence was 86% for both the surgical (95% CI 73%–94%) and radiosurgical (95% CI 46%–99%) patients. The rates of 1-year freedom from distant recurrence were 75% for the surgical (95% CI 57%–88%) and 69% for the radiosurgical (95% CI 10%–99%) patients. There was no statistically significant difference in the distant recurrence rates between the two groups ($p = 0.85$, RR = 1.11).

Figure 3 *right* shows a comparison of local control rates in the surgical and radiosurgical groups. Control of the treated lesion was significantly poorer in the radiosurgical group according to both univariate ($p = 0.0001$, RR = 5.00) and multivariate ($p = 0.05$) analyses.

Posttreatment Complications

Complications in the radiosurgery group included symptomatic radiation necrosis in four patients (12.9%). Spontaneous intratumoral hemorrhage occurred in three patients (9.7%), resulting in the death of one. Two of these patients had melanoma and one had lung adenocarcinoma. Three patients underwent craniotomy for tumor resection after radiosurgery failed to control the lesion size; one of these patients had significant radiation necrosis in addition to local tumor recurrence, the second had recurrent tumor, and the third had significant spontaneous intratumoral hemorrhage. Four patients developed significant deep-vein thrombosis within 30 days after radiation treatment and required anticoagulation therapy or placement of a Greenfield filter. Radiosurgery patients generally remained in the hospital overnight and left the next day.

Complications in the surgery group included postoperative hematoma in two patients (one case of melanoma and one of unknown primary adenocarcinoma), neither requiring additional surgery. One patient had a postoperative wound infection that was treated with antibiotic medication. The median hospital stay for the surgical group was 4 days (range 2–22 days). This length of stay was significantly longer than the 1-day stay for radiosurgery patients ($p < 0.0001$, Wilcoxon sign–rank task).

Discussion

Patients with surgically resected brain metastasis survived significantly longer than similar patients treated with radiosurgery. Patients with cancer that has metastasized to the brain usually die from systemic disease or from brain metastasis. Neurological death occurs from increasing size or mass effect of the presenting brain metastasis or from new brain lesions. Kaplan–Meier analysis[12] demonstrates similar rates of mortality from systemic disease in the two groups; hence, systemic disease was equally advanced in both groups. In addition, the two groups had equivalent rates of distant recurrence. Thus the development of new brain metastasis was not the cause of the higher mortality rate in the radiosurgery group. This is to be expected, because neither surgery nor radiosurgery should have an impact on the development of new brain lesions. Additionally, WBRT, which can impact on the development of new brain metastasis, was given equally to both groups (Table 1). However, analysis clearly demonstrated that in the radiosurgery group there was significantly poorer control of the treated lesions and this was the cause of the shorter overall survival periods in this group.

Patient Characteristics

The radiosurgery patients in our study are very comparable to patients in other selected reports in the literature (Table 3). The median size of the treated lesions in our study was 1.96 cm^3 and the median radiation doses at the isocenter and tumor margins were 20 Gy and 18.7 Gy, respectively, all of which are very similar to those in other studies.[1,5,7–9,11,12,14,16,18,19,24] The 7.5-month median survival period is also quite comparable to those of other studies (Table 4). Primary oncology care for our patients was delivered at our institution, assuring the completeness of our follow-up study.

The surgery group in this paper is similar to those specified in published series from our own and other institutions (Table 4).[2–5,9,17,18,21,23,27] The recurrence and complication rates for this group were also similar to those reported in the literature. The median survival period in our surgical series is slightly longer than that of other published series due to the lower rate of systemic disease and higher KPS scores.

Recurrence of Tumor

Overall, 38.7% of the patients in the radiosurgery group had radiographic progression of disease. In this study, radiographic progression of disease includes tumor recurrence, radiation necrosis, and tumor hemorrhage. Recent literature has demonstrated that local tumor recurrence in surgical series occurs a median of 2.5 to 2.8 months prior to death for patients who do not undergo reoperation.[2,3] Hence, to assess local recurrence accurately, the time from the last MR image to death should be as short as possible. In this study, the median time from the last MR image to death was 2 months.

Recent studies have reported that tumor recurrence occurs in 30% to 40% of all patients undergoing surgery. Local recurrence occurs in 5% to 15% of patients, distant recurrence occurs in 10% to 20%, and both local and distant recurrence in 5% to 10% of patients.[2,18,20,24] The recurrence results in this surgical series are similar to results found in the literature.

Study Limitations

We retrospectively matched, by known prognostic indicators, radiosurgically treated patients to similar patients who were surgically treated. Features that were not matched included lesion location and size. The radiosurgery group generally had smaller lesions than the surgery group; however, a volumetric analysis of lesion size was not performed for the surgery group. The great majority (80.5%) of radiosurgical lesions were in surgically accessible areas of the brain. This is well illustrated by the fact that three patients underwent craniotomy after radiosurgery failed to control the lesion. Lesion location may have a small impact on survival, but this impact is possible only if the lesion is not locally controlled. The differences in lesion location and size were unlikely to result in a difference in survival length as great as that seen in this study (7.5 months vs. 16.4 months). Perhaps most importantly, lesion location should have had no impact on local control rates, which were also significantly different.

Finally, this study was retrospective, not prospective and randomized in nature. However, a randomized trial could not match the patients for all known factors unless large numbers of patients were recruited into each arm of the study. Even so, we have taken special care to ensure that both patient groups were well matched by a variety of indicators.

Management Guidelines

Radiosurgery is a new method of treatment that has certain advantages over surgery. Radiosurgery is noninvasive, requires a shorter hospital stay, and is somewhat less

TABLE 3

*Literature review of radiosurgery for brain metastasis**

Authors & Year	No. of Cases	Size of Lesion	Isocenter Radiation Dose	Tumor Margin Radiation Dose	Cone Size	No. of Collimators	Time to Brain Metastasis	% With Systemic Disease	Median KPS Score	% With Multiple Lesions	Median Follow Up	Volumetric Analysis	Cause of Death	Median Survival (mos)
Sturm, *et al.*, 1987	7	median 2 cm diameter	median 27.5 Gy	median 22 Gy	NS	NS	NS	NS	NS	0%	3.5 mos	NS	25% ND, 75% SD	3.5
Kihlström, *et al.*, 1991	160	mean 4.5 cm^3	NS	mean 27 Gy	NS	NS	NS	NS	NS	NS	NS	NS	10% ND	7 (mean)
Adler, *et al.*, 1992	33	mean 5.93 cm^3	NS	mean 25 Gy	mean 2.0 cm	NS	NS	NS	NS	39%	mean 5.5 mos	yes	NS	UK
Mehta, *et al.*, 1992	40	mean 5.2 cm^3	mean 24 Gy	mean 18.3 Gy	median 2.5 cm	2–12	NS	NS	75	25%	6.5 mos	yes	25% ND, 75% SD	6.5
Engenhart, *et al.*, 1993	69	mean 12.1 cm^3	mean 21.5 Gy	NS	mean 2.9 cm	NS	NS	76%	NS	NS	mean 8.6 mos	NS	NS	6
Loeffler & Alexander, 1993	196	median 3.2 cm^3	median 20.3 Gy	median 16.5 Gy	median 2.75 cm	2–16	NS	NS	80	NS	9 mos	NS	38% ND, 47% SD, 14% CD	9
Somaza, *et al.*, 1993	23	mean 2.5 cm^3	NS	mean 16 Gy	NS	NS	mean 42.5 mos	91%	85	17%	NS	NS	78% SD, 4% ND, 18% alive	7
Valentino, *et al.*, 1993	86	NS	median 50 Gy	NS	NS	NS	NS	NS	65	0%	NS	NS	NS	9.9
Flickinger, *et al.*, 1994	116	mean 18.7 mm diameter	mean 34.5 Gy	mean 17.5 Gy	NS	NS	NS	NS	NS	0%	7 mos	yes	NS	11
Bindal, *et al.*, 1996 (current report)	31	median 1.96 cm^3	median 20 Gy	median 18.7 Gy	mean 2.27 cm	mean 5	median 11 mos	42%	80	23%	6.5 mos	yes	50% ND, 25% SD, 20% CD, 5% UK	7.5

* Abbreviations: CD = combined; KPS = Karnofsky Performance Scale; ND = neurological disease; NS = not stated; SD = systemic disease; UK = unknown.

TABLE 4
Literature review of surgical and radiosurgical series

Authors & Year	No. of Cases	Median Survival (mos)
surgical series		
Sundaresan & Galicich, 1985	125	12
Ferrara, *et al.*, 1990	100	13
Burt, *et al.*, 1992	185	14
Bindal, *et al.*, 1993	52	14
Bindal, *et al.*, 1996 (current report)	62	16.4
radiosurgical series		
Kihlström, *et al.*, 1991	160	7
Engenhart, *et al.*, 1993	69	6
Loeffler & Alexander, 1993	196	9
Flickinger, *et al.*, 1994	116	11
Bindal, *et al.*, 1996 (current report)	31	7.5

expensive than surgery. However, these advantages must be weighed against radiosurgery's potentially higher complication rate and shorter survival period compared with surgery. Additionally, surgery offers the advantage of providing histological verification. It is well established that 5% to 11% of patients with known systemic disease and a brain lesion consistent with brain metastasis actually have nonmetastatic disease.[18,26] Thus, although radiosurgery remains a powerful treatment option for brain metastasis, it should be used primarily as an adjunct to surgery. Radiosurgery is indicated for lesions in surgically inaccessible locations; however, the definition of surgically inaccessible is often a matter of opinion. Modern neurosurgical techniques, including stereotaxy and intraoperative ultrasonography, have made many previously inaccessible lesions accessible.[19] Recent advances in cortical mapping have also aided in aggressive complication-free resection. Not only is lesion location important in determining accessibility, but size is also a consideration. For example, a deep white-matter lesion may be considered inaccessible if very small but accessible if larger. Thus, when faced with a small white-matter lesion in an eloquent region of brain and moderately advanced systemic disease, one may opt for radiosurgery.

Radiosurgery can be used as part of a multimodality treatment for patients with multiple brain metastases. We previously showed that resection of all brain metastases markedly prolongs survival of patients with multiple brain metastases.[2] In a patient with a large, symptomatic lesion and a small, deep white-matter lesion, the large lesion may be treated with surgery and the small one with radiosurgery.

Because radiosurgery is a noninvasive treatment, it may also have a role in treating patients who are not surgical candidates because of advanced systemic disease or poor medical condition. Radiosurgery is more effective at local tumor control than WBRT and, therefore, may be used as an adjunct to, or even in lieu of, WBRT for patients in poor medical condition. Thus, radiosurgery remains an important and powerful tool in the treatment of brain metastasis.

Conclusions

On the basis of our data, we conclude that surgery has produced better results than radiosurgery in the treatment of brain metastasis. Patients who undergo surgical treatment survive longer and have better local tumor control. Our data lead us to suggest that the indications for radiosurgery should be limited to surgically inaccessible metastatic tumors or patients in poor medical condition. Surgery should remain the treatment of choice whenever possible.

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