



*Brain metastasis remains
a formidable challenge in
patients with melanoma.*

Catherine Hickson. *Quinces in Naples Yellow*. Oil on Belgian linen, 123 cm × 183 cm.

Diagnosis and Treatment of Melanoma Brain Metastasis: A Literature Review

Andrew E. Sloan, MD, FACS, Charles J. Nock, MD, and Douglas B. Einstein, MD, PhD

Background: Brain metastasis is common in patients with malignant melanoma and represents a significant cause of morbidity and mortality. Nearly 37% of patients with malignant melanoma eventually develop brain metastasis, and autopsy reports show that 75% of those who died of this disease developed brain metastasis.

Methods: We review the level I and level II evidence that guides indications for treatment with surgery, stereotactic radiosurgery, chemotherapy, and immunotherapy for patients with melanoma brain metastasis.

Results: Level I evidence supports the role of whole brain radiotherapy, microsurgery, and radiosurgery alone or in combination for the treatment of patients with melanoma brain metastasis. Chemotherapy has been ineffective. Ongoing studies continue to assess the effects of immunotherapy and agents in development.

Conclusions: Brain metastasis is a common and formidable challenge in patients with malignant melanoma. Although there have been no randomized controlled trials exclusively in patients with melanoma brain metastasis, care can be guided by the application of level I evidence for the treatment of brain metastasis in general and phase II studies focusing specifically on melanoma brain metastasis. Promising new agents and approaches are needed and will hopefully be identified in the near future.

Introduction

Malignant melanoma is the third most common cause of brain metastasis behind lung and breast cancer, with approximately 10,000 patients diagnosed yearly in the

United States.¹ While the incidence of brain metastasis in patients with melanoma is 9.6%, melanoma has the highest propensity to metastasize to the brain of all primary neoplasms in adults.² Nearly 37% of patients with

From the Brain Tumor & Neuro-Oncology Center and the Neurological Institute (AES), the Department of Medical Oncology (CJN), the Department of Radiation Oncology (DBE), and the Case Comprehensive Cancer Center (AES, CJN, DBE) at the University Hospital Case Medical Center, Cleveland, Ohio.

Submitted June 27, 2008; accepted May 4, 2009.

Address correspondence to Andrew E. Sloan, MD, FACS, University Hospital Case Medical Center, 11100 Euclid Avenue, HAN 525, Cleveland, OH 44106. E-mail: Andrew.Sloan@ubhospitals.org

Dr Sloan's work on this paper was supported in part by NIH grants

CA101954, TCGA, CA 456723, NS345654, NS 456125, the Ivy Brain Tumor Foundation, Ohio's Third Frontier Foundation, and the Neurological Institute of Case Western Reserve University School of Medicine. Dr Nock is supported in part by an NIH K-12 grant from the Case Comprehensive Cancer Center. Dr Einstein reports no significant relationship between himself and the companies/organizations whose products or services may be referenced in this article.

Abbreviations used in this paper: WBRT = whole brain radiotherapy, SRS = stereotactic radiosurgery, RTOG = Radiation Therapy Oncology Group, RPA = recursive partitioning analysis, KPS = Karnofsky performance status.

stage IV melanoma eventually develop clinically apparent brain metastasis, and autopsy series report the prevalence of brain metastasis at 55% to 75% of patients who died of melanoma.^{2,5} Risk factors associated with melanoma brain metastasis include male gender, mucosal or head and neck primaries, thick or ulcerated neoplasms, acral lentiginous or nodal lesions, and stage IV disease.⁶ Brain metastasis typically occurs relatively late in the course of melanoma — a median interval of 2.2 to 3.8 years after the diagnosis of the primary disease.^{7,9} Patients with a single lesion and an absence of extracranial metastasis who initially present with brain metastasis have a better prognosis.⁶ Current management strategies appear unsatisfactory, and brain metastasis contributes to death in nearly 95% of patients, with a median survival of less than 1 year despite treatment.^{3,6,10,11} There has been little improvement in this prognosis during the last 3 decades; thus, patients with melanoma brain metastasis are usually excluded from melanoma clinical trials.^{3,12} However, new approaches appear to offer new hope to selective patients.

Diagnosis

Most brain metastases present with headaches or other symptoms due to increased intracranial pressure, mass effect, impaired cerebrospinal fluid drainage, focal deficits (eg, weakness, numbness, imbalance, visual loss, behavioral changes related to particular brain regions), cranial nerves affected by the mass, or seizures. Because melanotic tumors frequently hemorrhage, sudden onset of symptoms, dubbed a “tumor TIA,” may also occur. Given the recognized neurotropism of melanoma, neurological symptoms in a melanoma patient should prompt diagnostic imaging studies. Asymptomatic metastases are increasingly diagnosed through increased screening due to known risk factors as well as mandatory imaging required during screening for many melanoma clinical trials. Eighty percent of brain metastases are supratentorial, while 15% are infratentorial or leptomeningeal, and 5% affect the brainstem itself. Computed tomography (CT) scans of the brain with and without contrast can detect most metastases ≥ 10 mm in the supratentorial region and most hemorrhagic lesions. However, magnetic resonance imaging (MRI) with and without gadolinium is far more sensitive, particularly for smaller lesions, lesions in the posterior fossa, and leptomeningeal disease. Melanoma metastases are typically enhancing and are frequently associated with hemorrhage and edema.

Treatment for Parenchymal Brain Metastasis

The prognosis of patients with melanoma brain metastasis has historically been considered to be significantly worse than that of other brain metastasis, with the possible exception of sarcoma. Melanoma brain metastasis most often leads to neurologic deterioration that progresses rapidly to death within 1 month without treat-

ment, which approximately doubles with corticosteroids alone.^{5,11,13,14} Chemotherapy, immunotherapy, and biochemotherapy have been effective in the treatment of melanoma brain metastasis, and treatment has usually been composed of radiotherapy, surgery, and stereotactic radiosurgery (SRS) with palliative intent.¹⁵ Treatment outcomes are difficult to generalize because of the complex interdependence of the patient’s performance status, age, and the extent of extracranial metastasis on survival. The location, size, and number of brain metastases must also be considered in treatment decisions. There is no level I evidence that specifically guides the treatment of patients with melanoma brain metastasis. However, the existing outcomes studies for patients with brain metastasis from all etiologies serves as a framework for further consideration of the studies specifically focused on melanoma brain metastasis. In the sections below, we review the level I evidence for brain metastasis from all etiologies and then focus on how this, combined with level II data in patients with melanoma brain metastasis, can guide treatment decisions.

In general, patients can usually be classified at presentation into one of three typical scenarios: patients with a single brain metastasis, those with small numbers of brain metastases (typically 2 to 4), and those with multiple brain metastases (> 4). Treatment considerations include whole brain radiotherapy (WBRT), SRS, and conventional open surgery. WBRT involves the delivery of fractionated megavoltage radiotherapy to the entire brain and meninges via two opposing lateral photon beams, allowing for the treatment of gross and microscopic tumor in the brain. Typically, this is delivered in 2- to 3-Gy daily fractions to a total dose of 30 to 40 Gy, though some centers use 4-Gy daily fractions to a total of 20 Gy for patients with poor performance status. SRS is a technique using single-fraction, high-dose megavoltage radiation directed at a discrete target identified in 3-dimensional stereotactic space. Brain SRS is delivered via collimator-modified linear accelerators using multiple arcing beams intersecting at the defined target (linear accelerator [LINAC]-based SRS) or via a Leksell Gamma Knife (Elekta Instruments, Inc, Stockholm, Sweden) using 201 fixed cobalt sources, with the target moved into the intersection of the beams (GK-SRS). Traditionally, the head position has been fixed using a stereotactic frame or bite block for most high-dose, single-fraction treatments. However, more recent LINAC devices such as the Novalis Tx (BrainLab AG, Feldkirchen, Germany) and CyberKnife System (Accuray, Inc, Sunnyvale, California) use only a mask and compensate for patient movement by using digitally reconstructed radiographs performed at various times during treatment. This allows the LINAC device to make small adjustments in the planned treatment to achieve the desired result. Outcomes for adult patients with metastatic brain tumors who present with these typical scenarios are discussed separately.

Patients With Single Brain Metastasis of Any Type

The seminal outcome studies establishing the efficacy of WBRT for brain metastasis — considered the standard of care for most cases during this time — were conducted by the Radiation Therapy Oncology Group (RTOG). A recursive partitioning analysis (RPA) of three randomized controlled RTOG trials conducted between 1979 and 1993, including more than 1,200 patients with brain metastasis treated with WBRT alone, classified patients with brain metastasis into three groups (class I, II, and III) with statistically different prognoses (Table 1).¹⁶ Class I patients, accounting for approximately 15% of all patients with brain metastasis, were less than 65 years of age, had a Karnofsky performance status (KPS) score of ≥ 70 , well-controlled primary disease, and the best median survival at 7.1 months. In contrast, RPA class III patients, who accounted for 20% of patients, had a KPS score of < 70 , uncontrolled primary disease, and a median survival of 2.3 months. Class II patients, those who did not qualify for class I or III, comprised 65% of patients and had median survival of 4.2 months. This level I evidence serves as a basis of comparison for subsequent therapeutic trials of surgery, SRS, chemotherapy, and biochemotherapy with or without WBRT.

The role of surgery for brain metastasis was somewhat controversial until the mid to late 1990s. Three randomized controlled studies compared WBRT to surgery

combined with WBRT. Patchell et al¹⁷ demonstrated significantly improved median survival (40 weeks vs 15 weeks; $P < .01$), functional independence (38 weeks vs 8 weeks; $P < .005$), and local control (80% vs 48%; $P < .02$) in 48 patients (KPS score of ≥ 70) with biopsy-proven brain metastasis treated with surgery and WBRT (36 Gy) compared with those treated with biopsy and WBRT (Table 2). For patients in the surgical group, perioperative and 30-day mortality was 4%, perioperative morbidity was 8% vs 17% in the radiation group, and 30-day morbidity was 8% vs 17% in the radiation group. Similar results for 63 patients with a KPS score of ≥ 50 were reported by Vecht et al,¹⁸ who noted that the improvement in median survival (12 months vs 7 months) applied only to patients with stable extracranial disease. These two trials have served as level I evidence supporting the role of surgery in patients with single brain metastasis, particularly for RPA class I patients. A third randomized controlled study published later included 84 patients and failed to confirm the benefit of surgery, but consensus opinion had already established surgical resection for patients in RPA I as the treatment of choice.¹⁹ Patchell et al²⁰ then established the role of postoperative WBRT after surgical resection in a randomized controlled trial of 95 patients with single lesions (Table 3). WBRT increased local control (82% vs 30%; $P < .001$) and brain control (86% vs 63%; $P < .01$) and decreased neurologic death (14% vs 44%; $P = .003$,

presumable as a result of neutralizing microscopic disease, but this approach did not alter survival. Noordijk et al²¹ published similar conclusions from their own randomized controlled trial. A recent randomized controlled trial of surgery and WBRT vs SRS for RPA class I patients with single brain metastasis demonstrated no difference in survival between groups.²² The patients treated with SRS alone had a slight increase in distal recurrence ($P = .04$) that was lost after adjustment for salvage SRS. Radiosurgery was associated with shorter hospital stay, lower corticosteroid requirements, few toxicities, and improved scores for function and quality of life between 6 weeks and 6 months postoperatively.²²

Table 1. — Recursive Partitioning Analysis for Brain Metastases From Retrospective Studies of 1,176 Patients in RTOG Clinical Trials

	Class I	Class II	Class III
KPS score	≥ 70	≥ 70	< 70
Primary status	Controlled	Uncontrolled	Uncontrolled
Age (yrs)	< 65	> 65	Any
Extracranial disease	Brain only	Brain + other sites	Brain + other sites
Incidence (%)	15	65	20
Median survival (mos)	7.1	4.2	2.3

Data from 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.* 1997;37(4):745-751.

Table 2. — Randomized Controlled Trial of Whole Brain Radiotherapy (WBRT) With or Without Surgery for a Single Lesion

	WBRT	Surgery + WBRT
No. of patients	23	25
Local control (%)	48	80 ($P < .02$)
Median survival (wks)	15	40 ($P < .01$)
Neurologic survival (wks)	26	62 ($P < .0009$)
Functional independence, KPS score > 70 (wks)	8	38 ($P < .005$)
Time to progression (wks)	21	59 ($P < .001$)
Morbidity (%)	17	8
30-day mortality (%)	4	4

Data from 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.* 1990;322(8):494-500.

Patients With Oligometastatic Brain Tumors (2 to 4)

Several phase III RTOG studies in the early to middle 1990s that increased the dose or the fractionation scheme in patients with 1 or more brain metastases demonstrated no survival advantage compared with a conventional regimen of 30 Gy in 10 fractions.²³ The role of surgery for multiple brain metastases is somewhat controversial as no randomized controlled studies have been performed. However, a retrospective, single-institutional cohort study

demonstrated that patients with a KPS score of ≥ 70 who underwent imaging-complete resection of 2 to 4 brain metastases had the same median survival (14 months) as patients undergoing imaging-complete resection of a single lesion, though patients who had some but not all lesions resected had a median survival of 6 months and did not appear to have any benefit.²⁴

Level I evidence supports the use of SRS for the treatment of patients in this subgroup with low morbidity and low mortality. The results of RTOG 9508 demonstrated that adding SRS boost to WBRT for patients with 1 to 3 brain metastases improved survival in patients in RPA class I (11.6 vs 9.6) (Table 4).²⁵ While 30% of patients in both groups died of progressive brain metastasis, SRS boost improved local control as well as KPS at 6 months and decreased corticosteroid use.²⁵ SRS also improved survival in three subgroups of patients, including those under age 50 years and those in RPA class I. A smaller randomized controlled trial demonstrated that the addition of SRS to WBRT improved local control and overall survival.²⁶ A randomized controlled study of SRS with and without WBRT in 132 patient with 1 to 4 brain metastases less than 3 cm in diameter demonstrated that the addition of WBRT to SRS improved local control (53.2% vs 23.6%) without significant differences in 1-year survival, neurological function, cause of death, and toxicity (Table 5).²⁷ There is no class I evidence comparing

Table 5. — Randomized Controlled Trial of Stereotactic Radiosurgery (SRS) With or Without Whole Brain Radiotherapy (WBRT)

	SRS	SRS + WBRT
No. of patients	67	65
Median survival (mos)	8	7.5
1-year survival (%)	28.4	38.5
Local control (%)	23.6	53.2 ($P < .001$)
Needing salvage radiation therapy (%)	43.3	15.4
Neurologic death (%)	19.3	22.8

Data from Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295(21):2483-2491.

surgery with SRS for the treatment of such patients, though class II studies are available for patients with oligometastatic brain lesions and are discussed in the following section.

In summary, level I evidence supports the efficacy of surgery and SRS with WBRT in patients with a KPS score of ≥ 70 with oligometastatic brain disease, and outcomes appear to be similar for both treatments at selected institutions. Yet, clinicians must use clinical judgment in making treatment decisions weighing the pros and cons of these approaches. The advantages of surgery compared with SRS are the ability to confirm the diagnosis, eliminate mass effect and, in some cases, improve tolerance to adjuvant therapy. It is preferentially used for large (> 3 cm) superficial tumors, for infratentorial lesions, or in combination with SRS. In contrast, SRS has minimal perioperative morbidity but is more effective on small masses (≤ 3.5 cm) with minimal mass effect or edema. It can be used in patients who are not surgical candidates due to medical comorbidity or advanced systemic disease and is easily applied to multiple brain metastases. In many instances, surgery and SRS are combined with or without WBRT.

Though a few patients with melanoma were included in the randomized controlled trials discussed in the previous section, the specific prognosis for the melanoma patients cannot be determined from the current data. Thus, reviewing the data from retrospective studies focused exclusively on melanoma brain metastasis is worthwhile. Few studies have limited analyses to patients receiving WBRT alone for treatment of single melanoma brain metastasis; thus, data from those with 1 to 4 metastatic lesions will be considered. In their study of 61 melanoma patients treated with WBRT alone in two RTOG trials, Carella et al²⁸ found that melanoma patients had median

Table 3. — Randomized Controlled Trial of Surgery With or Without Whole Brain Radiotherapy (WBRT) for Single Brain Metastasis

	Surgery	Surgery + WBRT
No. of patients	46	49
Local control (%)	30	82 ($P < .001$)
Brain control (%)	63	86 ($P < .001$)
Time to local recurrence (wks)	27	52 ($P < .001$)
Neurologic death (%)	44	14 ($P < .003$)
Functional independence, KPS score > 70 (wks)	35	37
Median survival (wks)	43	48

Data from Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA*. 1998;280(17):1485-1489.

Table 4. — Randomized Controlled Trial of Whole Brain Radiotherapy (WBRT) With or Without Stereotactic Radiosurgery (SRS): RTOG 9508

Survival Analysis	WBRT + SRS (mos)	WBRT (mos)	P Value
Overall	6.5	5.7	.13
Single brain metastasis	6.5	4.9	.04
1 to 3 brain metastases, patient age < 50 yrs	9.9	8.3	.04
1 to 3 brain metastases, non-small cell lung cancer	5.9	3.9	.05
1 to 3 brain metastases, RPA class I	11.6	9.6	.05

Data from Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomized trial. *Lancet*. 2004;363(9422):1665-1672.

survivals similar to the nonmelanoma patients of 10 to 14 weeks (~ 3.5 months). The largest single report of melanoma patients treated with WBRT alone found a median survival of 4 months for 180 patients treated with WBRT alone, similar to the RTOG results, though stratification by RPA class was not reported.⁶ In the second largest study of 102 patients with melanoma treated by WBRT alone (20 Gy in 5 fractions), the overall median survival was 51 days (~ 1.7 months). Stratification by RPA revealed that median survival increased to 151 days (~ 5 months) for class I patients, by 71 days (2.4 months) for class II patients, and by 21 days (0.7 month) for class III patients.²⁹ The authors concluded that this study validated the use of RPA classification for melanoma patients but suggested that the prognosis for patients with melanoma was somewhat worse than for most other tumors and supported consideration of WBRT for patients in RPA class I or II but not class III.²⁹

Similarly, randomized trials to assess the role of post-operative WBRT have not been performed exclusively in melanoma patients. However, in one of the largest reported retrospective analyses of 636 melanoma patients with brain metastasis, 158 patients treated with both surgery and WBRT had a median survival of 8.9 months compared with 3.4 months for the 236 patients treated with WBRT alone ($P < .01$), echoing the benefit of resection in addition to WBRT for melanoma patients.¹² Indeed, surgery conveyed most of the treatment benefit in multivariate analysis ($P < .0001$). The median survival of 47 patients treated with surgery alone was 8.7 months, while WBRT alone yielded a survival of 3.4 months in 236 patients, and supportive care yielded 2.1 months in 210 patients.¹² Similarly, Sampson et al⁶ noted a median survival of approximately 8.9 months in 87 patients with melanoma brain metastasis treated surgically but did not detect any survival advantage conveyed by WBRT treatment compared to 52 patients treated with surgery alone. Buchsbaum et al³⁰ employed the RPA classification to assess the benefit of adding local therapy (surgery or SRS) to WBRT in a retrospective series of 74 patients with melanoma brain metastasis. This study demonstrated median survivals of 10.5 months, 5.9 months, and 1.8 months for RPA I, II, and III, respectively, validating the RPA classification for melanoma brain metastasis. Moreover, WBRT with local therapy resulted in improved median survivals of 8.8 months vs 4.8 months with local therapy alone and 2.3 to 3.6 months with WBRT alone ($P < .01$), suggesting that, unlike other series,³¹⁻³³ WBRT improved not only local control but also survival.³⁰

Several studies have addressed the role of SRS with and without WBRT in patients with melanoma brain metastasis. While some retrospective studies have demonstrated that melanoma metastasis is a negative prognostic indicator,³⁴ others have demonstrated clinical results comparable to other types of brain metastasis,

with a median survival of 7 to 8 months, which is comparable to nonmelanoma brain metastasis. The local control rate was 85% to 97% with or without WBRT, respectively.^{35,36} One large study of 754 metastases in 244 patients demonstrated that, while RPA class and WBRT correlated with survival in univariate analysis, the most important factors in multivariate analysis were the absence of extracranial disease, multiple brain metastases, and a posterior fossa lesion, while large volume and the presence of intratumor hemorrhage were associated with decreased local control.³³ Most studies concluded that adding WBRT to SRS did not convey survival benefit in patients with melanoma brain metastasis, though two studies suggested that it did improve local control.³¹⁻³⁵ A more recent prospective phase II trial of SRS in 44 patients with 156 metastatic tumors and 1-year follow-up demonstrated a median survival of 11.1 months and the failure of WBRT to improve survival.³⁷ The retrospective nature of these studies makes it difficult to assess the possible role of selection bias in these results. However, a recent Eastern Cooperative Oncology Group (ECOG) phase II trial of SRS only in 31 patients with radioresistant lesions (45% of which were melanoma) demonstrated a median survival of 8.3 months with local failure rates of 26% and 48% at 3 and 6 months, respectively, and suggested that "routine avoidance of WBRT should be approached judiciously."³⁸

An early randomized controlled trial of SRS with and without WBRT done at the M. D. Anderson Cancer Center was discontinued due to poor accrual. Currently, two randomized controlled trials of SRS with and without WBRT led by the American College of Surgeons Oncology Group (ACOSOG) and the North Central Clinical Trials group (NCCTG) are underway.

Patients With Multiple Brain Metastases (> 5)

No level I evidence defines optimal treatment of patients with more than 5 brain metastases. WBRT remains the standard of care in most patients with life expectancy greater than 3 months based on systemic disease. Level II evidence suggests that SRS may be effective in up to 10 brain metastases if they are smaller than 3 cm and are not associated with mass effect or edema.³⁴ However, there are no prospective studies of patients with multiple melanoma brain metastases treated with a modality other than WBRT, and prognosis has remained poor in this group of patients.³⁹

Chemotherapy

Most studies of malignant melanoma have excluded patients with central nervous system (CNS) involvement. Systemic chemotherapy has shown little benefit in the treatment of stage IV melanoma, including those with brain metastasis. In general, chemotherapy for melanoma brain metastasis is usually reserved for salvage therapy. The failure of chemotherapy is thought to

be due to the inability of most agents to cross the blood-brain barrier, which is maintained by endothelial tight junctions and P-glycoprotein-mediated efflux of chemotherapeutic agents out of the brain. However, newer agents have been developed that may offer benefit as single agents, combination chemotherapy, or concurrent chemoradiotherapy.

Dacarbazine (DTIC) was the first chemotherapy approved by the FDA for treatment of metastatic melanoma. Single-agent DTIC has remained the standard of care for 3 decades, with response rates of 8% to 20% and mean duration of response of approximately 4 to 6 months. However, there have been no randomized controlled studies comparing survival in patients treated with DTIC vs best supportive care.⁴⁰ Thus, there is no level I evidence to support this regimen. Various combination chemotherapy regimens have been investigated, but none has shown superiority over single-agent DTIC.

Fotemustine is a chloroethylnitrosourea, which readily penetrates the blood-brain barrier. In a large European phase II trial, fotemustine demonstrated objective response rates of 24% with significant activity in patients with brain metastasis.⁴¹ Of the 153 assessable patients, more than one-quarter had brain metastasis; 2 complete responses and 9 partial responses were seen.⁴² This led to a phase III trial comparing fotemustine to DTIC in patients with and without brain metastasis.⁴³ The trial was fraught with problems, including lower than expected DTIC responses when compared to previous trials as well as a less than favorable drug administration schedule for DTIC. Overall response was better in patients treated with fotemustine (15.2% vs 6.8%) with the intent to treat the population ($P = .043$). However, cerebral responses were disappointing in the fotemustine arm (5.9% vs 0%) compared with previously published phase II data, and there was no decrease in the number of brain relapses, though time to CNS progression increased.^{41,42} Lomustine, another alkylating agent, was assessed in combination with temozolomide, but no objective responses were observed.⁴⁴

Fotemustine has been studied in conjunction with radiotherapy. A French phase III study assessed fotemustine alone vs fotemustine plus WBRT. Of the 76 patients who were randomized, 39 received fotemustine alone and 37 received the combination therapy. Despite worse prognostic factors in the group receiving fotemustine alone, no significant difference was seen in cerebral response, overall response, and overall survival.⁴⁵ Fotemustine plus whole brain radiation delayed cerebral progression, but no improvement in response rate or survival was observed.

Temozolomide, which has the capacity to cross the blood-brain barrier, is an oral analog of DTIC. In the phase III setting, temozolomide was found to be equivalent to DTIC concerning response rate and survival with better quality of life, but patients with brain metas-

tasis were excluded.⁴⁶ This led to four phase II, multicenter, open-label studies of patients with metastatic melanoma, including those with brain metastasis who did not require emergent radiation treatment. Two studies failed to observe any benefit, while one appeared to demonstrate that temozolomide might prevent CNS metastasis. Another trial indicated a response rate of 7% and stable disease in 29% of newly diagnosed patients, while 24% of patients with recurrent disease were stable or responsive to regimen.⁴⁷⁻⁵⁰ Median survival in previously untreated patient who did not receive WBRT or SRS prior to treatment was 3.5 months, while survival in patients with progressive disease was 2.2 months.⁵⁰

Several studies have looked at combining temozolomide with radiation therapy. The Cytokine Working Group evaluated concurrent therapy in a phase II trial of 31 patients, demonstrating 1 complete response and 2 partial responses. Median progression-free survival was 2 months, with a median survival of 6 months.⁵¹ The authors concluded that results were below expectations and, though temozolomide was well tolerated with concurrent radiotherapy, the combination had limited efficacy. A second phase II study by Hofmann et al⁵² observed 1 complete and 2 partial responses in 34 patients for a response rate of 8.8%, but median survival was 7 months in those receiving WBRT and 8 months in patients treated with SRS.

The angiogenic nature of melanoma has prompted investigators to assess the potential use of thalidomide, an oral antiangiogenic agent used in a variety of malignancies for additive antitumor activity in addition to WBRT.⁵³ Response was observed in 12% of the 26 patients with progressive brain metastasis.⁵⁴ This led to a multicenter phase II study by the Cancer and Leukemia Group B (CALGB) to assess patients with advanced melanoma with brain metastasis.⁵⁴ However, the trial was stopped early due to concerns regarding safety and efficacy. No objective responses were seen. Seven of 16 patients withdrew due to progressive disease, and another 7 were removed due to adverse events during the first cycle, including death of 1 patient and pulmonary emboli in 3 others.

Despite recent advances with novel agents that actively cross the blood-brain barrier, CNS responses in advanced melanoma are infrequent. It is imperative that newer systemic agents are developed and tested in the setting of clinical trials to successfully treat such an aggressive and lethal disease as melanoma with its strong predilection for CNS metastasis.

Immunotherapy

Melanoma is one of the more immunogenic solid tumors, and numerous trials of immunotherapy for metastatic melanoma have been performed, though response remains infrequent.⁵⁵ Traditionally, the presence of brain

metastasis was an exclusionary criterion for immunotherapy for melanoma.⁵⁶ However, rare responses to brain metastasis have been observed in response to both biological response modifiers (BRMs) and cellular immunotherapy. Savas et al⁵⁷ noted a near complete response of brain metastasis unresponsive to radiation therapy after treatment with a regimen consisting of interleukin-2 (IL-2), interferon (IFN), and 5-fluorouracil; the patient returned to work for 18 months. Similarly, Majer et al⁵⁵ report a series of 70 patients with or without brain metastasis treated with DTIC or temozolomide in combination with BRMs IL-2 (continuous intravenous infusion) and IFN- α 2B. They found that patients with brain metastasis, all of whom were also treated with SRS \geq 28 days prior to treatment with a BRM, appeared to benefit from treatment, with a median survival of 15.8 months in patients with brain metastasis vs 11.1 months in those without CNS involvement. Investigators from the National Cancer Institute reported that a patient with brain metastasis refractory to IL-2 and chemotherapy responded to therapeutic lymphodepletion followed by infusion with autologous MART-reactive tumor infiltrating lymphocytes (TILs) and high-dose IL-2.⁵⁸ However, there are also cases of patients with metastatic melanoma and renal cell carcinoma whose systemic disease was responsive to tumor vaccines and cytotoxic chemotherapy but who relapsed with an antigen-loss variant in the brain in the absence of systemic disease.^{59,60} Yet, the recent demonstration that aggressive immunotherapeutic approaches induced immune responses in the eye — another immunologically privileged site — suggests that immunotherapy for melanoma brain metastasis may be feasible, though not without risk. Additional studies have been proposed.⁶¹

Leptomeningeal Brain Metastasis

The prognosis for patients with neoplastic meningitis (NM) from melanoma and other primary solid tumors remains poor. NM occurs in nearly one-fourth of all melanoma patients.⁶² A retrospective study of NM in two well-matched cohorts found that patients with NM-related encephalopathy had a median survival of 2.5 months, while nonencephalopathic patients had median survival of 6 months ($P < .001$).⁶³ Generally, patients with encephalopathy have a poor KPS score and are treated with supportive care only. However, melanoma patients with NM appear to do poorly even when no encephalopathy is present. WBRT yields a median survival of only 10 weeks, and results of intrathecal treatment with etoposide, IFN- α , and intrathecal sustained-release cytarabine (DepoCyt) have been poor.^{62,64-66}

Conclusions

Brain metastasis is a common and formidable challenge in patients with malignant melanoma. There have been no randomized controlled trials exclusively in patients

with melanoma brain metastasis, but care can be guided by application of the level I evidence for the treatment of brain metastasis in general and phase II studies focusing specifically on melanoma brain metastasis. For patients with a KPS score \geq 70 and stable extracranial disease (ie, RPA I-II), therapeutic intervention is usually indicated. Surgery or SRS remains the standard of care for patients with single and/or small brain metastasis without mass effect. Surgery continues to be the standard of care in patients suffering from mass effect. SRS is most likely the treatment of choice for patients with 2 to 5 brain metastases with similar high levels of function, as long as mass effect is not problematic. While WBRT appears to improve local control in patients with brain metastasis from most other primary sites, the role of WBRT in patients with melanoma remains controversial. However, palliative WBRT continues to be the treatment of choice for poorly functioning patients as well as those with multiple brain metastases or leptomeningeal symptoms. Several chemotherapeutic agents have been tested alone and in combination with radiotherapy in patients with melanoma brain metastasis, though none has been shown to be significantly better than DTIC. Promising new agents and approaches are needed and will hopefully be identified in the near future.

References

1. Wen PY, Black PM, Loeffler JS. Treatment of metastatic brain cancer. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
2. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol*. 2004;22(14):2865-2872.
3. Budman DR, Camacho E, Wittes RE. The current causes of death in patients with malignant melanoma. *Eur J Cancer*. 1978;14(4):327-330.
4. Bullard DE, Cox EB, Seigler HF. Central nervous system metastases in malignant melanoma. *Neurosurgery*. 1981;8(1):26-30.
5. Amer MH, Al-Sarraf M, Baker LH, et al. Malignant melanoma and central nervous system metastases: incidence, diagnosis, treatment and survival. *Cancer*. 1978;42(2):660-668.
6. Sampson JH, Carter JH Jr, Friedman AH, et al. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. *J Neurosurg*. 1998;88(1):11-20.
7. Choi KN, Withers HR, Rotman M. Metastatic melanoma in brain: rapid treatment or large dose fractions. *Cancer*. 1985;56(1):10-15.
8. Retsas S, Gershuny AR. Central nervous system involvement in malignant melanoma. *Cancer*. 1988;61(9):1926-1934.
9. Salvati M, Cervoni L, Caruso R, et al. Solitary cerebral metastasis from melanoma: value of the 'en block' resection. *Clin Neurol Neurosurg*. 1996;98(1):12-14.
10. Gogas HJ, Kirkwood JM, Sondak VK. Chemotherapy for metastatic melanoma: time for a change? *Cancer*. 2007;109(3):455-464.
11. Barth A, Wanek LA, Morton DL. Prognostic factors in 1,521 melanoma patients with distant metastases. *J Am Coll Surg*. 1995;181(3):193-201.
12. Fife KM, Colman MH, Stevens GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol*. 2004;22(7):1293-1300.
13. Ewend MG, Carey LA, Brem H. Treatment of melanoma metastases in the brain. *Semin Surg Oncol*. 1996;12(6):429-435.
14. Stevens G, Firth I, Coates A. Cerebral metastases from malignant melanoma. *Radiother Oncol*. 1992;23(3):185-191.
15. Kanner A, Barnett GH. Management of brain metastasis in malignant melanoma patients. In: Sawaya R, ed. *Treatment of Metastatic Brain Tumors*. Oxford, UK: Futura Blackwell; 2004.
16. 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*. 1997;37(4):745-751.

17. 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.* 1990; 322(8):494-500.
18. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol.* 1993;33(6):583-590.
19. Mintz AH, Kestle J, Rathbone MP, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer.* 1996;78(7):1470-1476.
20. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA.* 1998;280(17):1485-1489.
21. 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.* 1994;29(4):711-717.
22. Muacevic A, Wowra B, Siefert A, et al. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. *J Neurooncol.* 2008;87(3):299-307. Epub 2007 Dec 22.
23. Sause WT, Scott C, Krisch R, et al. Phase I/II trial of accelerated fractionation in brain metastases RTOG 85-28. *Int J Radiat Oncol Biol Phys.* 1993;26(4):653-657.
24. Bindal RK, Sawaya R, Leavens ME, et al. Surgical treatment of multiple brain metastases. *J Neurosurg.* 1993;79(2):210-216.
25. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet.* 2004;363(9422):1665-1672.
26. Kondziolka D, Patel A, Lunsford LD, et al. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys.* 1999;45(2):427-434.
27. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA.* 2006; 295(21):2483-2491.
28. Carella RJ, Gelber R, Hendrickson F, et al. Value of radiation therapy in the management of patients with cerebral metastases from malignant melanoma: Radiation Therapy Oncology Group Brain Metastases Study I and II. *Cancer.* 1980;45(4):679-683.
29. Morris SL, Low SH, A'Hern RP, et al. A prognostic index that predicts outcome following palliative whole brain radiotherapy for patients with metastatic malignant melanoma. *Br J Cancer.* 2004;91(5):829-833.
30. Buchsbaum JC, Suh JH, Lee SY, et al. Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. *Cancer.* 2002;94(8):2265-2272.
31. Brown PD, Brown CA, Pollock BE, et al. Stereotactic radiosurgery for patients with "radioresistant" brain metastases. *Neurosurgery.* 2002;51(3): 656-665; discussion 665-667.
32. Selek U, Chang EL, Hassenbusch SJ 3rd, et al. Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. *Int J Radiat Oncol Biol Phys.* 2004;59(4):1097-1106.
33. Mathieu D, Kondziolka D, Cooper PB, et al. Gamma knife radiosurgery for malignant melanoma brain metastases. *Clin Neurosurg.* 2007; 54:241-247.
34. DiLuna ML, King JT Jr, Knisely JP, et al. Prognostic factors for survival after stereotactic radiosurgery vary with the number of cerebral metastases. *Cancer.* 2007;109(1):135-145.
35. Mori Y, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. *Int J Radiat Oncol Biol Phys.* 1998;42(3):581-589.
36. Lavine SD, Petrovich Z, Cohen-Gadol AA, et al. Gamma knife radiosurgery for metastatic melanoma: an analysis of survival, outcome, and complications. *Neurosurgery.* 1999;44(1):59-64; discussion 64-66.
37. Samlowski WE, Watson GA, Wang M, et al. Multimodality treatment of melanoma brain metastases incorporating stereotactic radiosurgery (SRS). *Cancer.* 2007;109(9):1855-1862.
38. Manon R, O'Neill A, Knisely J, et al. Phase II trial of radiosurgery for one to three newly diagnosed brain metastases from renal cell carcinoma, melanoma, and sarcoma: an Eastern Cooperative Oncology Group study (E 6397). *J Clin Oncol.* 2005;23(34):8870-8876.
39. Yamamoto M, Ide M, Nishio S, et al. Gamma Knife radiosurgery for numerous brain metastases: is this a safe treatment? *Int J Radiat Oncol Biol Phys.* 2002;53(5):1279-1283.
40. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. *N Engl J Med.* 2004;351(10):998-1012. Erratum in: *N Engl J Med.* 2004;351(23):2461.
41. Jacquillat C, Khayat D, Banzet P, et al. Final report of the French multicenter phase II study of the nitrosourea fotemustine in 153 evaluable patients with disseminated malignant melanoma including patients with cerebral metastases. *Cancer.* 1990;66(9):1873-1878.
42. Jacquillat C, Khayat D, Banzet P, et al. Chemotherapy by fotemustine in cerebral metastases of disseminated malignant melanoma. *Cancer Chemother Pharmacol.* 1990;25(4):263-266.
43. Avril MF, Aamdal S, Grob JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. *J Clin Oncol.* 2004;22(6):1118-1125.
44. Larkin JM, Hughes SA, Beirne DA, et al. A phase I/II study of lomustine and temozolomide in patients with cerebral metastases from malignant melanoma. *Br J Cancer.* 2007;96(1):44-48. Epub 2006 Dec 5.
45. Mornex F, Thomas L, Mohr P, et al. A prospective randomized multicenter phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma. *Melanoma Res.* 2003;13(1):97-103.
46. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol.* 2000;18(1):158-166. Erratum in: *J Clin Oncol.* 2000;18(11):2351.
47. Danson S, Lorigan P, Arance A, et al. Randomized phase II study of temozolomide given every 8 hours or daily with either interferon alfa-2b or thalidomide in metastatic malignant melanoma. *J Clin Oncol.* 2003;21(13): 2551-2557.
48. Richtig E, Soyer HP, Posch M, et al. Prospective, randomized, multicenter, double-blind placebo-controlled trial comparing adjuvant interferon alfa and isotretinoin with interferon alfa alone in stage IIA and IIB melanoma: European Cooperative Adjuvant Melanoma Treatment Study Group. *J Clin Oncol.* 2005;23(34):8655-8663. Epub 2005 Oct 31.
49. Bafaloukos D, Gogas H, Georgoulis V, et al. Temozolomide in combination with docetaxel in patients with advanced melanoma: a phase II study of the Hellenic Cooperative Oncology Group. *J Clin Oncol.* 2002;20(2): 420-425.
50. Agarwala SS, Kirkwood JM, Gore M, et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *J Clin Oncol.* 2004;22(11):2101-2107.
51. Margolin K, Atkins B, Thompson A, et al. Temozolomide and whole brain irradiation in melanoma metastatic to the brain: a phase II trial of the Cytokine Working Group. *J Cancer Res Clin Oncol.* 2002;128(4):214-218. Epub 2002 Mar 12.
52. Hofmann M, Kiecker F, Wurm R, et al. Temozolomide with or without radiotherapy in melanoma with unresectable brain metastases. *J Neurooncol.* 2006;76(1):59-64.
53. Hwu WJ, Lis E, Menell JH, et al. Temozolomide plus thalidomide in patients with brain metastases from melanoma: a phase II study. *Cancer.* 2005;103(12):2590-2597.
54. Krown SE, Niedzwiecki D, Hwu WJ, et al. Phase II study of temozolomide and thalidomide in patients with metastatic melanoma in the brain: high rate of thromboembolic events (CALGB 500102). *Cancer.* 2006;107(8): 1883-1890.
55. Majer M, Jensen RL, Shrieve DC, et al. Biochemotherapy of metastatic melanoma in patients with or without recently diagnosed brain metastases. *Cancer.* 2007;110(6):1329-1337.
56. Eton O, Talpaz M, Lee KH, et al. Phase II trial of recombinant human interleukin-2 and interferon-alpha-2a: implications for the treatment of patients with metastatic melanoma. *Cancer.* 1996;77(5):893-899.
57. Savas B, Arslan G, Gelen T, et al. Multidrug resistant malignant melanoma with intracranial metastasis responding to immunotherapy. *Anti-cancer Res.* 1999;19(5C):4413-4420.
58. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol.* 2005;23(10):2346-2357.
59. Hurst R, White DE, Heiss J, et al. Brain metastasis after immunotherapy in patients with metastatic melanoma or renal cell cancer: is craniotomy indicated? *J Immunother.* 1999;22(4):356-362.
60. Voelter V, Pica A, Laurent J, et al. An unusual case of metastatic melanoma sensitive to chemotherapy and immunotherapy, with late immune escape in the brain. *Cancer Immun.* 2008;8:6.
61. Palmer DC, Chan CC, Gattinoni L, et al. Effective tumor treatment targeting a melanoma/melanocyte-associated antigen triggers severe ocular autoimmunity. *Proc Natl Acad Sci U S A.* 2008;105(23):8061-8066. Epub 2008 Jun 3.
62. Groves MD. Leptomeningeal metastasis: still a challenge. *ASCO Educational Book.* 2008:80-87.
63. Chamberlain MC, Tsao-Wei D, Groshen S. Neoplastic meningitis-related encephalopathy. *J Neurooncol.* 2005;72(2):185-189.
64. Chamberlain MC, Tsao-Wei DD, Groshen S. Phase II trial of intracerebrospinal fluid etoposide in the treatment of neoplastic meningitis. *Cancer.* 2006;106(9):2021-2027.
65. Chamberlain MC. A phase II trial of intra-cerebrospinal fluid alpha interferon in the treatment of neoplastic meningitis. *Cancer.* 2002;94(10): 2675-2680.
66. Glantz MJ, Jaeckle KA, Chamberlain MC, et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin Cancer Res.* 1999;5(11):3394-3402.