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Gamma surgery for melanoma metastases in the brain

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Object. The aim of this study was to evaluate the usefulness and limitations of gamma surgery (GS) in the treatment of brain metastases from melanoma.

Methods. Imaging and clinical outcomes in 45 patients treated for 92 brain metastases from melanoma between October 1989 and October 1999 were retrospectively analyzed. Follow-up imaging studies were available in 35 patients with 66 treated lesions. Twenty-four percent of the lesions disappeared, 35% shrank, 23% remained unchanged, and 18% increased in size. No undue radiation-induced changes were observed in the surrounding brain. Clinical data were available in all patients. No deaths or neurological morbidity related to GS was observed. The median survival time, calculated using the Kaplan–Meier method, was 10.4 months from the time of GS. In both univariate and multivariate Cox regression analyses, a single brain lesion and lack of visceral metastases were statistically predictive of a better prognosis. Six of eight patients with solitary metastasis (that is, a single brain metastasis with no primary visceral tumor) were still alive at the close of the study, none of them with disease progression, with a follow-up period ranging between 14 and 82 months. Sixteen patients in this series received adjunctive whole-brain radiation therapy, which had no impact on their survival time or local and distant control of the brain disease.

Conclusions. Gamma surgery is effective in treating melanoma metastases in the brain. It appears that the radiobiology of a single high dose overcomes the radioresistance barrier, yielding better results than fractionated radiation.

KEY WORDS • melanoma • metastasis • radiosurgery • gamma knife

THE incidence of melanoma has progressively risen over the decades, with annual rates in the United States for 1990 to 1997 recorded at 12.4 per 100,000 persons, an annual increase of 2%. The associated death rate in the same period was reported as 2.2 per 100,000 persons, an annual increase of 0.1%.[28] Involvement of the CNS is the cause of the death in approximately one third of all patients,[7] although brain metastases were found in up to 75% of cases at autopsy.[1,9] The median survival time for untreated patients with brain melanoma metastases is estimated to be less than 1 month. According to Sampson, et al.,[31] survival can be prolonged up to 2 months by the use of corticosteroids.

The aim of the therapy in these patients is the palliation of symptoms and prolongation of survival. Surgery,[5,19,24,31,43] radiation therapy,[12,17,31,33,39,41] chemotherapy,[6,16,40] immunotherapy,[21,32] and radiosurgery[11,13,14,20,22,34,35,37,44] have all been used in the management of this disease. In single metastatic tumors, surgery usually prolongs survival and improves the quality of life, although its use is limited to surgically resectable lesions in patients in good clinical condition.[19,24,43] Unfortunately, the mortality and morbidity rates associated with surgery are not negligible. Considering only the studies conducted in the CT era, postsurgical mortality ranged from 5 to 10%, whereas associated morbidity occurred in 18.7%.[19,31,43] Whole-brain radiation therapy is limited in its benefit by the relative radioresistance of these tumors and the risks of radiation-induced complications manifesting in the event of prolonged patient survival.[23,42]

Our aim in this study was to analyze the results of a consecutive series of 45 patients treated for 92 melanoma metastases in the brain at the Lars Leksell Center for Gamma Surgery and to assess the utility and limitations of this method in the management of these lesions.

Clinical Material and Methods

Patient Population

Between October 1989 and October 1999, 92 melanoma metastases in the brain were treated with GS in 45 consecutive patients; 20 were women and 25 were men. The mean age of the patients at the time of GS was 53 years (range 27–80 years; Table 1). The mean KPS score before GS was

Abbreviations used in this paper: CNS = central nervous system; CT = computerized tomography; GS = gamma surgery; KPS = Karnofsky Performance Scale; LINAC = linear accelerator; MR = magnetic resonance; WBRT = whole-brain radiation therapy.

TABLE 1

*Patient population and treatment results in 45 cases of melanoma metastases in the brain**

Characteristic	Clinical Outcome					Tumor Presence on Imaging Studies			
	No. of Patients	Death	Median Survival (mos)	No. of Lesions		Disappeared	Decreased	Unchanged	Increased
				Treated	W/ FU				
total	45	33	10.4	92	66	16	23	15	12
age									
>50 yrs	27	19	10.4	56	36	10	12	8	6
≤50 yrs	18	14	11.2	36	30	6	11	7	6
sex									
male	25	19	11.0	49	32	8	11	9	4
female	20	14	7.7	43	34	8	12	6	8
no. of treatments									
1	38	28	8.2	72	47	8	19	11	9
2–3	7	5	14.9	20	19	8	4	4	3
no. of brain metastases									
single	23	13	14.5	30	24	5	10	5	4
multiple	22	20	7.6	62	42	11	13	10	8
KPS score									
≥80	36	26	14.3	73	56	15	16	14	11
<80	9	7	4.8	19	10	1	7	1	1
tumor location									
infratentorial	11	10	7.9	31	21	4	5	9	3
supratentorial	34	23	11.0	61	45	12	18	6	9
visceral metastases									
yes	28	23	7.9	59	43	8	19	9	7
no	17	10	13.2	33	23	8	4	6	5
WBRT									
yes	16	13	7.9	43	28	7	8	6	7
no	29	20	13.2	49	38	9	15	9	5
previous surgery	13	9	10.6	28	21	6	6	5	4

* FU = follow up.

80 (range 60–100). Five patients were treated twice and one thrice, resulting in a total of 52 treatment sessions. Thirteen patients had previously undergone brain surgery, 16 had WBRT, and 16 underwent chemotherapy or immunotherapy. Nineteen patients were asymptomatic, 12 had focal neurological deficits, six had seizures, six presented with headache, two with memory deficits, and one with tremor.

Tumor Characteristics

Histological confirmation of the diagnosis was obtained in 15 (33%) of 45 patients, in 13 by previous tumor removal and in two by stereotactic biopsy sampling; in the rest of the cases the diagnosis was presumptive based on the presence of a known primary tumor. The mean volume of tumors was 3.63 cm^3 (range 0.1–57 cm^3). The location of the tumors was anterior frontal in 14%, posterior frontal in 18%, occipital in 18%, parietal in 15%, temporal in 13%, cerebellar in 9%, thalamic in 3%, brainstem in 8%, and clival and fifth cranial nerve in 1% each. In 23 patients single metastases (that is, a metastatic deposit in the brain in addition to a visceral tumor) were treated, and in eight of these the lesion was solitary (that is, it was a single metastasis in the brain with no visceral primary tumor). Evidence of intratumoral hemorrhage was present in four cases. No lesion was treated more than once.

Treatment Parameters

The GS was performed using the Leksell gamma unit (model U; Elekta Instruments, Inc., Norcross, GA). The dose rate varied from a maximum of 3.66 Gy/minute to a minimum of 1.59 Gy/minute. Treatment planning software, which was continuously updated and approved by the United States Food and Drug Administration, was used. From 1989 to 1990, CT scanning was the only imaging modality available. From 1991, MR imaging was used for the treatment plan unless it was contraindicated. The mean maximum dose delivered was 45 Gy (range 30–80 Gy), and the mean peripheral dose was 19 Gy (range 13–25 Gy). Lower doses were used when prior WBRT had been administered. The average number of isocenters used was 1.9 (range 1–7). The prescription isodose varied from the 30% to the 50% line.

Follow-Up Evaluation

Clinical follow-up data were available in all 45 patients, having been obtained by correspondence and/or verbal communications with the referring physician and the patients themselves. The diagnosis of a neurological or systemic cause of death was based on the last clinical and imaging data available. Imaging follow-up data were available in 35 patients with 66 lesions. Five patients died before they were scheduled for their first follow-up imaging session, and in the other five cases the patient and the family refused MR imaging because of the advanced systemic disease. Software developed at the University of Virginia based on a polygonal area algorithm[38] was used for volumetric assessment of outcome. This software allows esti-

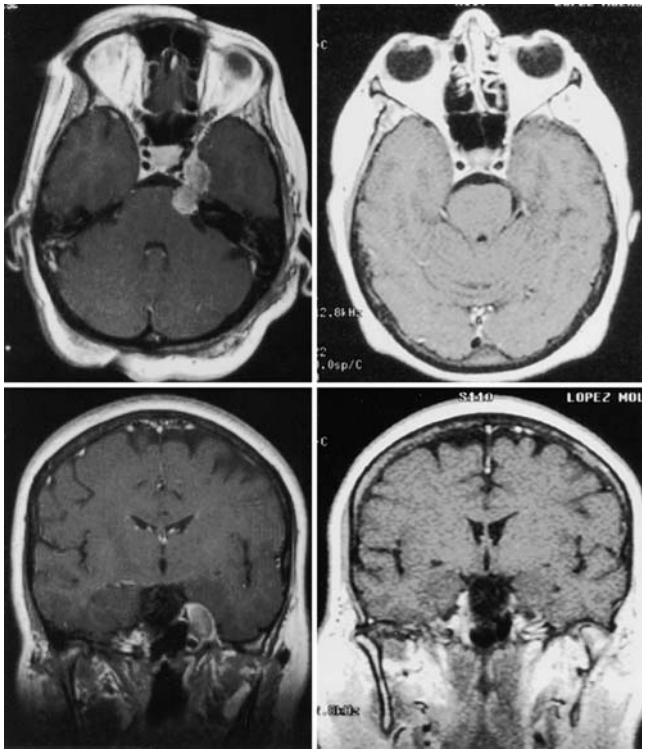

FIG. 1. Axial *(upper left)* and coronal *(lower left)* postcontrast T_1-weighted MR images obtained in a 50-year-old woman, demonstrating a metastatic melanoma measuring 3.83 cm^3 in volume in the left cavernous sinus, with extension to the Meckel cave and the prepontine cistern. Follow-up contrast-enhanced T_1-weighted axial *(upper right)* and coronal *(lower right)* MR images obtained 7 years later, demonstrating no evidence of residual tumor. The lesion was not visible after the 12-month follow-up studies. The patient is in good health and is working full time at her usual occupation.

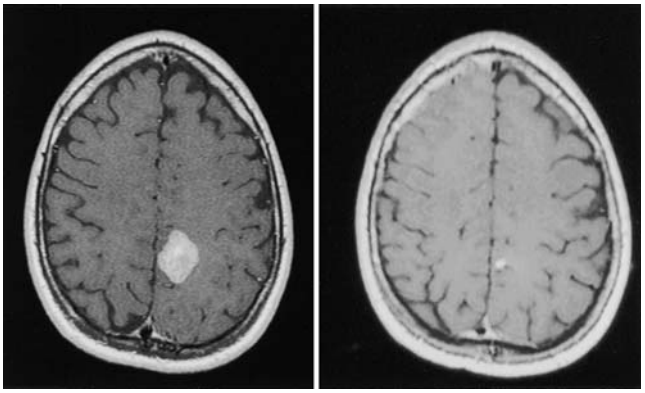

FIG. 2. Axial T_1-weighted contrast-enhanced MR images obtained in a 45-year-old man presenting with headaches and sensory symptoms, demonstrating sensory strip melanoma metastases at the time of GS *(left)* and 6 months later *(right)*. A small residual enhancement is seen that was not associated with metabolic activity on fluorodeoxyglucose–positron emission tomography scanning. The patient's condition has improved and he continues an active lifestyle. He was subsequently treated for two new brain metastases.

mation of the tumor volume based on MR or CT studies performed without a stereotactic frame. The margin of error is ± 7% for lesions smaller than 1 cm^3 and ± 2% for those with volumes larger than 1 cm^3. Variations of more than 10% in the size of the tumor were considered significant. The median follow-up period was 8.6 months, and the 12 patients who were alive at the end of the study had been followed for a median of 15.4 months (range 10–82 months).

Statistical Analysis

For the survival analysis, Kaplan–Meier curves were used and the length of survival was measured in months from the date of the first GS. Univariate and multivariate Cox regression analyses were used to study the possible effects of eight independent variables on the length of survival. We used commercially available software (SPSS, Inc., Chicago, IL) for statistical analysis.

Results

Imaging Outcome

Of the 66 tumors in 35 patients in whom follow-up images were available, 16 lesions (24%) completely disappeared (Fig. 1), 23 (35%) shrank (Fig. 2), 15 (23%) remained unchanged, and 12 (18%) increased in size. Of the 23 tumors that decreased in size, six decreased more than 75%, eight between 50 and 75%, and nine between 15 and 50%. In no case were undue radiation-induced changes observed in the surrounding brain. In three cases hemorrhage was observed in the tumor on images obtained in the follow-up period; however, none was symptomatic. In 13 patients, new lesions occurred in different locations in the brain within a median follow-up period of 6 months; in three the lesion was associated with intratumoral hemorrhage. Six patients were retreated with GS. Of the 16 patients who received WBRT before or after GS, follow-up imaging was available in 10. In this group of patients, in whom there were 28 tumors, seven lesions (25%) disappeared, eight (29%) decreased, six (21%) remained unchanged, and seven (25%) increased in size.

Clinical Outcome

Twelve patients are alive at the end of our observation period, with a median follow-up time of 15.4 months (range 10–82 months). The other 33 patients died between 1 and 28 months posttreatment; in 27 cases (82%) the cause of the death was the progression of systemic disease, and six (18%) died of progression of CNS disease. No deaths were related to GS. Of 26 patients with neurological symptoms at the time of GS, 10 improved and 16 remained unchanged. Of the 19 asymptomatic patients, none developed a new neurological deficit related to GS. In one patient who experienced headache 3 months after the treatment and another with visual field deficit, MR images revealed hemorrhage in an untreated lesion.

The overall median length of survival in the 45 patients, which was calculated using the Kaplan–Meier method, was 10.4 months from the time of GS (Fig. 3 *upper left* and Table 2), 13.1 months from the diagnosis of brain metastasis, and 50.5 months from the diagnosis of primary skin mela-

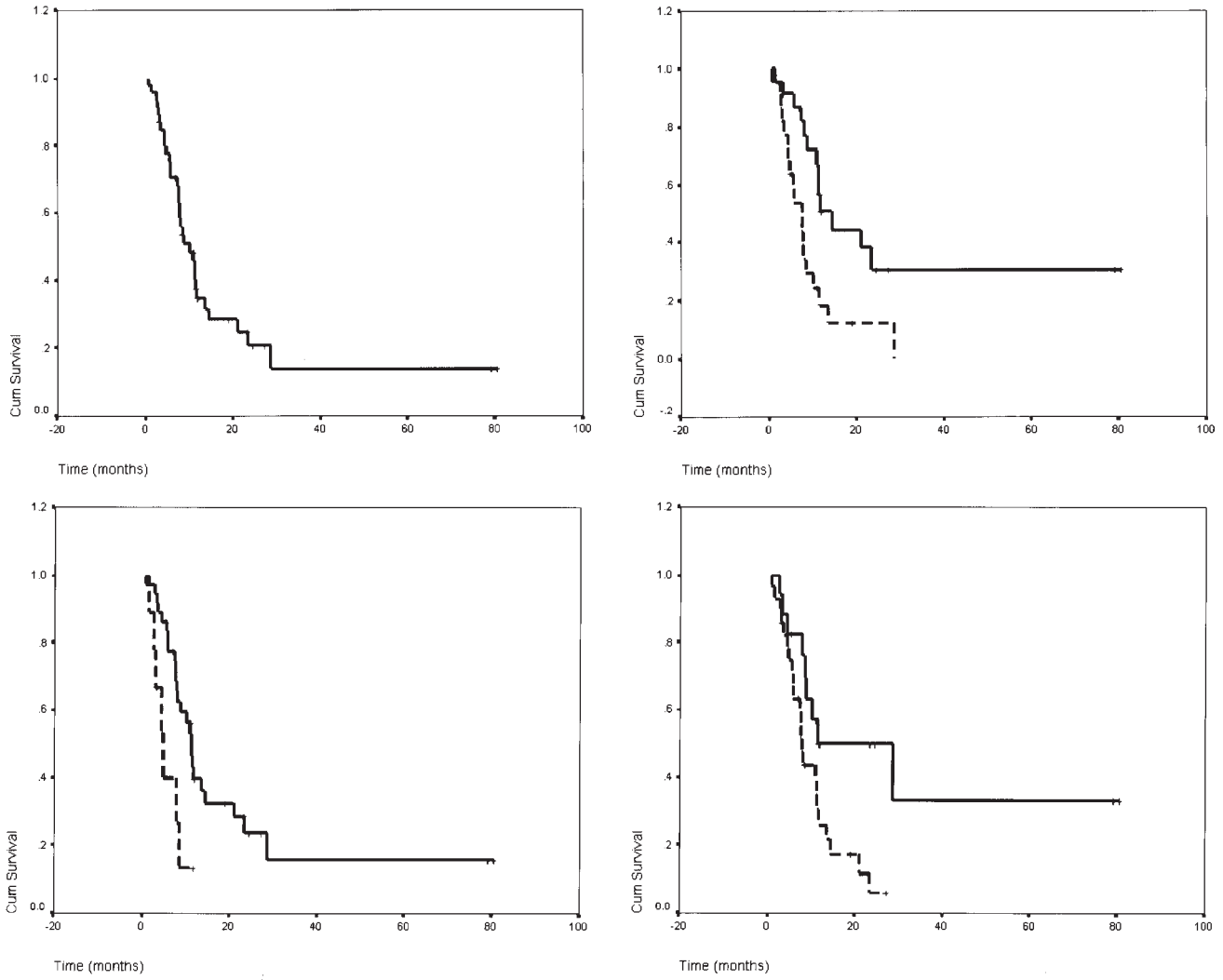

FIG. 3. *Upper Left:* Graph showing Kaplan–Meier plot of cumulative (cum) survival of the entire patient population. *Upper Right:* Graph showing Kaplan–Meier curve comparing survival in patients with single *(solid line)* and multiple *(dashed line)* brain metastases. *Lower Left:* Graph showing Kaplan–Meier curve comparing survival in patients with KPS scores of 80 or more *(solid line)* and KPS scores less than 80 *(dashed line)*. *Lower Right:* Graph showing Kaplan–Meier curve comparing survival in patients without *(solid line)* and with visceral metastases *(dashed line)*.

noma. The number of survivors at 1, 2, and 5 years was 14 (31.1%), seven (15.6%), and two (4.4%), respectively. In 13 patients who underwent craniotomy before GS, the median survival time was 11.5 months. The length of survival in the 16 patients who received WBRT (13 before and 3 after GS) was 7.9 months. In 23 patients who presented with a single brain lesion at the time of the first GS, the survival time was 14.5 months, compared with 7.6 months in the 22 patients with multiple lesions (Fig. 3 *upper right*). Eight patients presented with a solitary metastasis, and six of them are still alive, with follow-up periods ranging between 14 and 82 months and without signs of cerebral or systemic progression. In nine patients with a KPS score of less than 80, the median survival time was 4.8 months, compared with 11.3 months in those with a KPS score of 80 or more (Fig. 3 *lower left*). The 11 patients with infratentorial lesions at the time of GS survived for a median of 7.9 months, compared with 11 months in patients with only supratentorial lesions.

In a Cox univariate analysis of eight variables (sex, age > 50, KPS score < 80, single or multiple metastases, infratentorial location, previous craniotomy, previous conventional radiation therapy, and visceral metastases), factors associated with a better survival were single metastasis ($p = 0.0375$) and absence of visceral metastases ($p = 0.0029$; Fig. 3 *lower right*). There was also an evident, but not statistically significant trend for better outcome in patients with KPS scores of 80 or greater and those with only supratentorial metastases. In a Cox multivariate analysis, single brain lesions ($p = 0.031$), absence of visceral metastases ($p = 0.0301$), and a KPS score of 80 or less ($p = 0.003$) were statistically predictive of a better prognosis.

Discussion

Melanomas are considered to be relatively radioresistant tumors;[12,17,25] in vitro melanoma cells have been shown

TABLE 3

Literature review of GS and LINAC radiosurgery in brain metastases from melanoma

Authors & Year	Tx	No. of Patients		No. of Lesions		Tumor Presence (%)			Median Overall Survival (mos)
		Total	W/ Single Brain Met	Total	W/ FU Imaging	Disappeared or Decreased	Unchanged	Increased	
Seung, et al., 1996	GS	40	13	97	77		77*†	23*†	8.2
Gieger, et al., 1997	LINAC	12		21	21		57†‡	43†	
Grob, et al., 1998	GS	35	17	56			98†‡	2†‡	7
Mori, et al., 1998	GS	60	36	118	72	55†	25†	10†	7
Lavine, et al., 1999	GS	45	18	93	32§	78†§	19†§	3†§	8
present study	GS	45	23	92	66	59‖	23‖	18‖	10.4

* Reported as 1-year actuarial freedom from progression. Abbreviation: met = metastasis.
† Based on linear measurement alone.
‡ Reported as tumor control.
§ Number and percentage relative to patients (not lesions).
‖ Based on computerized volumetry.

from 12 to 82 months. Grob, et al.,[14] reported similar results. Fidler, et al.,[10] observed a slower growth rate and lower metastatic potential in brain metastases from melanoma compared with visceral metastases, indicating that brain metastases do not always represent the last stage in the metastatic cascade, and can develop directly from the primary disease.

Multiple Brain Metastases

In multiple brain metastases the choice of treatment is based on the clinical condition of the patients. In those with a KPS score of less than 70, the presence of active systemic disease, and a resultant low expectancy of survival, WBRT can be considered to be the only salvage treatment.[31] If the patients are in good condition, GS may be used. We treated up to seven metastases in a single patient and up to five metastases in a single GS session. Although some of these patients have done well, the overall results have been meager. The median survival time of 22 patients with multiple lesions was 7.2 months, compared with 12.2 months in 23 patients with single lesions.

Treatment With LINAC Radiosurgery

In the only series of brain metastases from melanoma treated with LINAC radiosurgery that has been reported in the literature (Table 3), 43% of the lesions showed enlargement after treatment,[13] compared with 18% reported in our study and 3 to 23% reported in other GS series.[14,20,22,34,37]

Comparison of GS With Open Surgery

In selected patients surgical removal of brain metastases from melanoma significantly improves the length of survival and quality of life, with median survival times of 6 to 10 months.[19,31,43] Open surgery eliminates the mass effect and removes the clot in hemorrhagic lesions. Hence, in large lesions and in large intracranial hemorrhages, open surgery is more appropriate than radiosurgery.[19] It is difficult to compare outcomes in surgical and GS series because of the difference in tumor variables. In the surgical series that were compared with this study, the patients presented with single metastases in 83 to 85% of cases, few had infratentorial, and practically none had brainstem metastases.[31,43] In contrast, in our series 49% of tumors were multiple, 24.4% were located infratentorially, and 8% were in the brainstem. The mean size of the lesion treated with surgery is generally larger compared with those treated using radiosurgery.[19,43] In Wronski and Arbit's series[43] the mean diameter of the tumors was 3.7 cm, and larger sizes were not significantly correlated with a worse prognosis. The mean diameter of lesions in our study (1.94 cm, range 0.7–4.94 cm) is significantly smaller. Taking this fact into consideration is important for a careful comparison of the results of the surgical series with those obtained by us.

The median length of survival and the survival rate at 1 and 2 years observed in our study do not differ significantly from those found in recent surgical series (Table 2), except in patients with infratentorial lesions, in whom survival was 7.6 months in our series compared with 2.1 months in the series reported by Wronski and Arbit.[43] On the other hand, the risk of procedure-related complications and death are higher in surgical series.[31,43] Sampson and colleagues[31] report a 22.4% incidence of increased neurological deficit and an 8.4% rate of death or life-threatening morbidity. In the series reported by Wronski and Arbit, neurological complications occurred in 18.7% of the patients, and 5.5% died within the 1st month postsurgery. In our series no death was related to GS and only one patient died in the 1st month; this death was due to progression of systemic disease. No patient experienced neurological complications related to the procedure, and in both patients who developed new neurological deficits the cause was the bleeding of an untreated lesion.

Role of Histological Confirmation

Histological confirmation of the diagnosis from surgical specimens is another advantage of the open procedure.[19] Although its necessity in patients with known primary cancer and the presence of brain lesions on MR imaging is questionable,[18] the risk of diagnostic error in the absence of histological studies for single brain lesions has been reported to be as high as 10 to 15%.[19,24] In two thirds of our patients with known primary melanoma and the presence of single or multiple brain lesions, treatment was performed without histological confirmation of the diagnosis. In the remaining third, except for two patients who underwent stereotactic biopsy procedures, tissue diagnosis was secured at craniotomy. The rationales behind our conserva-

tive policy in using stereotactic biopsy sampling are as follows: 1) the risk of lethal or severe complications with incidences as high as 3%, with an additional 3% risk of mild complications;[4,15] and 2) the risk of tumor seeding along the trajectory of the needle.[18]

Cost Effectiveness of GS

The median time of hospitalization reported by Wronski and Arbit[43] was 14 days (7 days in the patients treated more recently). The patients in our series were hospitalized the evening before the treatment and discharged the morning after GS. In a comparison of costs and benefits between GS and surgical resection for solitary brain metastasis, Rutigliano and colleagues[30] concluded that radiosurgery has a lower cost per procedure in uncomplicated cases, a lower average cost attributable to complications, and a lower total cost per procedure.

Conclusions

Gamma surgery seems to overcome the problem of radioresistance occasionally observed in melanoma after conventional radiotherapy. In retrospective unmatched trials, survival times in patients treated with GS are comparable with those in patients who undergo surgery, with less neurological morbidity and practically no mortality (Table 2). The controversy about WBRT as an adjunct therapy remains unsettled. The finding that a single brain metastasis and absence of visceral lesions is associated with better survival is not surprising, nor is it unreasonable to state that patients with solitary brain lesions treated only with GS have a chance for cure, but both of these conclusions might seem like truisms for any modality of therapy.

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