

Treatment of Brain Metastases From Melanoma

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Brain metastases from malignant melanoma have a poor prognosis, and treatment can be difficult because of rapid progression of the disease. To help define the treatment of this disease, we reviewed the published literature on brain metastases from melanoma. If a solitary metastasis is present, surgery might be beneficial, especially if systemic disease is absent. Stereotactic radiosurgery is a less invasive, attractive option for solitary or oligometastatic (up to 6) lesions. External beam whole-brain radiation therapy can produce responses and frequently palliates symptoms,

but as the sole therapy, it is unlikely to eradicate brain metastases. Chemotherapy may be gaining a role with newer agents that penetrate the blood-brain barrier. Combined modality therapy appears to be the future direction of treatment of multiple metastases.

Mayo Clin Proc. 2003;78:1529-1536

KPS = Karnofsky performance score; RPA = recursive partitioning analysis; WBRT = whole-brain radiation therapy

Brain metastases are common, often devastating consequences of metastatic cutaneous melanoma. Autopsy series have shown that 50% to 75% of those who die of melanoma have evidence of metastatic disease in the brain or meninges.^{1,2} Two thirds of such patients will receive clinical diagnoses before death and will have symptoms of headache, seizures, or hemorrhage³; the vast majority will be unable to be weaned from corticosteroid therapy before death.⁴ Overall, of those who die of melanoma, 20% to 55% die because of brain metastases.^{2,4,5} In addition, the diagnosis of brain metastases confers an exceedingly poor prognosis, with mean survival ranging from 2.75 to 4.0 months after diagnosis.^{3,4,6} Currently, most therapeutic trials of melanoma exclude patients with brain metastases because of their detrimental effect on survival rates.⁷ We review the clinical data (Figure 1) on the treatment of brain metastases in melanoma to date and discuss some potential future treatment avenues.

TREATMENT MODALITIES

Surgery

One of the successful treatment methods for patients with brain metastases in general, including those with melanoma, is resection of a solitary metastasis. Because of the vast improvement in imaging techniques that began

with the advent of computed tomography and magnetic resonance imaging, identification of these patients has improved substantially. Several large surgical series (Table 1) were reported recently and are discussed subsequently.

In a Memorial Sloan-Kettering Cancer Center surgical series of 91 patients identified during a period of 20 years, the median durations of survival of selected patients who underwent craniotomy were 6.7 months after surgery and 8.5 months after diagnosis of brain metastases.⁹ The 76 patients who had a resectable solitary metastasis survived longer than those who had multiple metastases resected (7.8 vs 5.4 months), although the difference was not statistically significant ($P=.12$). Overall, 47% of patients died of neurologic causes, including 15 with carcinomatous meningitis. In fact, the duration of survival of those with leptomeningeal involvement was half that of those without such involvement (4.7 vs 9.0 months). Forty patients had no recurrence of their brain metastases, with a median survival of 8.3 months.⁹

Another series reviewed 147 patients, 84% of whom had a solitary metastasis.¹¹ Gross total resection was accomplished in 85%, and only 27% died of intracranial disease. This statistic is especially remarkable because the criteria for surgery required either stable or absent distant metastases. Surgical morbidity was infrequent, with 4 patients requiring additional surgery because of bleeding and 6 because of wound infections. Five patients died within 30 days of surgery, including 3 who died of progression of brain metastases in tumors that could not be fully resected. Sixty-six patients (45%) had no recurrence of brain metastases, although their median survival was only 6 months. The main variable affecting survival was the number of intracranial metastases, with 1, 2, or more than 2 sites

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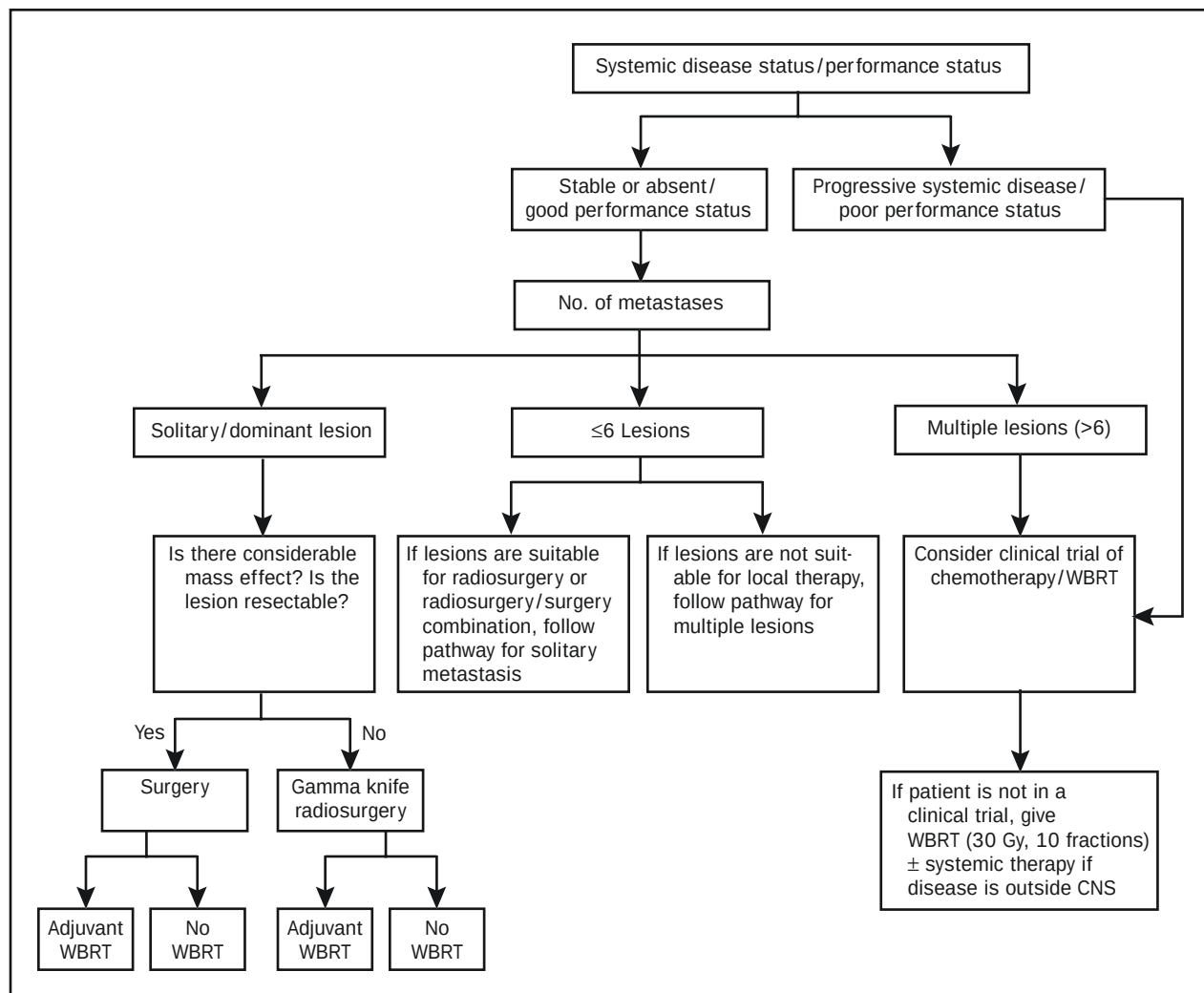


Figure 1. Clinical treatment of brain metastases from melanoma. CNS = central nervous system; WBRT = whole-brain radiation therapy.

conferring survival of 8, 6, and 3.5 months, respectively. These differences were statistically significant. Thirteen patients (age range, 17-72 years) survived at least 3 years after surgery for a solitary metastasis. All had macroscopic total resections and underwent postoperative whole-brain radiation therapy (WBRT).¹¹

A series from Duke University Medical Center reported median survival of 8.2 months in 118 patients with a solitary metastasis who underwent resection.⁸ This was significantly longer than in those with a solitary brain metastasis who underwent external beam radiation alone (4.2 months). The authors reported that 50% of patients who underwent surgery had neurologic improvement, 19% had no change, and 22% experienced worsening neurologic symptoms. During the postoperative period, the risk of death or life-threatening morbidity was 8.6%.⁸

A series from Roswell Park Cancer Center described 32 patients who underwent surgical resection.¹⁰ Median survival was poor (5 months), although 1-year survival was 28.3%. For those receiving nonsurgical treatment (chemotherapy or radiation), median survival was 3 months, and 6.6% survived for 1 year. For those undergoing no treatment, median survival was 1 month, and 3.5% survived for 1 year.¹⁰

Selection bias is inherent in retrospective surgical series; therefore, data on survival must be reviewed with that bias in mind. However, in the above-mentioned series and other smaller series, the number of long-term survivors among patients with a resected solitary metastasis and the decreased percentages of those dying of their brain metastases compared with historical controls argue in favor of surgical resection.¹²⁻¹⁵ Additionally, 2 prospective randomized trials of patients with a solitary brain metastasis (of

Table 1. Summary of Surgical Series of Patients With Brain Metastases*

Reference	No. of patients	% of patients with		Median survival after resection (mo)	Deaths due to brain metastases (%)	Recurrence of brain metastases after surgery (%)	Long-term survivors (>3 y) (%)	Median age (y)	Symptoms at presentation (%)	Deaths within 30 days of surgery (%)
		Solitary metastases	Extracranial disease							
Sampson et al, ⁸ 1998	118	85	46†	8.2	95†	NR	12.1	NR	93	8.6 (includes life-threatening morbidity)
Wronski & Arbit, ⁹ 2000	91	76	37	6.7 (overall)	47	44	8.8	47	95	14.2
Konstadoulakis et al, ¹⁰ 2000	32	84	NR	5.0	NR	NR	4.4	47	NR	NR
Zacest et al, ¹¹ 2002	147	84	56	8.5 (overall)‡	27	55	8.8	53	99	3.4

*NR = not reported.

†Data from overall numbers of patients with brain metastases from melanoma when those numbers for patients who underwent craniotomy only were not available.

‡Median survival was 9.9 months in 124 patients with 1 metastasis and 5.6 months in 23 patients with more than 1 metastasis.

several different eligible primary cancers including melanoma) showed that surgical resection combined with postoperative WBRT provided significantly longer survival than WBRT alone for patients with a highly resectable solitary metastasis.^{16,17} In addition to improving survival, surgery may decrease morbidity of the disease because a decrease in neurologic symptoms has been reported consistently.^{8,18}

On the basis of the aforementioned data, there appears to be a role for surgical resection of a solitary metastasis of melanoma in the brain because of a considerable possibility of eradicating the disease. For patients with multiple metastases, the data are less convincing. These patients should be selected carefully, although surgery may be necessary for lesions that cause severe symptoms such as hydrocephalus or refractory seizures not amenable to other therapeutic interventions.

External Beam WBRT

Melanoma has been considered relatively resistant to radiotherapy. In 1971, *in vitro* data showed resistance to radiation among melanoma cell lines.¹⁹ However, in the absence of other effective modalities for treatment of multiple metastases to the brain, external beam WBRT has been used to treat these patients. Retrospective and prospective studies have assessed the efficacy of external beam WBRT for brain metastases, the largest of which are summarized in Table 2.

In a recent series from the M. D. Anderson Cancer Center, Ellerhorst et al²² reported outcomes in 65 patients with multiple metastases treated with doses ranging from 15 to 50 Gy divided into 4 to 25 fractions, although most patients (61%) received 30 Gy in 10 fractions. Of the 28 patients assessed by imaging studies after therapy, 36%

had decreases in lesion sizes; 9% had complete responses, and 35% had stable disease. Of the 65 patients, 52% were able to have their corticosteroid therapy for symptoms discontinued, although palliation of symptoms was obscured by the corticosteroid use. Median survival was 4.4 months from initiation of radiation therapy, and causes of death were not reported.²²

In a retrospective analysis from Norway,²¹ 39 patients with brain metastases from melanoma were treated with 33.6 to 50 Gy over 7 to 31 fractions, and 21 patients had an objective clinical improvement. Of 12 patients who had follow-up imaging, 6 had regression of disease. Patients who received concomitant dacarbazine and carmustine chemotherapy may have had slightly better improvement, although no statistical analysis was performed. Median survival for the entire group was 2 months.²¹ Other similar retrospective studies of patients treated with external beam WBRT alone showed similar improvements in symptoms but dismal median survival times of 2 to 3 months.²⁴⁻²⁷

In 1980, 2 prospective studies from the Radiation Therapy Oncology Group regarding the use of external beam WBRT for melanoma metastatic to the brain were reported together.²⁰ The treatment schedules were varied (although thought to be equivalent), and the use of chemotherapy and corticosteroids was not controlled. Nonetheless, the authors reported symptomatic improvement with regard to headache (73%), seizures (83%), motor loss (61%), and impaired mentation (62%). The use of corticosteroids or chemotherapy did not alter the outcome. Two thirds of patients died of progression of their brain metastases. Median survival for all patients was 2.8 months.²⁰

In a series from the Cleveland Clinic, 74 patients with brain metastases from melanoma were examined and, im-

Table 2. Summary of Series of Patients Treated With and Without WBRT*

Reference	No. of patients	Median age (y)	Dosage/schedule (Gy/fractions)	Median survival	
				With WBRT (mo)	Without WBRT (mo)
Carella et al, ²⁰ 1980	60	NR	10-40/1-28	2.8	NA
Stridsklev et al, ²¹ 1984	39	47	33.6-50/7-31	2.0	NA
Sampson et al, ⁸ 1998	180	NR	15-60/NR (majority, 30/10)	3.9	3.6
Ellerhorst et al, ²² 2001	65; 7 had solitary lesions, 30 had ≥ 5 lesions	45	15-50/4-25	4.4	NA
Buchsbaum et al, ²³ 2002	74	53	22-55/NR (majority, 30/10)	6.1	3.9

*NA = not applicable; NR = not reported; WBRT = whole-brain radiation therapy.

portantly, stratified by the Radiation Therapy Oncology Group's recursive partitioning analysis (RPA).²⁸ The RPA, developed to stratify patients with brain metastases by risk, categorizes patients according to the Karnofsky performance score (KPS), extracranial disease, and patient age. Patients in class 1 (age <65 years, KPS ≥ 70 , controlled primary cancer, and no extracranial metastases) have the longest survival; those in class 2 (all others not meeting criteria for class 1 or 3) have intermediate survival; and those in class 3 (KPS <70) fare poorest.²⁸ In this retrospective series, survival expectedly correlated with RPA class: 10.5, 5.9, and 1.8 months for classes 1, 2, and 3, respectively. Overall survival was 5.5 months. Patients were also categorized into those who received WBRT alone, local therapy alone (surgery or radiosurgery), both, or no therapy. Those who received both interventions survived longer (8.8 months) than those who received radiation alone (2.3 months), local therapy alone (4.8 months), or no therapy (1.1 months). However, those in the combined WBRT/local therapy category were much more likely than those in the other categories to be in RPA class 1 (30% vs 3%) and less likely to be in class 3 (0% vs 34%). The numbers were too small to analyze interventions by RPA class.²³

External beam WBRT clearly has some benefit with regard to palliation of symptoms, but patients who receive this therapy frequently die of neurologic causes due to progression of their intracranial disease. Clearly, an improvement in this modality or augmentation with other therapeutic modalities is needed.

Because melanoma is relatively resistant to radiation therapy and experimental cell survival curves have also shown radioresistance, many different fractionation schemes have been devised with larger doses per fraction.^{19,29-31} However, a review of several retrospective series reveals that no fractionation schedule is superior to the more standard fractionation schedule of 30 Gy in 10 fractions, with more toxicity in the higher-dose fractionation schedules.^{14,15,32}

With regard to the utility of external beam WBRT after surgical resection, to our knowledge, no prospective study has included a sufficient number of patients with melanoma metastases.³³ One retrospective comparison of 35 patients undergoing resection of a solitary metastasis showed lower mortality as a result of brain metastases (24% in the treated group vs 85% in the untreated group) in those treated with external beam WBRT after surgery.³⁴ By contrast, another retrospective series showed neither a decrease in central nervous system recurrence nor prolongation of survival,⁹ and another noted an insignificant increase in survival and decreased risk of subsequent neurologic symptoms.⁸ There is a need for a prospective randomized trial of external beam WBRT in the postoperative setting because its role is not clearly established, although some retrospective data appear suggestive.

Stereotactic Radiosurgery

Given the ability to focus high-intensity radiotherapy in a small area, this technique is increasingly being used in the management of unresectable solitary or oligometastatic disease in the brain in patients with good performance status and stable or absent systemic disease. Stereotactic radiosurgery is an especially attractive alternative to surgery, especially for lesions with no appreciable mass effect and for patients with more than 2 lesions or unresectable lesions. The first series,³⁵ published in 1993, reported 23 patients with lesions smaller than 3 cm in diameter (19 with a solitary metastasis and 4 with multiple lesions) who underwent gamma knife radiosurgery in addition to external beam WBRT (30 Gy/10 fractions). Nineteen died of systemic disease, 1 died of intracerebral hemorrhage, and there were only 2 intracranial recurrences. One patient required craniotomy for hemorrhage into a tumor bed. Median survival was 9 months.³⁵

Subsequent series have shown similar, although not quite as dramatic, results. In a series from the University of California in San Francisco reported in 1996,³⁶ 40 patients were treated, although most had multiple metastases. The

gamma knife was used in varying capacities: as a rescue for progression after WBRT or surgery, after WBRT as a boost, and alone. Overall, only 3 patients died of recurrent tumors at the sites of treatment, and 5 died of new areas of progression in the brain. Median survival was 35 weeks.³⁶ In a similar study, Brown et al³⁷ reviewed the gamma knife radiosurgery experience in 23 consecutive patients (most had multiple metastases) treated at the Mayo Clinic. The local control rate was 91%, and the median survival time after radiosurgery was 9.7 months. One small study of 12 patients suggested that efficacy was diminished with lesions larger than 1.0 cm,³⁸ but 3 subsequent series noted no such observation, with local control rates of greater than 90% despite lesions up to 3.5 cm.^{37,39,40} Rates of hemorrhage into treated tumor beds were less than 10% in these same studies. Stabilization or improvement in neurologic symptoms was noted in 78% to 100% of treated patients.^{39,40} In a recent series, 18% of lesions progressed locally, although 6 of 45 patients who had a solitary metastasis in the brain and no visceral disease were alive at the end of the study, with survival ranging from 14 to 82 months.⁴¹

Overall, local control with stereotactic radiosurgery is excellent, and this method is less invasive than craniotomy. Long-term survival has been shown in patients with brain-only metastases, and the treatment is relatively well tolerated. Whole-brain radiation therapy in concert with radiosurgery has been shown to prevent new lesions but not to improve survival.^{39,41}

Chemotherapy

Given the poor overall response rate to chemotherapy for melanoma metastatic to extracerebral sites,⁴² it is not surprising that chemotherapy alone has been primarily unsuccessful in treating brain metastases. One prospective study showed a 0% response rate with cisplatin and etoposide compared with a 39% response rate in patients with brain metastases from breast cancer and a 30% response rate in non-small cell lung cancer.⁴³ Carmustine, a nitrosourea with modest activity against extra-central nervous system melanoma,⁴⁴ has been used with little success in melanoma metastatic to the brain,⁴⁵ ostensibly in part due to poor penetration of the blood-brain barrier.⁴⁶

Subsequently, attempts have been undertaken to identify agents that cross into the central nervous system in adequate quantities to have an antitumor effect. Fotemustine, a nitrosourea with high central nervous system penetration, was an early candidate. Phase 2 European studies suggested response rates for brain lesions from 12% to 25%.^{47,48} In one study,⁴⁷ response rates decreased from 12% to 5% as the eligibility criteria were loosened to make the drug more available to the population. Fotemustine is not available in the United States.

Temozolomide, a dacarbazine analogue with high central nervous system penetration, was recently approved by the US Food and Drug Administration for use in primary brain tumors because of the effective central nervous system concentrations of its active metabolite, 5-(3-methyl-1H-imidazol-1-yl)imidazole-4-carboximide.⁴⁹ One case of a complete response of multiple brain metastases from melanoma after 6 cycles of temozolomide has been reported.⁵⁰ Interestingly, the patient had a complete extra-central nervous system response to a combination of dacarbazine, interferon α , and cisplatin 2 months prior but had a relapse only in the brain, perhaps illustrating the superior central nervous system concentration of temozolomide and the unusual sensitivity to chemotherapy of this patient's melanoma.⁵⁰ Nonetheless, the role of chemotherapy is still limited in melanoma, with temozolomide producing a response rate of 12%.⁵¹

The combination of thalidomide, an antiangiogenesis agent, and temozolomide is being explored for activity in brain metastases from melanoma because of the very vascular nature of these tumors. One complete response in a patient with multiple brain metastases and leptomeningeal disease in a series of 16 patients treated at Memorial Sloan-Kettering Cancer Center was reported.⁵² Good tolerability prompted further study of this combination, and preliminary reports from a phase 2 trial from the Cytokine Working Group were reported at the meeting of the American Society of Clinical Oncology in 2003.⁵³ In 24 patients, 2 complete responses and 1 partial response were noted. Among frequent toxic effects noted were tremors, thrombosis, neuromotor effects, nausea, and neurosensory problems.^{52,53} The neurologic adverse effects of thalidomide are of concern regarding quality of life in patients who may be symptomatic from their brain metastases, although further study of this combination appears warranted.

Combination Therapy: Chemotherapy and External Beam WBRT

The combination of chemotherapy with external beam WBRT is being actively explored. A European study evaluated the role of fotemustine (100 mg/m² on days 1, 8, and 15) in patients with brain metastases with or without WBRT (37.5 Gy in 15 fractions).⁵⁴ The response rate (7.4% with fotemustine alone vs 10.0% with fotemustine and WBRT) and survival (86 vs 105 days) showed a trend toward being higher in the combination therapy arm, although the difference was not statistically significant.⁵⁴ Two phase 2 trials have been reported using concomitant temozolomide and radiation therapy followed by temozolomide alone. In the first study,⁵⁵ 20 patients were treated with daily temozolomide (60 mg/[m² • day]), and given ten

300-cGy fractions of WBRT with a 6- to 9-cGy boost, followed by standard-dose temozolomide (200 mg/m² for 5 days monthly for 6 months) after radiation. The response rate was 55%, with a brain tumor control rate (response rate plus stable disease) of 85% at 3 months. Fourteen patients were alive at 8 months, and only 1 grade 3 toxic effect (thrombocytopenia) was noted. No deaths due to toxicity were noted.⁵⁵ A multicenter US trial of 31 patients used a daily dose of temozolomide of 75 mg/m² for 6 of 10 weeks, starting with initiation of radiation and WBRT at a dose of 300 cGy for 10 fractions without a boost.⁴⁹ This was followed by the same schedule of temozolomide repeated every 10 weeks instead of the 5-day monthly regimen. The response rate was lower, only 10%, and median survival was 6 months, with median progression-free survival of 2 months. One patient died of neutropenic sepsis, but the treatment was otherwise well tolerated.⁴⁹ The reason for the disparity in these 2 studies is unclear and may be due to small sample sizes and statistical variation. However, the differences of boost treatment to tumor sites and the differing schedules of temozolomide are also possibilities. The combined modality approach appears promising and seems to be reasonably well tolerated. Further study is certainly warranted.

Immunotherapy

Immunotherapy alone for brain metastases from melanoma is fraught with the same challenges as chemotherapy alone: unclear levels of drug activity in the central nervous system and low overall response rates. The safety of high-dose interleukin 2 in these patients was shown in a retrospective review by the National Cancer Institute,⁵⁶ and some efficacy was noted (5.6% response rate); however, those with brain metastases had a lower overall response rate than those without. This will likely contribute to continued exclusion of patients with brain metastases from many clinical trials of immunotherapy.

CONCLUSIONS

Brain metastases from malignant melanoma are often terminal complications of advanced disease. The rapid progression and tendency of such metastases to bleed make treatment problematic, and cessation of their progression is paramount to improving patient survival and quality of life. Given the frequency of brain metastases in patients with metastatic melanoma, screening for brain lesions with magnetic resonance imaging in those with good performance scores is an unproven, although tempting, proposal. As more successful interventions are used and in light of the morbidity of brain metastases, more clinicians will likely image the brains of asymptomatic patients with metastatic melanoma.

The paucity of prospective randomized trials regarding brain metastases from melanoma makes treatment of patients with this diagnosis difficult. In the setting of a symptomatic solitary metastasis, surgery is likely of some benefit. However, the yield for this modality decreases with multiple metastases, and a reasonable cutoff is 3 lesions, only if they are accessible through a maximum of 2 craniotomy sites.

Stereotactic radiosurgery for solitary lesions smaller than 3 to 3.5 cm without mass symptoms is an excellent alternative to surgery because of its low morbidity, and surgery is still an option if a rescue is needed. Radiosurgery may also play a role in patients with oligometastatic disease (generally up to 6 lesions) or unresectable lesions and in patients who are too ill for craniotomy. Certainly, in patients with a good performance status and a reasonably small number of lesions (≤ 6), neurosurgical consultation with a surgeon experienced in radiosurgery and microsurgery should be considered. For patients with several lesions but one dominant tumor who are primarily symptomatic, surgical excision of the dominant tumor with radiosurgery for the remainder would be a reasonable approach. For patients who have had local therapies for brain metastases, monitoring lesions by magnetic resonance imaging at 3-month intervals is a reasonable approach because these patients are at risk of development of subsequent metastases, and rescue by surgery, radiosurgery, or WBRT is often a feasible strategy.

The use of WBRT in patients with lesions not amenable to local therapies is appropriate because some patients experience improvement in quality of life. However, the low response rate and limited effect on survival suggest a clear need for improvement. The role of adjuvant WBRT after surgery and radiosurgery has not been proved, although WBRT is used often. In this setting, the possibility of radiation-induced dementia should be considered,⁵⁷ because of the potential, albeit small, of long-term survival after successful treatment of brain metastases.^{8,9,11} For now, the decision to use WBRT in the adjuvant setting must weigh the unproven possibility of decreasing the risk of recurrence against the long-term complications, and a discussion of these factors between the clinician and the patient is necessary.

Chemotherapy, specifically temozolomide, may play a role in augmenting the benefit of WBRT, and combined modality approaches appear to be promising avenues for future investigations. Prospective randomized trials would provide the best guidance for treatment of this disease, but in their absence, RPA stratification may provide the most helpful means of comparison between groups with differing interventions. Future series would be most helpful if this analysis were included, and prospective trials should

include this stratification. The need for improvement in treatment of these patients is evident in their poor survival rates, and an evidence-based approach is a sine qua non to this end.

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