

Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter

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Object. The aim of this retrospective study was to compare treatment results of surgery plus whole-brain radiation therapy (WBRT) with gamma knife radiosurgery alone as the primary treatment for solitary cerebral metastases suitable for radiosurgical treatment.

Methods. Patients who had a single circumscribed tumor that was 3.5 cm or smaller in diameter were included. Treatment results were compared between microsurgery plus WBRT (52 patients, median tumor dose 50 Gy) and radiosurgery alone (56 patients, median prescribed tumor dose 22 Gy). In case of local/distant tumor recurrence in the radiosurgery group, additional radiosurgical treatment was administered in patients with stable systemic disease. Survival time was analyzed using the Kaplan-Meier method, and prognostic factors were obtained from the Cox model. The patient groups did not differ in terms of age, gender, pretreatment Karnofsky Performance Scale (KPS) score, duration of symptoms, tumor location, histological findings, status of the primary tumor, time to metastasis, and cause of death. Patients who suffered from larger lesions underwent surgery ($p < 0.01$). The 1-year survival rate (median survival) was 53% (68 weeks) in the surgical group and 43% (35 weeks) in the radiosurgical group ($p = 0.19$). The 1-year local tumor control rates after surgery and radiosurgery were 75% and 83%, respectively ($p = 0.49$), and the 1-year neurological death rates in these groups were 37% and 39% ($p = 0.8$). Shorter overall survival time in the radiosurgery group was related to higher systemic death rates. A pretreatment KPS score of less than 70 was a predictor of unfavorable survival. Perioperative morbidity and mortality rates were 7.7% and 1.6% in the resection group, and 8.9% and 1.2% in the radiosurgery group, respectively. Four patients presented with transient radiogenic complications after radiosurgery.

Conclusions. Radiosurgery alone can result in local tumor control rates as good as those for surgery plus WBRT in selected patients. Radiosurgery should not be routinely combined with radiotherapy.

KEY WORDS • cerebral metastasis • radiosurgery • surgery • radiotherapy

STANDARD treatment of patients with a solitary brain metastasis and limited or stable systemic disease is tumor resection in combination with whole-brain radiation therapy (WBRT).^{26,27,36} Radiosurgical treatment has gained increasing therapeutic relevance for selected patients with small, circumscribed metastases in any location in the brain. It is minimally invasive, and local tumor control rates in the range of 64 to 97% have been reported.^{1-5,9-11,14,17,29,31,33,35,39,40} In a recently published retrospective study, however, the efficacy of radiosurgery has been questioned; patients treated with radiosurgery had a significantly worse outcome in terms of local tumor control rates and length of survival as compared with standard treatment.⁴ Although Bindal, et al.,⁴ have been criticized by others regarding the applied technique of radiosurgery, patient selection, and statistical analysis, they were the first to compare a surgical and a radiosurgical group treated during a comparable time interval.^{25,32,37,41} All other studies have been based on historical control groups. Thus far, no investigator has reported treatment results from

surgery plus WBRT for brain metastases that might also have been amenable to radiosurgical treatment. It remains unclear whether radiosurgery should be performed in combination with WBRT. Therefore, our two-institution study was conducted retrospectively to establish the efficacy of surgery plus WBRT compared with radiosurgery alone in a homogeneous patient population in whom small, solitary cerebral metastases were treated; all patients in the surgery group were considered to have been eligible for radiosurgical treatment as well. We sought to determine whether the use of a local treatment concept such as radiosurgery could achieve results as good as microsurgery combined with WBRT.

Clinical Material and Methods

Patient Population

Patients with single circumscribed brain metastases 3.5 cm or smaller in diameter and stable systemic disease

were included in the present study. Patients who experienced intracranial tumor recurrence after previously performed surgery plus WBRT were excluded. No patient showed clinical signs of increased intracranial pressure necessitating emergency neurosurgical intervention. A decision in favor of surgery or radiosurgery was made independently in each treatment center (Gamma Knife Center, Munich, or the Department of Neurosurgery, Ludwig-Maximilians University, Munich). The primary tumor was regularly evaluated using chest x-ray films, computerized tomography (CT) scanning of the abdomen, radionuclide scanning, and a hematological and chemical profile. Patients with small cell lung cancer, malignant lymphoma, germ cell tumors, and documented or suspected leptomeningeal disease or intracranial tumor deposits other than a single parenchymal brain metastasis were excluded.

Treatment Protocol

Surgical Group. Between August 1990 and July 1997, 228 patients underwent operation for metastatic lesions in the Department of Neurosurgery at the Ludwig-Maximilians University Hospital, Munich, Germany. A time interval in this range was chosen so as to include an adequate number of patients to compare with the radiosurgery group. Fifty-two patients in the surgery group were considered eligible for radiosurgical treatment according to the criteria of the study protocol and were included in the present study. Preoperative magnetic resonance (MR) images with gadolinium enhancement were available for each patient. Tumor resection was performed using microsurgical techniques. All patients received WBRT beginning within 2 weeks postsurgery at a conventional fractionated dose of 40 Gy plus an additional boost to the tumor bed of 10 Gy. No patient in the surgery group received additional radiosurgical treatment prior to or after surgical treatment. Surgical retreatment was not an exclusion criterion. The median hospital stay for surgery was 10 days. Conventional fractionated radiotherapy with a tumor dose of 50 Gy required 5 weeks of treatment. Radiotherapy was performed only in part on an outpatient basis.

Radiosurgical Group. Between December 1994 and July 1997, a consecutive series of 56 patients who had a single cerebral metastasis were treated radiosurgically by using the gamma knife. No patient was lost to follow up or excluded from this study. Additional surgical treatment and/or WBRT was not performed before or after radiosurgery. The diagnosis of brain metastasis was based on radiological findings and the histological findings in the primary tumor. In three patients with no known primary tumor, a stereotactic biopsy procedure was performed. Gadolinium-enhanced MR images were used for treatment planning as well as for the follow-up examinations in all patients. The minimum dose applied to the tumor margin (prescribed tumor dose) varied from 14 to 27 Gy (mean 21 Gy). The prescribed tumor dose (range 20–27 Gy) was higher for radioresistant diseases such as melanoma and hypernephroma, as compared with more radiosensitive tumors such as breast or lung cancer (range 14–20 Gy). The maximum dose varied from 28 to 54 Gy (mean 41 Gy). The outline of the target volume was on average within the 50% isodose contour (range 35–85%). In seven pa-

tients with larger tumor volumes the prescribed dose was within the 35% isodose contour. In three patients with very small tumors the prescribed dose was within the 85% isodose. Multiple isocenters (mean number seven) were chosen to match the tumor volume as accurately as possible.³⁸ In cases of local or distant tumor recurrences, an additional radiosurgical procedure was performed if the patient was in good clinical condition with stable systemic disease.

Follow-Up Evaluation

Neurological examination and tumor response as verified on MR imaging were used to evaluate patients during follow-up review. Follow-up examinations were performed 6 and 12 weeks after surgery or radiosurgery and then at 3-month intervals until death of the patient or closure of the study (November 1, 1997). The Karnofsky Performance Scale (KPS) score was used to define improvement.¹⁶ When the KPS score remained unchanged or was better than the preoperative findings, this was referred to as stabilized/improved status. Otherwise, the status was considered to be deteriorated. Complete response after radiosurgery was defined as disappearance of the enhanced lesion, and partial response was defined as tumor shrinkage of more than 50%. Stable disease indicated the lack of any significant increase in tumor volume ($\geq 25\%$) or tumor shrinkage of less than 50%. An increase in tumor size of more than 25% was classified as progressive disease or local recurrence. A local recurrence was defined as the reappearance of a metastasis at exactly the same site as the first one, and a distant recurrence was defined as the appearance of a new brain metastasis at a site different from that of the original one. Freedom from local or distant recurrence was calculated from the date of the initial surgery/radiosurgery to the date that a local or distant recurrence was detected on MR imaging; neither calculation was confounded by the effects of new treatment or retreatment. To analyze the effects of a new radiosurgical treatment in patients with a distant recurrence we created a new term: freedom from distant tumor progression. Freedom from distant tumor progression was defined as the time from the initial radiosurgical treatment to the date of irreversible distant tumor progression that was considered for new radiosurgical procedures.

Tumor volume in follow-up CT and MR studies was calculated for the radiosurgery group by using a computerized planning system. For the surgical group the contrast-enhanced area was measured on the successive image slices and the volume was calculated manually. A transient radiogenic complication was assumed when new clinical symptoms seen after radiosurgery were associated with increased edema in the follow-up MR imaging.

The cause of death was determined according to the prospective study protocol of Patchell, et al.,²⁷ that is, patients with stable extracerebral disease and progressive neurological dysfunction, patients with severe neurological disability who were dying from intercurrent illness, and patients with progressive systemic and neurological disease were counted as neurological deaths; otherwise a systemic death was assumed. Autopsy data were not available for these patients.

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Statistical Analysis

The reference point for survival was the date of the surgical or radiosurgical procedure. Endpoints were death, date of local or distant recurrence, and date of distant tumor progression. Length of survival, freedom from local recurrence, distant recurrence, and distant tumor progression were estimated using the Kaplan–Meier method.¹⁵ When survival curves were based on neurological causes, deaths from other causes were treated as censored. When survival curves were based on nonneurological causes, deaths from neurological causes were treated as censored. Comparisons of Kaplan–Meier curves were performed using the log-rank statistic. The prognostic value of the individual covariates was obtained using the Cox proportional hazards model.⁶ Because of the small number of events in the study only a limited number of covariates could be tested multivariately. Thus, only covariates that appeared important ($p < 0.05$) after univariate analysis plus the “prescribed treatment” covariate were included in the final prognostic model. The following covariates were entered: prescribed treatment (surgery compared with radiosurgery); age at resection or radiosurgery (> 60 compared with ≤ 60 years); pretreatment KPS score (≥ 70 compared with < 70); tumor size (< 3 cm in diameter compared with ≥ 3 cm); tumor location (supratentorial compared with infratentorial); histological findings in the primary tumor (bronchial carcinoma compared with other); status of the primary tumor (localized compared with disseminated); and the latency period between diagnosis of the primary tumor and development of cerebral metastasis. The distribution of the covariates between the two patient groups was analyzed using the chi-square test (for dichotomized covariates) or the Wilcoxon test (for continuously scaled covariates).

Results

One hundred eight patients (50 males and 58 females) with a mean age of 59 years (range 17–83 years) and a median follow-up period of 69 weeks for the survivors were included in the present study. The distribution of pretreatment clinical and radiological factors is summarized in Table 1. Treatment groups did not differ in terms of age, KPS score, gender, duration of symptoms, tumor location, incidence of bronchial carcinoma, time to metastasis, or cause of death. The status of the primary tumor was more often classified as disseminated in the radiosurgery group (32 patients compared with 27 patients); however, the difference was not statistically significant ($p > 0.05$). Patients treated with radiosurgery had significantly smaller tumor volumes ($p < 0.01$); also, the incidence of melanoma metastases was higher in this treatment group (16 patients compared with seven patients). The median hospital stay after surgery plus WBRT was 5 weeks. Radio-surgery was usually performed on an outpatient basis.

Prognostic Factors in Survival

Thirty-one of the surgically treated patients died, 18 from progressive central nervous system disease and 13 from systemic illness, whereas 33 patients in the radiosurgery group died, 16 from progressive central nervous

TABLE 1

*Distribution of pretreatment clinical parameters in 108 patients with small, solitary cerebral metastases**

Variable	No. of Patients (%)		p Value
	Surgery Group	Radiosurgery Group	
total no. treated	52	56	
sex (M/F)	22:30	28:28	0.3
age (yrs)			0.3
mean \pm SD	56.3 \pm 10.6	59.3 \pm 13.7	
median	59	59	
range	17–74	27–83	
KPS score			0.7
mean \pm SD	74.4 \pm 15.1	81.1 \pm 9.3	
median	70	80	
range	60–100	70–100	
tumor diameter (cm)			<0.001
mean \pm SD	2.7 \pm 0.7	2.07 \pm 0.9	
median	3	2	
tumor location			0.16
supratentorial	39 (75)	48 (85.7)	
infratentorial	13 (25)	8 (14.3)	
site of primary tumor			0.9
lung/other	17/35	17/39	
lung (NSC)	17 (32.7)	17 (30.4)	
genitourinary tract	10 (19.2)	8 (14.3)	
gastrointestinal tract	7 (13.5)	3 (5.4)	
melanoma	7 (13.5)	16 (28.6)	
breast	6 (11.5)	8 (14.3)	
other	1 (1.9)	1 (1.8)	
unknown	4 (7.7)	3 (5.4)	
status of primary tumor			0.42
localized	25 (48.1)	24 (42.6)	
disseminated	27 (51.9)	32 (57.1)	
time to metastasis (mos)			0.59
mean \pm SD	25.7 \pm 23.2	31 \pm 35.6	
median	15	14	

* NSC = nonsmall cell bronchial carcinoma; SD = standard deviation.

system disease and 17 from systemic illness. The median survival was 68 weeks after surgery plus WBRT and 35 weeks after radiosurgery alone. The 1-year survival rates for the surgical and radiosurgical groups were 53% and 43%, respectively (Fig. 1). The difference was not statistically significant ($p = 0.19$). Patients with bronchial carcinoma had a median survival time of only 24 weeks. Patients with metastasis from breast cancer survived longest, with a median survival of 80 weeks. A KPS score of less than 70 was prognostically unfavorable after univariate and multivariate analysis ($p < 0.05$). The treatment variable (surgery compared with radiosurgery) gained no significant influence.

Treatment Response: Cause of Death Analysis

A complete response, partial response, and stable disease after radiosurgery were obtained in 12.5%, 42.9%, and 39.3% of patients, respectively. Progressive disease was seen in three (5.4%) of the 56 patients in this group. Four patients underwent additional gamma knife treatment to achieve local tumor control. In two patients radiosurgical retreatment did not stop tumor progression. One patient with tumor progression was not considered suitable for retreatment because of poor clinical condition. The 1-year freedom from local recurrence rate was 75% in

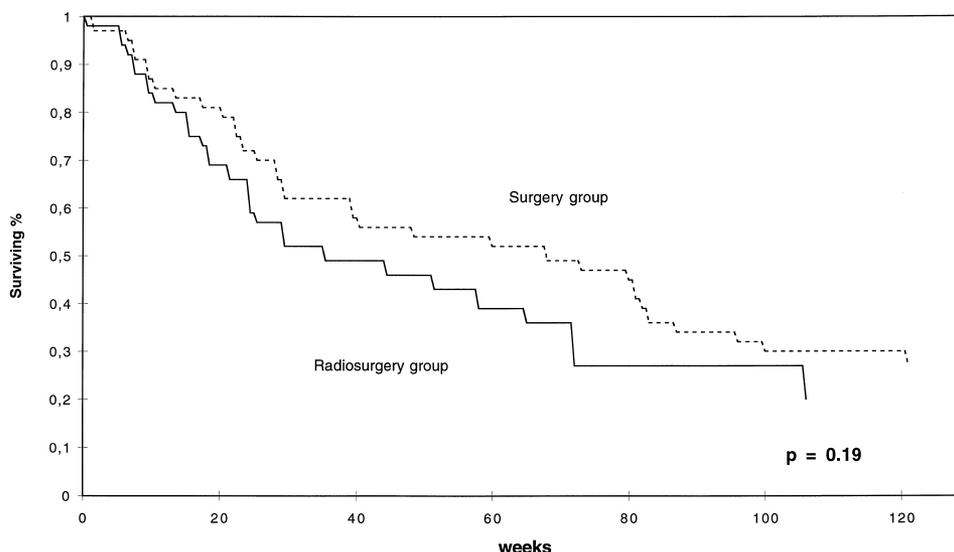


FIG. 1. Graph showing cumulative overall survival rates after surgery plus WBRT (52 patients) and radiosurgery (56 patients). Surgically treated patients (*dashed line*) demonstrated a longer overall survival time (median 68 weeks) than radiosurgically treated patients (*solid line*; median 35 weeks). The difference was not statistically significant.

the surgery group and 83% in the radiosurgery group (Fig. 2). The difference was not statistically significant ($p = 0.49$). If the effects of radiosurgical retreatment in four patients had been considered, the 1-year local tumor control rate would have increased to 87%.

A distant recurrence was observed in six patients (11.5%) in the surgery group and in 11 patients (19.6%) in the radiosurgery group. The 1-year freedom from distant recurrence was significantly worse in the radiosurgery group than in the surgery group (68% compared with 90%, $p = 0.0025$). Six of the 11 patients in the radiosurgery group who had a distant recurrence underwent new radiosurgical treatment, which resulted in tumor control in all cases. In the other five patients an additional radiosurgical treatment was not performed because of

progressive systemic disease. No patients in the surgery group were treated with subsequent surgical resection because of their poor clinical condition. The rate of freedom from distant tumor progression after 1 year was 90% in the surgery group and 75% in the radiosurgery group (Fig. 3). The difference was not statistically significant ($p = 0.21$).

The neurological death rates were similar in both groups, that is, 37% in the surgery group and 39% in the radiosurgery group ($p = 0.8$) after 1 year (Fig. 4 *upper*). There was a trend toward a lower systemic death rate in the surgery group, that is, the 1-year systemic death rates were 37% after surgery and 51% after radiosurgery (Fig. 4 *lower*). The difference was not statistically significant ($p = 0.3$).

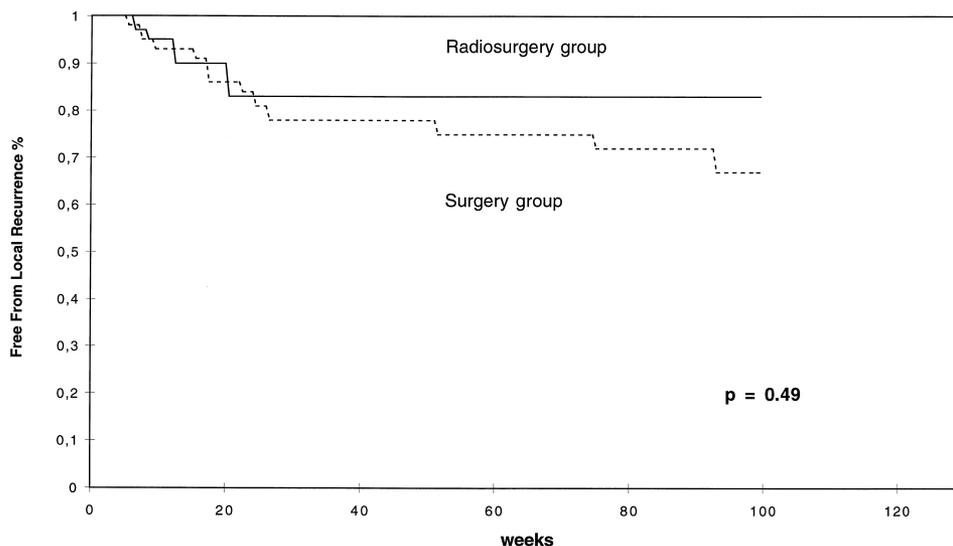


FIG. 2. Graph illustrating freedom from local tumor recurrence after surgery (*dashed line*) and radiosurgery (*solid line*). Nearly identical tumor control rates were achieved.

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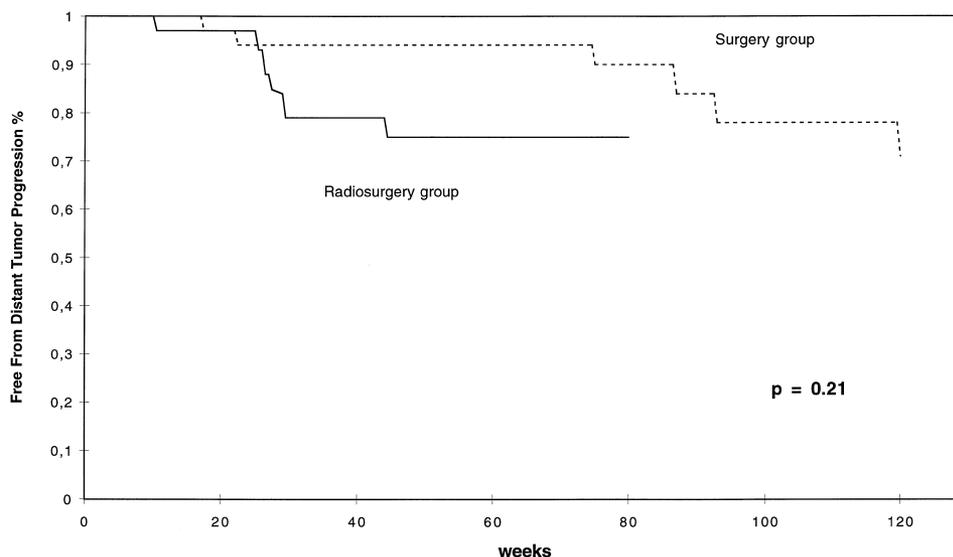


FIG. 3. Graph illustrating freedom from distant tumor progression. Six of 11 patients in the radiosurgery group (*solid line*) who experienced a distant recurrence received a new radiosurgical treatment; tumor control was achieved in all six patients. There was a 90% distant tumor control rate in the surgery group (*dashed line*) in comparison with 75% in the radiosurgery group after 1 year. The difference was not statistically significant.

Postoperative Course

Forty-six patients in the surgery group and 51 in the radiosurgery group demonstrated a stabilized or improved KPS score 6 weeks posttreatment. Six patients deteriorated after surgery plus WBRT, and five deteriorated after radiosurgery. The difference was not statistically significant ($p > 0.1$). Steroid medications were given less frequently, in 21 patients compared with 56 patients, and for a shorter time interval (median 2 weeks compared with 8 weeks) in the radiosurgery group compared with the surgery group ($p < 0.01$).

Complications After Surgery and Radiosurgery

Perioperative transient morbidity and mortality rates were similar in both groups, that is, 7.6% and 1.9% after surgery and 8.9% and 1.8% after radiosurgery, respectively ($p < 0.1$). One patient died of meningitis after surgery, and one died 2 weeks after radiosurgery for unknown reasons. Transient morbidity after surgery included postoperative hydrocephalus, acute psychosis, and postoperative pneumonia in one patient each. Two patients in the radiosurgery group suffered from seizures and one from nausea for 5 days posttreatment. Two patients presented with headache caused by intratumoral hemorrhage 1 day and 8 weeks, respectively, after radiosurgery. Even though we could not determine whether the hemorrhages occurred spontaneously or were treatment related, they were included in the morbidity statistics. Four patients (7.1%) had transient radiogenic complications, mostly within the first 6 months after radiosurgery, with minor clinical symptoms that were treated using steroids. No patient underwent decompressive surgery because of space-occupying radionecrotic lesions. There was complete recovery from the specific complications in each treatment group. Patients who underwent radiosurgical retreatment were not at a higher risk to develop radiogenic complications. Data on the transient minor side effects of radiation therapy,

such as nausea, hair loss, and dermatitis were not available for this study.

Discussion

It has been suggested that improved treatment of the extracerebral disease resulting in longer survival times has led to a higher incidence of brain metastases. Treatment with WBRT alone yields a median survival time in the range of 6 months and is still considered the treatment of choice in patients with multiple metastases and/or those in poor clinical grades.²⁹ Microsurgical tumor resection plus WBRT, which is more effective than WBRT alone, is the standard treatment in patients with single metastases accessible with open surgery.^{18,19,22,24,26,27,30,34,36} Compared with surgery, radiosurgical treatment has recently gained important therapeutic relevance in selected patients with a solitary, circumscribed, small metastasis in any area of the brain.^{20,21,28} Radiosurgical treatment seems attractive because of its low risk and minimal invasiveness. Local tumor control rates and length of patient survival, as reported in numerous retrospective single treatment-arm studies, seem to be as good as those for tumor resection plus WBRT.^{1-3,5,9,11,17,21,23} Even though in many studies radiosurgery is now considered to be the treatment of choice for small metastases, in one more recent report radiosurgery has been found to be less effective than surgery plus WBRT by using a matched-pair analysis.⁴ Thus, uncertainties continue to exist as to the therapeutic role of surgery and radiosurgery. No prospective randomized data are available. No investigator has analyzed treatment results after surgery in patients considered to have been eligible for radiosurgical treatment. Our two-institution study was conducted to analyze retrospectively the efficacy of surgery plus WBRT compared with radiosurgery alone in a highly selected patient population; only patients eligible for radiosurgical treatment were included.

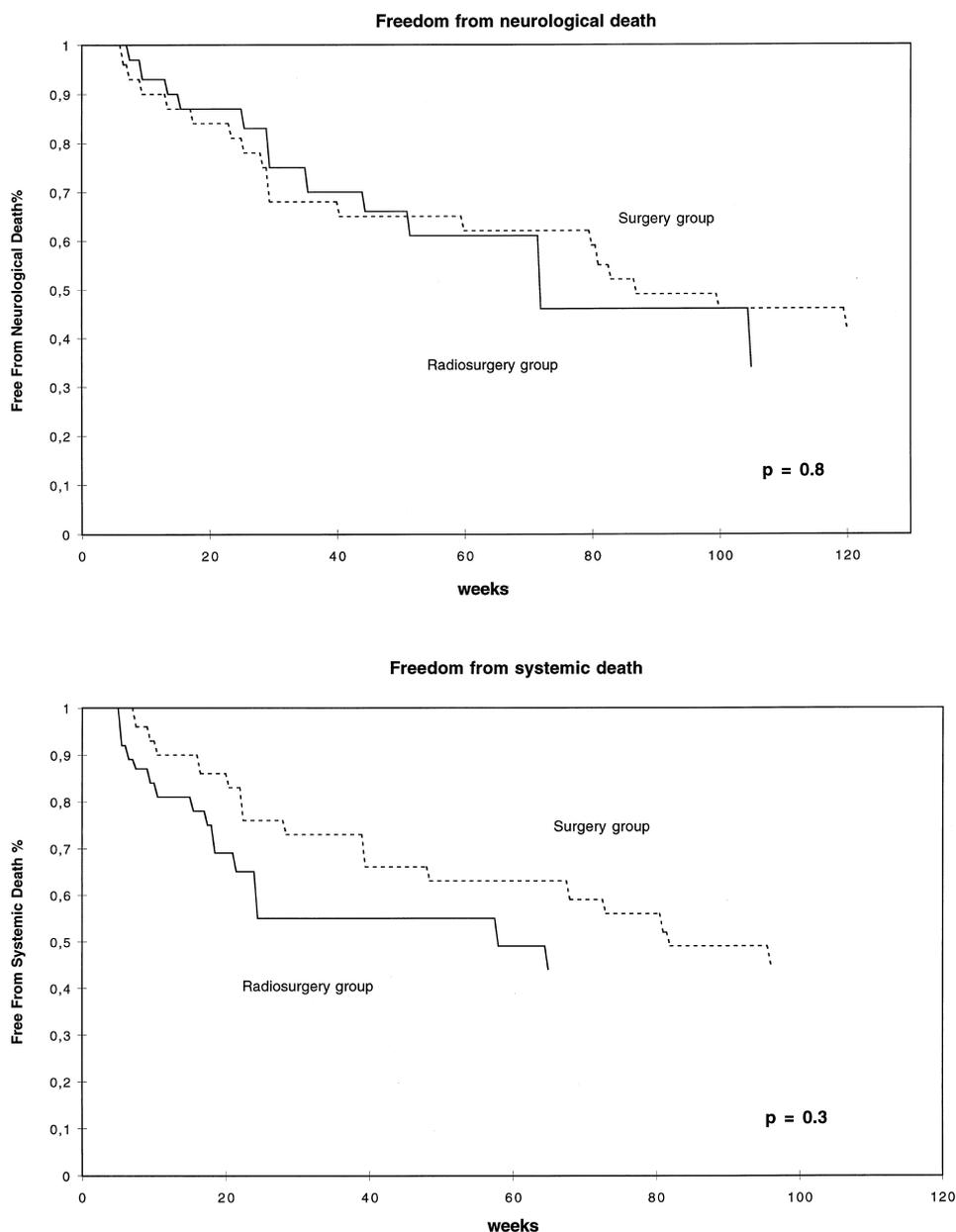


FIG. 4. Graphs showing comparisons of neurological (*upper*) and systemic survival (*lower*). There was no statistical difference in deaths from neurological causes in the surgery (*dashed line*) and radiosurgery groups (*solid line*). More patients in the radiosurgery group suffered a death from systemic causes than in the surgery group after 1 year (51% compared with 37%). The difference was not statistically significant.

Treatment Efficacy

A high percentage of local tumor control was achieved after both radiosurgery and surgery plus WBRT in the present study. Patients in the radiosurgery group had distant recurrences more often; these could be controlled effectively with additional radiosurgical treatment if necessary. Accordingly, rates of freedom from neurological death were nearly identical in both groups. A longer overall survival time after standard treatment was explained by a trend toward higher systemic death rates for patients in the radiosurgery group, who were more likely to suffer from extracerebral disseminated disease. The current

study demonstrates for the first time that a local treatment protocol such as radiosurgery alone is as effective as surgery plus WBRT in selected patients with small, circumscribed, solitary metastases. Moreover, the postoperative clinical course was uneventful in the majority of cases. The incidence of clinical improvement or stabilization at 6 weeks posttreatment was similar in both groups. There has been speculation that patients who undergo radiosurgery may have to receive high doses of steroid medications for longer intervals.¹⁹ This was not supported by our data; steroid drugs were given significantly less frequently and for a shorter time interval in the radiosurgery group.

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TABLE 2
*Literature review of radiosurgery for brain metastasis**

Authors & Year	No. of Patients	Surgical Control Group	% W/ Multiple Lesions	No. of Patients & Treatment				RS Dose (Gy)	% Local Control
				RS Only	Pre WBRT	Peri WBRT	Post WBRT		
Kihlström, et al., 1991	160	no	NS	160	0	NS	NS	27 mean	94
Fuller, et al., 1992	27	no	NS	6	10	NS	10	24.6 med	88
Engelhart, et al., 1993	69	no	NS	48	4	10	NS	NS	NS
Flickinger, et al., 1994	116	no	0	14	45	NS	NS	17.5 mean	85
Alexander, et al., 1995	248	no	31	0	211	37	0	15 med	84.6
Auchter, et al., 1996	122	no	0	5	0	117	0	17 med	86
Bindal, et al., 1996	31	yes	23	9	16	6	NS	18.7 med	61.3
present study	56	yes	0	56	0	0	0	22 mean	87

* Med = median; NS = not stated; peri = peritreatment; post = posttreatment; pre = pretreatment; RS = radiosurgery.

A decrease in peritumoral edema after radiosurgery has already been described and was confirmed by the present data.³³

Histological examination and verification of the metastatic nature of the lesion was performed only in patients in the radiosurgery group who harbored an unknown primary tumor. This approach may be criticized; 11% of patients with systemic cancer were found to have nonmetastatic lesions in the study published by Patchell, et al.,²⁷ even though findings on CT and MR studies were consistent with a single metastasis.

The results of our study could not be compared with available data in the literature comparing the results of surgery with those of radiosurgery. No author has yet analyzed treatment results postsurgery in patients eligible for radiosurgery. Radiosurgical treatment without adjuvant WBRT has not yet been stringently performed. A high degree of heterogeneity of available data hampers a proper analysis of many reports (Table 2). In other studies, WBRT was given inconsistently, either before or after radiosurgery. Radiosurgery was used as primary treatment and also for tumor recurrences. Because of the vaguely defined selection criteria in most studies, it remains unclear which type of tumor was treated by which kind of therapy. For example, in their multiinstitutional study, Flickinger, et al.,¹¹ lumped together treatment results after radiosurgery alone (14 patients), radiosurgery plus WBRT (65 patients), and radiosurgery for disease recurrences after previously performed radiotherapy/surgery (45 patients). In the study published by Bindal, et al.,⁴ 16 of 22 patients in the radiosurgery group who received WBRT did so before the radiosurgery was actually administered, and only nine patients were treated with radiosurgery alone. It is important to note that applied doses of fractionated radiotherapy administered after or before radiosurgery vary among numerous studies, which leads to over- or underestimation of the efficacy of WBRT as compared with radiosurgery.^{1-3,10,12} Considering the heterogeneity of available datasets, it is not surprising that there is no consensus as to the therapeutic role of surgery and radiosurgery. Our study has overcome many of these shortcomings. The stated imbalance regarding tumor size in favor of the radiosurgery group indicates a limitation in the retrospective study design. However, in the absence of prospective, randomized data, our study may provide a

standard against which other treatment results for similar metastases can be measured in future trials. Microsurgery remains an extremely important treatment modality in the era of radiosurgery. Only 52 of 228 patients in the surgery group were considered eligible for radiosurgical treatment in our series.

Prognostic Factors

In agreement with many studies, a KPS score of 70 or higher was associated with longer survival.^{8,13} Age, histological findings, status of the primary tumor, and time to metastasis did not reach prognostic importance. Whether this lack of prognostic impact is related to the applied selection criteria or the small sample size (small number of events) remains unclear. In our study the median survival was slightly longer after surgery plus WBRT in patients eligible for radiosurgery, as compared with recent prospective randomized studies;^{27,36} however, the tumor control rates were completely in line with those reported by Patchell, et al.²⁷ Apparently, eligibility for radiosurgical treatment does not significantly improve results after microsurgery. In contrast with radiosurgery, the prognostic influence of tumor size and tumor delineation appears to be minor with regard to the efficacy of surgery plus WBRT.

Therapeutic Role of Adjuvant Radiotherapy

Whole-brain radiation therapy after surgery is highly effective. It destroys residual cancer cells at the resection site and microscopic metastatic foci at other sites, as has been demonstrated in the recently published prospective randomized study of Patchell, et al.²⁶ In contrast, the efficacy of additional WBRT after radiosurgery remains unclear. It has been assumed that improvement of local tumor control would be the most compelling reason for combining WBRT and radiosurgery.¹¹ Flickinger, et al.,¹¹ found a higher local control rate but no improvement in the median survival time when WBRT was administered after radiosurgery. Fuller, et al.,¹² documented their best results after combined therapy, with a local tumor control rate of 80% for a small number of individuals (10 patients). Kihlström, et al.,¹⁷ concluded that using the gamma knife conferred no survival advantage after combined therapy. The series published by Moriarty, et al.,²³ confirms the failure of WBRT to make an impact on survival

rates in patients treated radiosurgically. Unfortunately, no study as yet has defined criteria for a treatment decision in favor of either radiosurgery plus WBRT or radiosurgery alone. Therefore, a selection bias must be assumed in all of these retrospective studies, which hampers proper evaluation of the therapeutic role of adjuvant WBRT. Local tumor control rates after radiosurgery alone in our study ranked with the best results reported in the literature after radiosurgery plus WBRT. Auchter, et al.,³ analyzed treatment results after radiosurgery plus WBRT in a relatively homogeneous patient population eligible for surgery and reported a 1-year survival rate of 53% and a 1-year local tumor control rate of 86%, which were nearly identical with the results reported in the present study for radiosurgery alone. Moreover, radiosurgical retreatment of small local recurrences appears feasible; it was performed in four patients in our study and increased the final 1-year local tumor control rate to 87% in the radiosurgery group (median diameter of the retreated tumor, 10 mm). The excellent local tumor control rate presented in our study raises serious doubts about the concept of combining WBRT with radiosurgery for improvement in local tumor control.

Considering the data recently published in the prospective randomized study of Patchell, et al.,²⁶ it was not surprising that patients in the radiosurgery group experienced distant recurrences significantly more often than patients treated with surgery plus WBRT. In the current study, however, tumor control could be effectively achieved for distant recurrences with additional radiosurgical treatment, resulting in nearly identical death rates from cerebral tumors after radiosurgery or surgery plus WBRT. Follow-up MR imaging examinations performed at well-defined time intervals after radiosurgery proved to be a mainstay for local treatment with radiosurgery alone, allowing the identification of local or distant recurrences as early as possible. Thus, the possibility of distant recurrences appears not to be a compelling reason for adjuvant WBRT.

Risk of Complications

The risk of complications from microsurgery and radiosurgery was low. Within the first 6 months after radiosurgery, four patients developed transient radiogenic complications with mild clinical symptoms that could be controlled with steroid medications in every case. Patients who received radiosurgical retreatment were not at higher risk for a radiogenic complication. This result must be interpreted with caution because of the small number of retreated patients in this series. Most important, severe, progressive radiogenic complications were not observed. No patient underwent decompressive surgery because of a space-occupying radionecrotic lesion. Transient side effects after WBRT, such as nausea, hair loss, and dermatitis could not be analyzed systematically in the current study. Radiation-induced dementia was not observed. The side effects of WBRT, however, should not be underestimated, particularly for long-term survivors. For example, DeAngelis, et al.,⁷ found radiation-induced dementias in 11% of their patients treated with WBRT.

Conclusions

Radiosurgery alone can be used to achieve local tumor

control rates as good as surgery plus WBRT and radiosurgery plus WBRT for highly selected patients harboring single, circumscribed brain metastases with a diameter of 3.5 cm or less. Distant and local tumor recurrences can be recognized early on MR imaging and treated effectively with repeated radiosurgery. Radiosurgery is attractive because of its minimal invasiveness and the possibility of withholding adjuvant radiotherapy. Microsurgery plus radiotherapy should be saved for larger tumor volumes not suitable for radiosurgical treatment. Results of retrospective studies should be regarded cautiously and must be confirmed in the framework of a prospective randomized study.

References

1. Adler JR, Cox RS, Kaplan I, et al: Stereotactic radiosurgical treatment of brain metastasis. **J Neurosurg** **76**:444-449, 1992
2. Alexander E III, Moriarty TM, Davis RB, et al: Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. **J Natl Cancer Inst** **87**:34-40, 1995
3. Auchter RM, Lamond JP, Alexander E III, et al: A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. **Int J Radiat Oncol Biol Phys** **35**:27-35, 1996
4. Bindal AK, Bindal RK, Hess KR, et al: Surgery versus radiosurgery in the treatment of brain metastasis. **J Neurosurg** **84**:748-754, 1996
5. Coffey RJ, Flickinger JC, Lundsford LD: Solitary brain metastasis: radiosurgery in lieu of microsurgery in 32 patients. **Acta Neurochir Suppl** **52**:90-92, 1991
6. Cox DR, Oakes D: **Analysis of Survival Data**. New York: Chapman and Hall, 1984
7. DeAngelis LM, Mandell LR, Thaler HT, et al: The role of post-operative radiotherapy after resection of single brain metastases. **Neurosurgery** **24**:798-805, 1989
8. Diener-West M, Dobbins TW, Phillips TL, et al: Identification of an optimal subgroup for treatment evaluation of patients with brain metastases using RTOG study 7916. **Int J Radiat Oncol Biol Phys** **16**:669-673, 1989
9. Engelhart R, Kimmig BN, Höver KH, et al: Long-term follow-up for brain metastases treated by percutaneous stereotactic single high-dose irradiation. **Cancer** **71**:1353-1361, 1993
10. Flickinger JC, Kondziolka D: Radiosurgery instead of resection for solitary brain metastasis: the gold standard redefined. **Int J Radiat Oncol Biol Phys** **35**:185-186, 1996
11. Flickinger JC, Kondziolka D, Lundsford LD, et al: A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. **Int J Radiat Oncol Biol Phys** **28**:797-802, 1994
12. Fuller BG, Kaplan ID, Adler J, et al: Stereotactic radiosurgery for brain metastases: the importance of adjuvant whole brain irradiation. **Int J Radiat Oncol Biol Phys** **23**:413-418, 1992
13. Gaspar L, Scott C, Rotman M, et al: Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trials. **Int J Radiat Oncol Biol Phys** **37**:745-751, 1997
14. Jokura H, Takahashi K, Kayama T, et al: Gamma knife radiosurgery of a series of only minimally selected metastatic brain tumours. **Acta Neurochir Suppl** **62**:77-82, 1994
15. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. **J Am Stat Assoc** **53**:475-481, 1958
16. Karnofsky DA, Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer, in MacLeod CM (ed): **Evaluation of Chemotherapeutic Agents**. New York: Columbia University Press, 1949, pp 191-205
17. Kihlström L, Karlsson B, Lindquist C, et al: Gamma knife sur-

Surgery compared with radiosurgery for single brain metastasis

- gergy for cerebral metastasis. **Acta Neurochir Suppl** **52**:87–89, 1991
18. Kim M, Berenstein M: Current treatment of cerebral metastasis. **Curr Opin Neurol** **9**:414–418, 1996
 19. Lang FF, Sawaya R: Surgical treatment of metastatic brain tumors. **Semin Surg Oncol** **14**:53–63, 1998
 20. Loeffler JS, Shrieve DC: What is appropriate therapy for a patient with a single brain metastasis? **Int J Radiat Oncol Biol Phys** **29**:915–917, 1994
 21. Mehta MP, Rozental JM, Levin AB, et al: Defining the role of radiosurgery in the management of brain metastases. **Int J Radiat Oncol Biol Phys** **24**:619–625, 1992
 22. Miller JD: Surgical excision for single cerebral metastasis? **Lancet** **341**:1566, 1993
 23. Moriarty TM, Loeffler JS, Black PM, et al: Long-term follow-up of patients treated with stereotactic radiosurgery for single or multiple brain metastasis, in Kondziolka D (ed): **Radiosurgery 1995**. Basel: Karger, 1996, Vol 1, pp 83–91
 24. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al: The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. **Int J Radiat Oncol Biol Phys** **29**:711–717, 1994
 25. Ott K: Surgery or radiosurgery? **J Neurosurg** **86**:165–166, 1997 (Letter)
 26. Patchell RA, Tibbs PA, Regine WF, et al: Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. **JAMA** **280**:1485–1489, 1998
 27. Patchell RA, Tibbs PA, Walsh JW, et al: A randomized trial of surgery in the treatment of single metastases to the brain. **N Engl J Med** **322**:494–500, 1990
 28. Reulen HJ, Spuler A: Therapie von Hirnmetastasen aus neurochirurgischer Sicht. **Munch Med Wschr** **137**:477–482, 1995
 29. Schweitzer VG, Selch MT, De Salles A, et al: Stereotactic irradiation for the treatment of brain metastases-prognostic factors and the role of whole brain irradiation. **Int J Radiat Oncol Biol Phys** **36 (Suppl)**:288, 1996 (Abstract)
 30. Smalley SR, Laws ER Jr, O'Fallon JR, et al: Resection for solitary brain metastasis. Role of adjuvant radiation and prognostic variables in 229 patients. **J Neurosurg** **77**:531–540, 1992
 31. Somaza S, Kondziolka D, Lundsford LD, et al: Stereotactic radiosurgery for cerebral metastatic melanoma. **J Neurosurg** **79**:661–666, 1993
 32. Stelzer KJ, Goodkin R, Winn HR: Surgery or radiosurgery? **J Neurosurg** **86**:168–169, 1997 (Letter)
 33. Sturm V, Kober B, Höver KH, et al: Stereotactic percutaneous single dose irradiation of brain metastases with a linear accelerator. **Int J Radiat Oncol Biol Phys** **13**:279–282, 1987
 34. Sundaresan N, Galicich JH: Surgical treatment of brain metastasis. Clinical and computerized tomography evaluation of the results of treatment. **Cancer** **55**:1382–1388, 1985
 35. Valentino V, Mirri MA, Schinaia G, et al: Linear accelerator and Greitz-Bergstrom's head fixation system in radiosurgery of single cerebral metastases. A report of 86 cases. **Acta Neurochir** **121**:140–145, 1993
 36. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al: Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? **Ann Neurol** **33**:583–590, 1993
 37. Warnke PC, Kreth FW, Ostertag CB: Surgery or radiosurgery? **J Neurosurg** **86**:166–167, 1997 (Letter)
 38. Wowra B, Czempel H, Cibis R, et al: Profil der ambulanten Radiochirurgie mit dem Gamma-Knife-System. Teil 1: Methode und multizentrisches Behandlungs-konzept. **Radiologe** **37**:995–1002, 1997
 39. Wowra B, Czempel H, Cibis R, et al: Profil der ambulanten Radiochirurgie mit dem Gamma-Knife-System. Teil 2: Klinischer Erfahrungsbericht. **Radiologe** **37**:1003–1015, 1997
 40. Young RF: Radiosurgery for the treatment of brain metastases. **Semin Surg Oncol** **14**:70–78, 1998
 41. Young RF: Surgery or radiosurgery? **J Neurosurg** **86**:167–168, 1997 (Letter)

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