Gamma Knife Radiosurgery for Malignant Melanoma Brain Metastases

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Melanoma is the third most common primary tumor associated with central nervous system (CNS) metastasis, after lung and breast cancer.[1,38,39] Cerebral metastases occur in 10 to 40% of patients diagnosed with Stage IV melanoma.[1,38] Survival usually varies from 2.75 to 4 months, with the majority of patients dying from complications of CNS disease.[23] For years, the management of melanoma brain metastases consisted of resection of symptomatic surgically accessible lesions followed by whole-brain radiation therapy (WBRT), or WBRT alone.[1,23,38] Stereotactic radiosurgery has emerged as a minimally invasive adjunct or alternative to microsurgical resection and fractionated WBRT for metastatic cancer. Radiosurgery provides high local tumor control rates in cancers often considered radioresistant, such as sarcomas, renal cell carcinomas, and melanomas.[2,4] To better understand factors that influence survival and tumor response, we reviewed our experience with gamma knife surgery for melanoma brain metastases.

MATERIALS AND METHODS

Patient Population

Between August 1987 and September 2005, 244 patients had gamma knife radiosurgery for the management of melanoma brain metastases at the University of Pittsburgh Medical Center. The population consisted of 79 female (32.4%) and 165 male (67.6%) patients, with age varying from 16 to 87 years (mean, 54.2 yr). Ninety-eight patients (40.2%) had a single metastasis and 146 patients (59.8%) had multiple metastases (range, 2–14 metastases). The mean interval from primary diagnosis to brain metastases diagnosis was 49.4 months (range, 0–49.8 yr). For the management of their brain disease, radiosurgery was used as the primary management modality in 115 patients (within 1 mo of brain metastasis diagnosis with no other previous therapy). One hundred ten patients (45.1%) had received previous WBRT, usually 30 Gy in 10 or 12 fractions (range, 21–60 Gy). Two patients had previous radiosurgery (one linear accelerator [LINAC]-based and one with a gamma knife) at other institutions. Fifty-three patients (21.7%) had previous surgery (craniotomy in 42, stereotactic biopsy in 8, and needle aspiration of tumor cyst in 3 patients). Evidence of previous tumor hemorrhage, either clinical or radiological, was present in 37 cases (15.2%). The median Karnofsky Performance Score (KPS) was 90% (range, 50–100%). According to the referring oncologist evaluation, the systemic cancer was considered controlled in 48 patients (19.7%) and active in 196 patients (80.3%). When stratified according to the recursive partitioning analysis (RPA) devised by the Radiation Therapy Oncology Group (RTOG),[8] 28 patients (11.5%) were in Class I, 200 patients (82%) were in Class II, and 16 patients (6.6%) were in Class III. *Table 39.1* summarizes the patient population, in more detail.

Radiosurgery Procedures

A total of 291 radiosurgery procedures were performed to manage 754 tumors. A single procedure was required in 207 patients, and 37 patients had multiple procedures (two procedures in 32 cases, three procedures in two cases, four procedures in one case, and five procedures in two cases). A mean of 2.6 tumors per patient were irradiated at each procedure (range, 1–14 tumors). Six hundred and twelve tumors (81.2%) were located in the cerebral hemispheres, 47 tumors (6.2%) in deep supratentorial parenchyma (thalamus, basal ganglia, corpus callosum), 67 tumors (8.9%) in the cerebellum, 14 tumors (1.9%) in the brainstem, and 14 tumors (1.9%) in the cranium (vault or base). The isodose line used to deliver radiation varied from 30 to 90% (median, 50%). The median margin dose delivered was 18 Gy (mean, 17.4 Gy; range, 10–22 Gy) and the median maximum dose was 32 Gy (mean, 33.3 Gy; range, 20–50 Gy). The doses were selected based on tumor size, location, and previous irradiation status of the patients. Individual tumor volume (largest tumor in case of multiple metastases) varied from 0.1 to 37.2 cm^3 (median, 3.4 cm^3; mean, 6.0 cm^3), whereas the total tumor volume (including all lesions in cases of multiple

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TABLE 39.1. Demographics and clinical data of patient population[a]

Characteristics	Value
Sex	
Female	79 (32.4%)
Male	165 (67.6%)
Initial cerebral presentation	
Staging imaging (no symptoms)	119 (48.8%)
Seizure	30 (12.3%)
Tumor hemorrhage	21 (8.6%)
Mass effect (without bleed)	74 (30.3%)
Number of metastases	
1	98 (40.2%)
2–3	85 (34.8%)
4–6	41 (16.8%)
7 or more	20 (8.2%)
Metastases location	
Lobar supratentorial	219 (89.8%)
Deep supratentorial	37 (15.2%)
Cerebellum	39 (16%)
Brainstem	13 (5.3%)
Cranium	6 (2.5%)
Previous systemic therapy	
Chemotherapy	105 (43%)
Immunotherapy	124 (50.8%)
Extracranial radiation	32 (13.1%)
Previous cerebral therapy	
Surgery	53 (21.7%)
WBRT	110 (45.1%)
Radiosurgery	2 (0.8%)
Extent of systemic disease	
CNS only	7 (2.9%)
Primary site only	21 (8.6%)
Primary + 1 lymph node chain	25 (10.2%)
Primary + >1 lymph chain or visceral met	49 (20.1%)
Disseminated (>2 visceral sites)	142 (58.2%)
Systemic disease status	
Active	196 (80.3%)
Controlled	48 (19.7%)
Main neurological symptomatology at radiosurgery	
Asymptomatic	131 (53.7%)
Headaches only	23 (9.4%)
Seizures only	14 (5.7%)
Focal deficits	63 (25.8%)
Cognitive deficits	13 (5.3%)
KPS	
90–100%	163 (66.8%)
<80%	81 (33.2%)
RPA class	
1	28 (11.5%)
2	200 (82%)
3	16 (6.6%)

[a]WBRT, whole-brain radiation therapy; CNS, central nervous system; KPS, Karnofsky Performance Score; RPA, recursive partitioning analysis.

metastases) varied from 0.1 to 44.8 cm^3 (median, 4.4 cm^3; mean, 7.7 cm^3).

Follow-up Evaluations

The first clinical and radiological follow-up assessments were scheduled at 8 weeks (earlier if a new symptom developed), and then every 3 months for the first year. Further evaluations were dictated by the status of the patients. A tumor was deemed stable on magnetic resonance imaging (MRI) scan follow-up if it remained within 25% of its initial size. Progression was recognized if the tumor increased by more than 25% compared with at the time of radiosurgery, whereas tumor regression occurred in cases of shrinkage of more than 25%. In addition to patients with increased tumor size, those who needed additional intervention on an irradiated lesion because of worsening symptoms, even without change in size, were classified as having progression.

RESULTS

Survival

At the time of the analysis, 212 patients were deceased and 18 were still alive. Fourteen patients were presumed dead (without confirmation) and were censored from survival analysis. The median survival after radiosurgery was 5.3 months (mean, 10 mo; range, 0.2–114.3 mo). Median survival was 7.8 months (mean, 13.4 mo) from the diagnosis of brain metastases and 44.9 months (mean, 69 mo) from the diagnosis of the primary tumor. Actuarial survival rates were 67.6 ± 3.1% at 3 months; 42.8 ± 3.3% at 6 months; 20.2 ± 2.7% at 12 months; and 9.3 ± 2.1% at 24 months after radiosurgery (*Fig. 39.1*). One hundred eight patients (50.9%) were thought

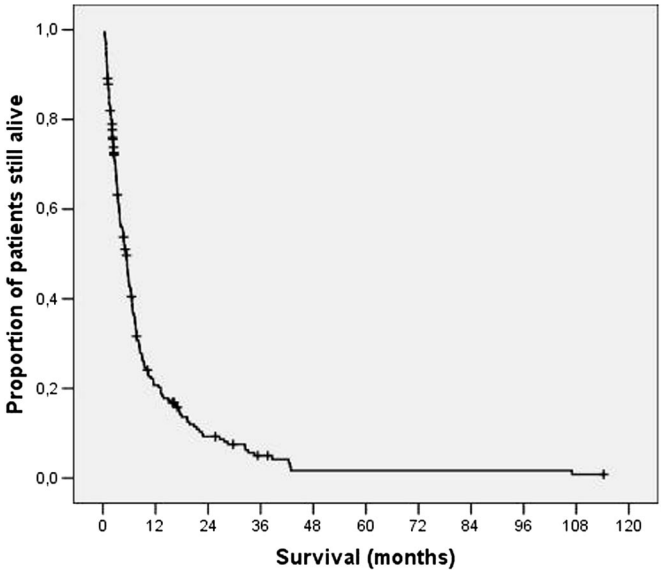

FIGURE 39.1. Kaplan-Meier plot showing overall survival from the time of radiosurgery for the entire patient series.

to have died from progression of the systemic disease and 86 patients (40.5%) from CNS disease. In the latter group, 77 patients died from increased cerebral tumor burden (most with multiple new metastases) whereas 9 patients died as a consequence of brain hemorrhage. Six patients (2.8%) died from causes unrelated to their neoplastic disease. The exact cause of death remained unknown in 12 patients (5.7%). On multivariate analysis, active extracranial disease ($P < 0.0005$); KPS, at most 80% ($P < 0.0005$); multiple metastases ($P = 0.005$); tumor volume greater than 8 cm^3 ($P = 0.041$); and cerebellar metastases ($P = 0.021$) were predictors of decreased survival (*Table 39.2*).

Local Control

Follow-up imaging was available for 175 patients after 208 procedures (a total of 507 metastases). The median follow-up interval was 4.3 months (mean, 8.1 mo; range, 0.3–114.3 mo). The best responses obtained were complete disappearance of 31 tumors (6.1%), regression of 162 tumors (32%), and no change in 268 tumors (52.8%). Early progression occurred in 46 tumors (9.1%). Delayed progression after previous regression or stabilization was noted in 24 tumors. Thus, a total of 70 tumors (13.8% of all metastases) eventually progressed. Overall, 54 patients (30.9%) had progression of at least one metastasis after radiosurgery. The median time to progression was 2.9 months (mean, 5.5 mo; range, 0.1–30.9 mo). For all patients with imaging follow-up, actuarial freedom from progression was 83.1 ± 2.8% at 3 months; 74.6 ± 3.6% at 6 months; 58.9 ± 5.2% at 12 months; and 42.8 ± 7.1% at 24 months (*Fig. 39.2*). On multivariate testing, increased total volume ($P < 0.0005$) and hemorrhagic metastasis ($P = 0.002$) were predictors of local failure (*Table 39.3*).

Distant Control

Of 175 patients with imaging follow-up, 73 patients (41.7%) were found to have new lesions on subsequent studies. The median time was 4.2 months after radiosurgery (mean, 5.9 mo; range, 0.5–41.1 mo). Actuarial freedom from distant failure was 78.6 ± 3.2% at 3 months; 57.5 ± 4.3% at 6 months; 32.5 ± 4.9% at 12 months; and 17.1 ± 4.6% at 24 months (*Fig. 39.3*). On multivariate testing, multiple metastases ($P < 0.0005$) and absence of immunotherapy after radiosurgery ($P = 0.002$) increased the odds of developing new brain metastases (*Table 39.4*).

Morbidity and Clinical Outcome

Clinical follow-up was available for 206 patients (range, 0.2–114.3 mo). Sixteen patients (6.6%) had symptomatic radiation effects demonstrated by increased contrast uptake with signal changes around the lesion on long relaxation time (TR) MRI scans. These imaging changes as well as symptoms were completely reversed with a temporary course of corticosteroids in 12 patients. Two patients required a

TABLE 39.2. Univariate and multivariate analyses of survival after radiosurgery[a]

Variable	Univariate (*P* value)	Multivariate (*P* value)	Hazard rate ratio (relative risk)
Age	0.014	0.149	NA
Sex	0.990	0.986	NA
Primary to brain metastasis interval	0.062	0.071	NA
Extracranial disease status	<0.0005	<0.0005	2.153
RPA class	<0.0005	0.225	NA
KPS	<0.0005	<0.0005	2.043
Number of metastases	<0.0005	0.275	NA
Single or multiple metastasis	<0.0005	0.005	1.544
Initial brain metastasis presentation (symptomatic or not)	0.267	0.125	NA
Neurological status at time of radiosurgery (symptomatic or not)	0.002	0.685	NA
WBRT at any time	0.055	0.316	NA
Chemotherapy	0.114	0.539	NA
Immunotherapy	0.761	0.897	NA
Total radiosurgery volume	0.001	0.571	NA
Total radiosurgery volume (±8 cm^3)	0.003	0.041	1.379
Presence of deep cerebral metastasis	0.328	0.241	NA
Presence of cerebellar metastasis	0.004	0.021	1.604
Presence of brainstem metastasis	0.798	0.406	NA

[a]NA, not applicable; RPA, recursive partitioning analysis; KPS, Karnofsky Performance Score; WBRT, whole-brain radiation therapy.

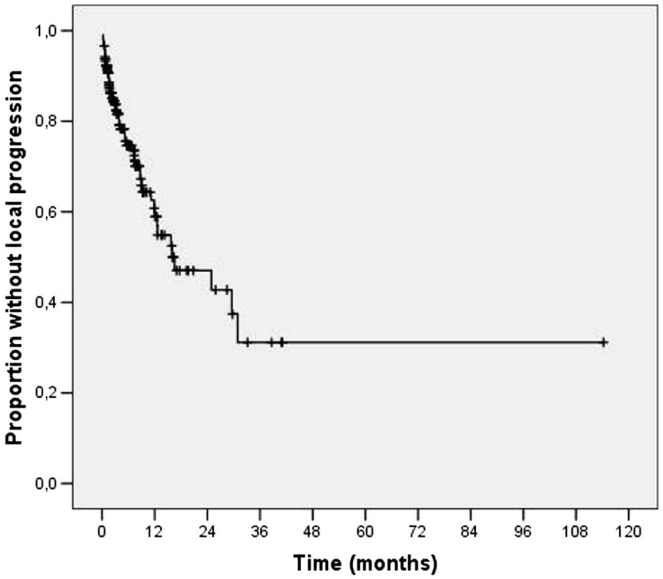

FIGURE 39.2. Kaplan-Meier plot depicting radiological control rate after radiosurgery.

craniotomy, one had fourth ventricle compression with hydrocephalus and the other had worsening level of consciousness and hemiparesis. The remaining two patients had partial resolution of radiation-induced motor deficits with steroids. Asymptomatic radiation-induced long TR changes were noted in eight patients (3.9%). Thus, radiation-induced changes were found on imaging in 10.5% of patients. The median occurrence time of radiation changes was 2.2 months (mean, 2.8 mo; range, 0.1–9.5 mo). No variable was found to predict the occurrence of complications on Cox regression analysis. Overall, the clinical condition improved in 17 patients (8.3%) after radiosurgery, remained stable in 130 patients (63.1%), and worsened in 59 patients (28.6%). In worsened patients, adverse radiation effects was the cause in 16 patients (27.1%), brain hemorrhage in 27 patients (45.8%), and increased lesion burden (either local or distant progression) in 16 patients (27.1%). Corticosteroids were not needed or were discontinued after radiosurgery in 108 patients (52.4%). After radiosurgery, 27 patients (13.1%) required a craniotomy. Local progression was the cause in 9 patients, brain hemorrhage in 13 patients, radiation injury in 2 patients, and new metastasis in 3 patients. Forty-two patients (20.4%) required at least one repeat radiosurgery procedure for the management of new brain metastases (33 cases), progression of a previously irradiated lesion (5 cases), or both (4 cases). Fifty-one patients (24.8%) underwent WBRT after radiosurgery because of the development of multiple new brain lesions.

DISCUSSION

The diagnosis of a cerebral metastasis is usually associated with a dismal prognosis in melanoma patients, because a significant proportion will die as a direct consequence of the neurological disease.[32] WBRT in currently used dose schedules has been demonstrated to be relatively ineffective at achieving local control and significantly prolonging survival for metastatic melanoma patients.[6,9,17,18,30] Stereotactic radiosurgery is a surgical procedure that allows single-session closed-cranium delivery of radiation in a conformal fashion. Its efficacy in the management of brain metastases has been

TABLE 39.3. Univariate and multivariate analyses of local control after radiosurgery[a]

Variable	Univariate (*P* value)	Multivariate (*P* value)	Hazard rate ratio
Number of brain metastasis	0.363	0.481	NA
Neurological status at treatment (symptomatic or not)	0.058	0.723	NA
KPS	0.063	0.901	NA
RPA class	0.115	0.176	NA
Hemorrhagic metastasis	<0.0005	0.002	2.528
Irradiation of cavity postresection of brain metastasis	0.323	0.370	NA
Superficial brain metastasis	0.933	0.989	NA
Deep brain metastasis	0.478	0.471	NA
Cerebellar metastasis	0.596	0.274	NA
Brainstem metastasis	0.940	0.854	NA
Volume of largest metastasis	<0.0005	0.669	NA
Total radiosurgery volume	<0.0005	<0.0005	1.055
Margin dose used	0.001	0.482	NA
Maximum dose used	0.024	0.421	NA
WBRT	0.838	0.937	NA
Radiosurgery as a boost to WBRT	0.323	0.425	NA

[a]NA, not applicable; KPS, Karnofsky Performance Score; RPA, recursive partitioning analysis; WBRT, whole-brain radiation therapy.

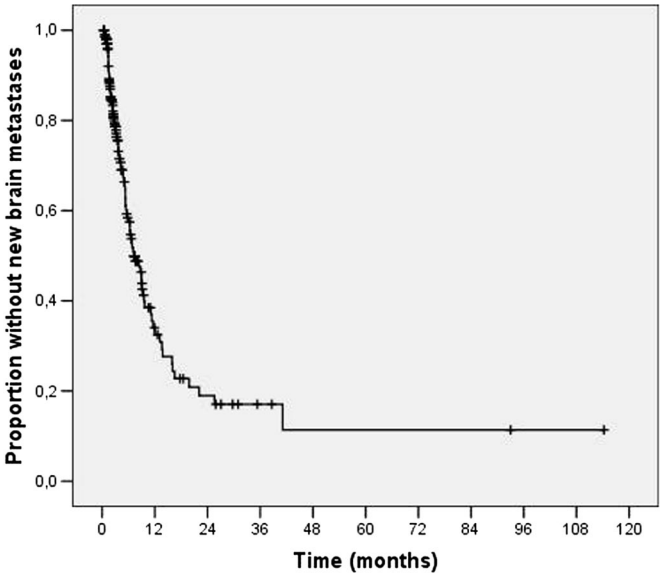

FIGURE 39.3. Kaplan-Meier plot demonstrating the proportion of patient without new brain metastases after radiosurgery.

proven in numerous publications.[15,24,40] Recent articles have also reported success using stereotactic radiosurgery to manage metastatic tumors from primary cancers often considered "radioresistant" (sarcoma, renal carcinoma, melanoma).[2,4]

Survival

The median reported survival after radiosurgery for melanoma brain metastases varies between 4.8 and 10.6 months (2, 3, 5, 10–12, 16, 19, 20, 22, 25, 26, 28, 29, 31, 34–36, 41). The median survival in the present series (5.3 mo) is in the lower end of what is reported in the literature. Increased evidence of the efficacy of radiosurgery has led us to offer this approach as palliative management to patients with more extensive CNS disease and more active extracranial disease, which might explain the lower survival. In the present study, 59.8% of patients had multiple metastases, and this was found to negatively impact survival. Other significant predictors of survival were systemic disease status, KPS, radiosurgery volume, and cerebellar location. Extracranial disease had the most impact on survival. Interestingly, RPA class was not a significant predictor of survival after multivariate analysis. This classification was devised using mostly data from lung cancer patients.[8] Applicability to melanoma patients has not been consistently demonstrated, although articles have reported it as a survival predictor (2–4, 31).

CNS Disease Control

Sustained local control was achieved in 86.2% of tumors and 69.1% of patients. Actuarial freedom from local progression was 74.6% at 6 months and 58.9% at 1 year. Twelve-month local control rates varying from 47 to 84% have been reported in the literature.[4,29,34,35] Radiosurgery volume greater than 8 cm^3 and hemorrhagic changes in a metastasis at the time of radiosurgery were the only predictors of local failure after multivariate analysis in our study. Signal changes on MRI scan associated with intratumoral blood render planning more difficult, blurring the lesion margins and often increasing its volume, which might explain the higher risk of failure. Increased tumor volume as a local failure prognostic factor has been confirmed by other investigators.[10,34,35] Radiation dose did not retain prognostic value after multivariate analysis in our series. Herfarth et al.[16] reported that margin doses of 20 Gy or more were associated with improved local control after radiosurgery.

New brain metastasis occurred in 41.7% of our patients. Patients presenting with multiple brain lesions were more

TABLE 39.4. Univariate and multivariate distant control analyses[a]

Variable	Univariate (*P* value)	Multivariate (*P* value)	Hazard rate ratio
Time interval from diagnosis of primary to brain metastasis	0.492	0.656	NA
Extracranial disease status	0.209	0.214	NA
RPA class	0.381	0.240	NA
Previous chemotherapy treatment	0.229	0.420	NA
Previous immunotherapy treatment	0.811	0.515	NA
Number of brain metastasis	<0.0005	0.070	NA
Single or multiple metastasis	<0.0005	<0.0005	2.629
Total radiosurgery volume	0.738	0.085	NA
WBRT	0.003	0.061	NA
Subsequent chemotherapy	0.555	0.974	NA
Subsequent immunotherapy	0.002	0.002	0.380

[a]NA, not applicable; RPA, recursive partitioning analysis; WBRT, whole-brain radiation therapy.

likely to develop new metastases, probably related to more active primary disease from the onset. Our data is consistent with that reported in other radiosurgery series. Yu et al.[41] identified increased total tumor volume and active systemic disease as significant predictors of new brain metastases after radiosurgery. Increased total volume was also significantly associated with distant failure according to Selek et al.[34] Immunotherapy after radiosurgery was another factor found to decrease the incidence of new brain metastases in our patients. Although it was thought that immunotherapy had a limited effect on cerebral metastases because of its inability to penetrate the blood-brain barrier,[13,27] recent studies have reported regression of CNS lesions with immunotherapy.[14,33] Such therapy may help in controlling cerebral micrometastases or in preventing continuous spread of systemic disease to the CNS.

Morbidity and Clinical Outcome

Gamma knife radiosurgery had a low complication rate in this series. Only 6.6% of patient suffered from symptomatic adverse radiation effects, 75% of those completely recovered with corticosteroids. This is similar to the study by Lavine et al.,[20] who reported that 3 of 45 patients experienced transient worsening of symptoms after radiosurgery. Brown et al.[2] had a higher complication rate, with 5% symptomatic radiation necrosis and an additional 12% symptomatic cerebral edema. Radiation-induced complications can be reduced by lowering the radiation dose for high-volume tumors or tumors located in critical areas, such as the brainstem or deep white matter. Dose adjustments are also required in cases of previous radiation exposure.[7] In our study, although no variable was found to be a predictor for complications, total radiosurgery volume approached statistical significance, reflecting what was previously reported in the literature.

Overall, neurological condition remained stable or improved in 71.4% of our patients. More than half (52.4%) were able to discontinue or avoid exogenous corticosteroid use after undergoing radiosurgery, which is a necessary requirement to continue with any immunotherapy. Moreover, corticosteroids are a well-recognized cause of morbidity for brain tumor patients, with a nonnegligible impact on quality of life. This suggests that gamma knife radiosurgery can positively impact the clinical condition in a significant majority of patients.

Impact of WBRT

The role of WBRT in the management of melanoma brain metastases has been questioned in the literature. Melanoma cells lines were reported to be relatively radioresistant to conventional fractionated doses regimen in vitro, having a better ability to repair radiation damage.[21] Clinical articles also suggest a modest impact of WBRT on melanoma metastases. Selek et al.[34] reported no difference in survival for patients managed with radiosurgery alone compared with patients receiving both WBRT and radiosurgery. Moreover, in that study, local control rates at 1 year were worse for patients who had combined treatment (0% versus 60.4%). In the article by Stone et al.,[37] median survival was 3.6 months after WBRT alone, and 10.9 months after WBRT combined with radiosurgery or surgical resection. According to Brown et al.,[2] adding WBRT to radiosurgery did not influence survival or the proportion of patients dying from CNS disease. It did, however, improve both local (100% versus 85%) and distant control (91% versus 35%) at 6 months. In our study, the addition of WBRT at any point during the course of management did not significantly affect survival and CNS disease control. Taken globally, these results indicate that radiosurgery without adjuvant WBRT can be considered for the primary management of melanoma brain metastases in eligible patients. Advantages of gamma knife radiosurgery over WBRT include its high spatial accuracy and its excellent tumor control rate, as well as the practical advantage of single-session irradiation for patients who are already challenged by aggressive systemic therapeutic options. However, when local therapies are not indicated, WBRT remains a valid option that can provide symptomatic improvement as palliative management of disseminated CNS disease.[9]

CONCLUSION

Stereotactic radiosurgery is an effective management option for primary and recurrent brain metastases from malignant melanoma. It improves survival and is associated with a high local control rate, with minimal morbidity. Improved survival can be achieved in patients with single metastasis, controlled systemic disease, and high KPS score.

However, survival in general remains limited primarily because of poor extracranial tumor control. Hopefully, with future improvements in systemic therapy, the impact of radiosurgery in allowing long-lasting CNS control will become more apparent and facilitate significant increases in patient survival.

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