

# Treatment of Brain Metastases

Teri Nguyen, MD, and Lisa M. DeAngelis, MD

**B**rain metastases are a dreaded yet common complication of cancer. Approximately 20% of cancer patients will have an intracranial metastasis at autopsy, including brain, dural, and leptomeningeal lesions, with brain metastases accounting for 75% of these lesions [1]. The most common primary cancers responsible for brain metastases generally correlate with the distribution of neoplasms in the population. Lung and breast carcinomas together account for about 60% of all brain metastases (Table 1) [2–10]. Other cancers with a predilection for seeding the central nervous system (CNS) include melanoma, colon, and renal carcinoma. Some cancers, such as prostate carcinoma, rarely involve the brain despite widespread systemic metastasis. About 5% of brain metastases arise from an unknown primary, even after a comprehensive systemic evaluation was conducted.

The most common presenting clinical features are cognitive impairment, headache, hemiparesis, seizures, ataxia, and visual changes (Table 2) [11–13]. The diagnosis is best established by magnetic resonance imaging (MRI) or, alternatively, computed tomography in patients unable to have an MRI scan (eg, patients with an implanted pacemaker). The identification on neuroimaging of an enhancing lesion, commonly at the gray-white matter junction with surrounding edema, in a patient with known cancer usually suffices to establish the diagnosis of brain metastasis (Figure 1). Tissue confirmation is necessary in patients without a prior cancer, in those whose history of cancer is remote, and in those for whom clinical or neuroimaging features may suggest an alternative diagnosis, such as a primary brain tumor.

Manuscript received May 21, 2004; accepted May 26, 2004.

Correspondence to: Lisa M. DeAngelis, MD, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; telephone: (212) 639-7123; fax: (212) 717-3296; e-mail: deangell@mskcc.org

J Support Oncol 2004;2:405–416 © 2004 Elsevier Inc. All rights reserved.

**Abstract** Brain metastases are a common complication of cancer, found in approximately 20% of patients at autopsy. The diagnosis is usually established by neuroimaging and carries a poor overall prognosis. Supportive therapies, such as corticosteroids, anticonvulsants, and anticoagulants, are necessary for most patients to address the common medical complications that often accompany brain metastases. These treatments often ameliorate symptoms and signs and improve neurologic function, but they require careful management to minimize their common toxicities. Definitive antitumor treatment may include whole-brain radiotherapy, surgery, stereotactic radiosurgery, and chemotherapy. A multimodal approach can yield prolonged survival of a year or more in some patients, particularly those with limited intracranial disease, high performance status, limited systemic cancer burden, young age, and certain tumor pathologies. However, even patients with poor prognostic factors can have some relief of neurologic symptoms and signs with the institution of therapy. Patients with recurrent brain metastases can also benefit from additional treatment, including all the modalities available at diagnosis.

A comprehensive approach to managing a patient with brain metastases includes therapies that (1) reduce mass effect and increased intracranial pressure; (2) provide treatment for medical complications, such as seizures, venous thromboses, and side effects from medication; (3) offer definitive treatments that prolong survival and quality of life; and (4) are considered in tandem with the patient's underlying systemic disease and end-of-life directives. Therapies are divided into two main categories: supportive and definitive.

## Supportive Management

### CORTICOSTEROIDS

Corticosteroids play an important role in the management of brain metastases and alone can extend median survival from 1 to 2 months. They are usually the first therapy administered to every patient with brain metastases. Their exact mechanism of action is unknown, but they are believed to stabilize the leaky blood-brain barrier within and around the metastatic lesion. This stabiliza-

Dr. Nguyen is Chief Resident, Department of Neurology, Weill Medical College of Cornell University, New York, New York.

Dr. DeAngelis is Chairman, Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, New York.

**Table 1****Incidence of Brain Metastases by Primary Tumor**

LOCATION OF PRIMARY TUMOR	BAKER <sup>2</sup> (n = 114)	GLOBUS AND MELTZER <sup>3</sup> (n = 41)	TOM <sup>4</sup> (n = 82)	CHASON ET AL <sup>5</sup> (n = 200)	HUNTER AND REWCASTLE <sup>6</sup> (n = 393)	POSNER AND CHERNIK <sup>7</sup> (n = 572)	ZIMM ET AL <sup>8</sup> (n = 191)	LAGERWAARD ET AL <sup>9</sup> (n = 1,291)	NUSSBAUM ET AL <sup>10</sup> (n = 729)
Lung	21%	46%	22%	61%	34%	18%	64%	56%	39%
Breast	21%	2%	16%	16%	19%	17%	14%	16%	17%
Colorectal	7%	12%	11%	4%	6%	2%	3%		
Melanoma	8%	7%	9%	5%	6%	16%	4%		11%
Renal	8%	2%	1%	4%	4%	2%	2%	4%	6%
Thyroid	1%	10%	1%	<1%	2%				
Leukemia						12%			
Lymphoma						10%			
Unknown	4%	2%	18%	1%	4%		8%	8%	5%

**Brain Metastases****Table 2****Presenting Clinical Features in 1,013 Patients With Brain Metastases**

SIGNS AND SYMPTOMS	PERCENTAGE WITH FEATURE
Cognitive or mental status change	34%
Headache	31%
Weakness	24%
Seizures	19%
Ataxia	11%
Visual changes	5%
Other	4%
Nausea or vomiting	4%
Sensory change	2%
Papilledema	0.5%
None	9%

Adapted from Pirzkall et al<sup>11</sup>, Alexander et al<sup>12</sup>, and Posner<sup>13</sup>

tion reduces the surrounding vasogenic edema that increases local mass effect and contributes to increased intracranial pressure. Treatment of edema reduces mass effect and can reverse global and focal neurologic deficits.

Dexamethasone is the corticosteroid of choice because of its minimal mineralocorticoid effects. It is usually given in a 10–24 mg bolus at diagnosis in patients presenting with significant neurologic symptoms and signs. The same dose is given in divided doses 2–4 times a day as maintenance therapy. Corticosteroids can improve neurologic symptoms within hours of administration, although it may take 24–48 hours before their maximum effect becomes apparent. Patients with brain metastases diagnosed incidentally by staging MRI or who are asymptomatic and have minimal edema surrounding their brain metastases do not require steroids.

The side effects of chronic steroid use are myriad and include diabetes mellitus, immunosuppression, psychosis, and insomnia (Table 3). Steroid myopathy is a common and early complication that may be confused with progression of CNS disease, often triggering an increase in dosage, thus exacerbating the problem. An easy way to assess for steroid myopathy is to look for neck flexor weakness, which does not occur as a consequence of brain metastases. Prophylaxis for *Pneumocystis carinii* pneumonia and blood glucose monitoring should be initiated in tandem with long-term steroid therapy. Given the frequency of systemic complications from steroid use, the physician should titrate to the lowest effective dose that controls neurologic symptoms. Most patients can reduce or taper their steroid dose once definitive therapy has begun. However, in patients with progressive disease, attempts to taper steroids can result in rebound cerebral edema and worsening of neurologic deficits.

**ANTICONVULSANTS**

Seizures are a common manifestation of brain metastases, affecting about 20% of patients at presentation. Patients who have had seizures require anticonvulsant medications. Commonly used agents such as phenytoin, carbamazepine, oxcarbazepine (Trileptal), and phenobarbital induce cytochrome P450 and can alter the metabolism of other pharmaceuticals, including antineoplastic agents and steroids (Table 4) [14]. Therefore, agents such as valproic acid, gabapentin, topiramate (Topamax), levetiracetam (Keppra), tiagabine (Gabitril), and lamotrigine (Lamictal) are better options. These agents may also carry a lower

risk of sedative and cognitive side effects than some of the older drugs.

Many of these newer agents are available only in oral formulations, so parenteral administration is not an option. Therefore, the acutely ill patient who requires intravenous anticonvulsants cannot be treated with these drugs. In addition, blood levels are not as widely or rapidly available for these newer agents, and this occasionally makes dose adjustments more challenging for the clinician.

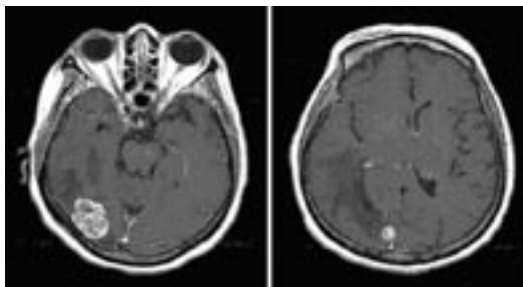
Identification of a mass lesion on imaging always raises a concern that the patient may have a seizure, even if one has not already occurred. Seizures are a frightening symptom, and many physicians automatically place such patients on anticonvulsant medication to prevent them. However, there are now extensive data from randomized studies and a practice parameter from the American Academy of Neurology showing that prophylactic anticonvulsants are ineffective in patients with brain metastases [15]. Prophylactic anticonvulsants do not prevent future seizures in these patients (which are almost always associated with intracranial tumor progression) and are associated with a high frequency of side effects, some of which may be life-threatening, such as Stevens-Johnson syndrome secondary to use of phenytoin or carbamazepine [16, 17]. Therefore, prophylactic anticonvulsants should be avoided in patients with brain metastases.

#### ANTICOAGULANTS

Deep venous thromboses are a common medical complication of brain metastases, affecting approximately 22%–45% of patients [18]. These patients are at particular risk due to immobility from their neurologic disability. Immediate prevention of a life-threatening pulmonary embolism in a cancer patient requires anticoagulation with low-molecular-weight heparin when possible [19].

Concern often arises in patients with brain metastases because hemorrhage into an intracranial lesion may be devastating. However, anticoagulation is safe and should be the first therapeutic choice. Patients can be followed safely for months to a year on chronic warfarin therapy without any increased risk of CNS hemorrhage, provided the patient's INR (International Normalized Ratio) is maintained in the therapeutic range.

Inferior vena cava filters may be necessary in patients with hemorrhagic brain metastases or immediately before or after craniotomy. However,



**Figure 1** MRI Scans of Brain Metastases

Post-gadolinium T<sub>1</sub> MRI scans demonstrating two brain metastases from colon cancer. The smaller lesion was not appreciated on a non-contrast CT scan. Note the prominent edema surrounding both lesions.

many cancer patients with filters develop progressive venous clots or pulmonary emboli that require subsequent anticoagulation.

#### Definitive Treatment

##### WHOLE-BRAIN RADIOTHERAPY

Definitive treatment of brain metastasis is the only effective means of extended palliation for patients. Whole-brain radiotherapy (WBRT) has long been a mainstay of definitive treatment and can prolong median survival 3–6 months [20]. The use of WBRT is standard in cases of multiple brain metastases, in patients whose overall clinical condition is poor and rapidly deteriorating, and in patients for whom easy palliation is the goal. Response may be predicted based on the radiosensitivity of the primary tumor. Small-cell lung carcinoma and germ cell tumors respond best. Non-small-cell lung and breast cancers have intermediate radiosensitivity, whereas renal cell tumors, sarcomas, and melanomas are relatively radioresistant; however, even patients with brain metastases from these cancers may achieve relief of neurologic symptoms for a time with WBRT.

Typical dosing is 30 Gy in 10 fractions. Higher cumulative doses (> 50 Gy), daily fractions > 2 Gy, concurrent chemotherapy, and patient age > 60 years are all factors that increase the rate of complications, such as acute and delayed encephalopathies and radiation necrosis [21]. Corticosteroids prevent acute radiation toxicity, which usually manifests itself as headache, nausea, and vomiting within hours of treatment. This toxicity is due to an increase in edema. Treating brain metastases with WBRT is never an emergency, and patients should receive corticosteroids for at least

*Peer viewpoints on this article by Drs. J. Gregory Cairncross, David G. Kirsch, Jay S. Loeffler, Samuel T. Chao, Steven A. Toms, and John H. Suh appear on pages 411, 412, and 414.*

**Table 3**  
Side Effects of Long-Term Steroid Use

COMMON	UNCOMMON	RARE
Hypertension	Metabolic alkalosis	Sudden death with rapid high-dose pulse therapy
Cushingoid appearance	Peptic ulcer disease, gastric hemorrhage	Allergy
Impaired wound healing	"Silent" intestinal perforation	Congestive heart failure
Acne	Glaucoma	Panniculitis
Adrenal insufficiency	Benign intracranial hypertension	Impotence, amenorrhea
Hyperglycemia, diabetes mellitus	Spontaneous fractures	Hepatomegaly
Sodium retention, hypokalemia	Psychosis	Pancreatitis
Immunosuppression	Hirsutism	Seizures
Myopathy		Epidural lipomatosis
Osteoporosis		Exophthalmos
Osteonecrosis		
Alterations in mood		
Cataracts		

48 hours before WBRT is started, to eliminate acute toxicity. Chronic radiotoxicities are usually delayed complications that do not appear for several months. Therefore, only long-term survivors are at risk for these late effects.

### SURGERY

Surgical resection of a brain metastasis is indicated for some patients with single lesions, when the diagnosis is unknown, or when a single lesion is immediately life-threatening. Metastases in the posterior fossa obstructing cerebrospinal fluid outflow and large hemorrhagic lesions often need immediate surgical attention, even if the patient has other cerebral metastases. However, surgery is used primarily for patients with a single metastasis.

Two prospective randomized trials have shown a survival benefit of surgery over WBRT alone in this select patient population [22, 23]. Patients undergoing resection plus WBRT had a median survival of 10 months, versus 4–6 months for those receiving WBRT alone. In addition to prolonging survival, surgery plus WBRT resulted in a sustained improvement in neurologic function and prolonged independence, compared with WBRT alone. Most patients succumbed to their systemic disease, highlighting that patients with brain metastases usually have active systemic tumor as well. Comparable survival has been reported in retrospective studies of surgery for multiple metastases (ie, two to four lesions). Positive prognostic factors include Karnofsky performance scores > 70 and limited systemic disease [24].

A second randomized trial evaluated the need for postoperative WBRT following complete re-

section of a single brain metastasis [25]. The authors found significantly improved control of neurologic disease at both the operative site and elsewhere in the brain, with prolonged freedom from neurologic disability when WBRT followed surgery. However, because these patients died of progressive systemic tumor, overall survival was the same as that for patients who did not receive postoperative WBRT, most of whom died of their neurologic disease. Therefore, the use of postoperative WBRT remains controversial because survival is unaffected and there is potential risk for neurotoxicity in long-term survivors. To reduce that risk, when it is used, postoperative WBRT should be delivered in 2- to 1.8-Gy fractions, to a total dose of about 40 Gy.

### STEREOTACTIC RADIOSURGERY

Stereotactic radiosurgery (SRS) is highly focused radiotherapy delivered only to the tumor, sparing the surrounding normal brain tissue. It can be accomplished by a linear accelerator or gamma knife with equal results. A single treatment consisting of 14–20 Gy is delivered to lesions not exceeding 3 cm in diameter.

The Radiation Therapy Oncology Group studied recurrent primary and metastatic brain tumors in a group of 156 patients and determined that the maximum tolerated dose of single-fraction SRS was inversely proportional to tumor size [26]. Therefore, SRS is most effective for small lesions, because there is less tumor and the SRS dose is higher. Ideally, candidates for SRS should have a single or maximum of three lesions, although some physicians have treated patients with numerous metastases. Me-

dian survival is extended to about 10 months. Local tumor control (which is usually defined as stable disease or better for the treated lesions) ranges from 80% to 95% [11, 12, 27, 28].

Higher concentrated doses of radiation correlate with a higher rate of radionecrosis (20% versus 5% for WBRT). Radionecrosis is difficult to distinguish from tumor recurrence on MRI, and management of this complication can be challenging; positron emission tomography or magnetic resonance spectroscopy may be helpful to differentiate tumor from radionecrosis, but the diagnosis may be uncertain, even with these techniques. Steroids may improve symptoms from radionecrosis, but occasionally patients develop prolonged steroid dependence. Resection may be necessary for symptom control and diagnosis in some patients.

The adjunctive role of WBRT in combination with SRS is as controversial as it is for the surgical management of metastases. There seems to be a significant delay in time to neurologic disease progression by adding WBRT to SRS. However, collective experience has not demonstrated an overall survival benefit except in certain patient populations [29].

Comparing SRS with surgery is difficult because no randomized trial has been done to assess their relative efficacy. However, retrospective data suggest they are equivalent, or nearly so, for most patients. SRS has some advantages for patients with a single lesion that is not surgically accessible (eg, in the brainstem) or in patients unable to undergo surgery for medical reasons. SRS may be preferred by patients because it is a noninvasive procedure that can be performed on an outpatient basis and is usually associated with faster recovery periods. However, resection is better for larger lesions and those associated with significant surrounding edema, which can be exacerbated by SRS.

#### SYSTEMIC CHEMOTHERAPY

Chemotherapy is not part of routine therapy for brain metastases and is used only after surgery, WBRT, and stereotactic radiosurgery have been exhausted. It is effective for only a small proportion of patients. Often a patient has developed CNS disease after chemotherapy fails, suggesting a drug-resistant subclone that may be responsible for the brain metastasis. Furthermore, these lesions may be partially protected by the blood-brain barrier, which reduces access of systemically

**Table 4**

#### Anticonvulsants Used in Patients With Brain Metastases and Seizures

ANTIEPILEPTIC AGENT	INDUCES CYTOCHROME P450	INTRAVENOUS FORMULATION	SERUM LEVEL MONITORING
Phenobarbital	+	+	+
Phenytoin	+	+	+
Valproic acid	-	+	+
Gabapentin	-	-	-
Lamotrigine	-	-	-
Levetiracetam	-	-	-
Oxcarbazepine	+	-	-
Tiagabine	-	-	-
Topiramate	-	-	-

administered agents to the lesion. Brain metastases visible on neuroimaging with contrast have an impaired blood-brain barrier, but drug penetration into the lesions is not reliable. Moreover, treatment of microscopic disease that is not visualized on MRI exists behind an intact blood-brain barrier and requires agents that can penetrate into these regions. There are few such agents (eg, nitrosoureas, high-dose methotrexate), and they have a restricted anticancer spectrum.

Response rates to varying regimens depend largely on the primary tumor in question. Highly chemosensitive tumors, such as breast tumors, have approximately a 50% response rate to agents such as cisplatin, etoposide, cyclophosphamide, methotrexate, and 5-fluorouracil. Brain metastases from small-cell lung cancer have a 33%–53% response rate to agents such as teniposide (Vumon), cyclophosphamide, topotecan (Hycamtin), carboplatin (Paraplatin), etoposide, and vincristine. Slightly poorer response rates (27%–45%) exist for intermediately sensitive tumors, such as non-small-cell lung cancer, with agents like vinorelbine, gemcitabine (Gemzar), cisplatin, and etoposide [12].

Temozolomide (Temodar) has been studied recently across different tumor types for the treatment of recurrent brain metastases. Its excellent tolerability, ease of oral administration, and good CNS penetration have made it a logical choice. As monotherapy, response rates are low (5%–10%), but response was seen primarily in patients with non-small-cell lung cancer, the most common cause of brain metastases. Synergism with WBRT has shown promise in a preliminary study and is currently being investigated [30].

Nguyen  
DeAngelis

## Brain Metastases

Peer viewpoints on this article by Drs. J. Gregory Cairncross, David G. Kirsch, Jay S. Loeffler, Samuel T. Chao, Steven A. Toms, and John H. Suh appear on pages 411, 412, and 414.

**Table 5**  
Positive Prognostic Factors for Survival From Brain Metastases

Limited systemic disease
Karnofsky Performance Score > 70
Age < 60 years
One to three intracranial lesions
Chemosensitive/radiosensitive primary tumor

### RECURRENT BRAIN METASTASES

The rationale used for choosing among the initial treatment options discussed can guide the physician in selecting therapy once a patient relapses. The same positive prognostic factors exist where patients with higher performance scores and limited systemic disease at recurrence fare better with additional treatment (Table 5). One retrospective study of a select population evaluated re-operation for recurrent brain metastases, with a mean time to relapse of 6.7 months. Me-

dian survival was 11.5 months after the second surgery [31]. Salvage SRS has also been studied. Patients undergoing salvage radiosurgery procedures have a median survival of 11–12 months, which includes an extension of 7 months from their second SRS procedure.

### Conclusion

Brain metastases are a life-threatening complication for many cancer patients. However, those who are candidates for aggressive focal therapies may do well, achieving a median survival of about 1 year, with some patients surviving several years. For some patients, only modest palliative and survival benefits can be achieved with a multimodal approach, but even these patients can achieve some relief from neurologic disability with definitive therapy. Supportive medications, such as corticosteroids and anticonvulsants, are important for managing symptoms, but they require careful monitoring because chronic use may contribute to morbidity.

### References

1. Lassman AB, DeAngelis LM. Brain metastases. *Neurol Clin* 2003;21:1–23.
2. Baker AB. Metastatic tumors of the nervous system. *Arch Pathol* 1942;24:495–537.
3. Globus JH, Meltzer T. Metastatic tumors of the brain. *Arch Neurol Psychiatr* 1942;48:163–226.
4. Tom MI. Metastatic tumors of the brain. *Can Med Assoc J* 1946;54:265–268.
5. Chason JL, Walker FB, Landers JW. Metastatic carcinoma in the central nervous system and dorsal root ganglia: a prospective autopsy study. *Cancer* 1963;16:781–787.
6. Hunter KM, Rewcastle NB. Metastatic neoplasms of the brain stem. *Can Med Assoc J* 1968;98:1–7.
7. Posner JB, Chernik NL. Intracranial metastases form systemic cancer. *Adv Neurol* 1978;19:579–592.
8. Zimm S, Wampler GL, Stablein D, et al. Intracerebral metastases in solid-tumor patients: natural history and results of treatment. *Cancer* 1981;48:384–394.
9. Lagerwaard FJ, Levendag PC, Nowak PJ, et al. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys* 1999;43:795–803.
10. Nussbaum ES, Djililian HR, Cho KH, Hall WA. Brain metastases: histology, multiplicity, surgery and survival. *Cancer* 1996;78:1781–1788.
11. Pirzkall A, Debus J, Lohr F, et al. Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. *J Clin Oncol* 1998;16:3563–3569.
12. Alexander E III, Moriarty TM, Davis RB, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. *J Natl Cancer Inst* 1995;87:34–40.
13. Posner JB. Brain metastases: 1995. A brief review. *J Neurooncol* 1996;27:287–293.
14. van den Bent MJ. The role of chemotherapy in brain metastases. *Eur J Cancer* 2003;39:2114–2120.
15. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;54:1886–1893.
16. Hoang-Xuan K, Delattre JY, Poisson M. Stevens-Johnson syndrome in a patient receiving cranial irradiation and carbamazepine. *Neurology* 1990;40:1144–1145.
17. Delattre JY, Safai B, Posner JB. Erythema multiforme and Stevens-Johnson syndrome in patients receiving cranial irradiation and phenytoin. *Neurology* 1988;38:194–198.
18. Carman TL, Kanner AA, Barnett GH, Deitcher SR. Prevention of thromboembolism after neurosurgery for brain and spinal tumors. *South Med J* 2003;96:17–22.
19. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;349:146–153.
20. Lohr F, Pirzkall A, Hof H, Fleckenstien K, Debus J. Adjuvant treatment of brain metastases. *Semin Surg Oncol* 2001;20:50–56.
21. Cross NE, Glantz MJ. Neurologic complications of radiation therapy. *Neurol Clin* 2003;21:249–277.
22. 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;322:494–500.
23. Veitch CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993;33:583–590.
24. Lang FF, Sawaya R. Surgical treatment of metastatic brain tumors. *Semin Surg Oncol* 1998;14:53–63.
25. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998;280:1485–1489.
26. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of the RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 2000;47:291–298.
27. Engenhart R, Kimmig BN, Hover KH, et al. Long-term follow-up for brain metastases treated by percutaneous stereotactic single high dose irradiation. *Cancer* 1993;71:1353–1361.
28. Auchter RM, Lamond JP, Alexander E, et al. A multi-institutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastases. *Int J Radiat Oncol Biol Phys* 1996;35:27–35.
29. 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;363:1665–1672.
30. Antonadou D, Paraskevaidis M, Sarris G, et al. Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. *J Clin Oncol* 2002;20:3644–3650.
31. Bindal RK, Sawaya R, Leavens ME, Hess KR, Taylor SH. Reoperation for recurrent metastatic brain tumors. *J Neurosurg* 1995;83:600–604.

## PEER VIEWPOINT

Commentary by J. Gregory Cairncross, MD

**D**rs. Nguyen and DeAngelis have reviewed the management of patients with brain metastasis, a complication of systemic cancer that is both common and vexing. All clinicians who treat patients with brain metastasis will find this article most helpful. With little to add or criticize, I have chosen to reflect on a few clinical issues that have been of interest to me and re-emphasized several points of patient care highlighted by the authors.

To begin, readers should recall that survival data are often a very poor measure of the success of treatment for brain metastasis. This is true for at least two reasons. First, any relief from the symptoms of brain metastasis is welcomed by patients and their families. Freedom from headache, seizures, or other disabling symptoms is an extremely important benefit of treatment, even if survival is short. Second, because metastasis to the brain is a manifestation of a serious systemic illness, even brilliant treatment of the metastatic brain tumor does not guarantee long life. Indeed, 50% of patients with brain metastasis die as a consequence of progressive systemic cancer [1]. Only when there are outstanding treatments for the common systemic cancers, such as those of the lung and breast, which frequently metastasize to the brain, will length of life be an accurate measurement of the effectiveness of treatment for the neurologic illness. If such treatments happen to cross the blood-brain barrier, readily reaching tumor cells in the central nervous system, they may also be highly effective therapies for brain metastasis.

Over the years, I have come to appreciate that large metastatic brain tumors in the posterior fossa require surgical removal, if possible. I have found it exceedingly difficult to manage such cases with medical therapies alone. Suffering due to severe headache, intractable vomiting, and steroid dependence is frequently the consequence of failure to remove a large metastasis from the posterior fossa. Hence, I was pleased to read that Drs. Nguyen and DeAngelis strongly recommend that large cerebellar tumors be removed, even when smaller metastases are visible elsewhere in the brain. Patients are best palliated by surgical removal of the tumor followed by radiotherapy.

Corticosteroids are a predictably effective treatment for the neurologic symptoms that accompany brain metastases. However, as Drs. Nguyen and DeAngelis emphasize, chronic steroid administration is accompanied by serious side effects, including disabling muscular weakness. In fact, steroid myopathy can sometimes be more disabling than the symptoms caused by the brain metastasis and can mimic neurologic worsening due to a metastatic brain tumor. In hindsight, I should have made greater use of posttreatment magnetic resonance imaging studies in patients with metastatic brain tumors. More frequent imaging might have allowed me to taper steroid medications more quickly or more wisely.

It is tempting to place patients with brain metastases on prophylactic anticonvulsants. However, as Drs. Nguyen and DeAngelis point out, there is no evidence that this practice is beneficial to patients. The best studies of this issue have concluded that prophylactic anticonvulsants do not significantly reduce the risk of seizure in patients with a brain tumor. Moreover, drugs such as phenytoin, carbamazepine, and valproic acid may have significant allergic, cognitive, or other toxic effects. Perhaps the newer anticonvulsant medications, which have similar antiseizure properties but more favorable side-effect profiles, will be helpful in this setting. However, randomized clinical trials testing these new compounds will be necessary to establish that prophylactic anticonvulsant therapy is a new standard of care for patients with brain metastases.

Drs. Nguyen and DeAngelis have emphasized the benefits of surgical therapy for a single brain metastasis, citing the results of two prospective randomized controlled clinical trials conducted by Patchell et al [2] and Vecht et al [3]. However, they omitted to cite a third trial by Mintz and colleagues [4], in which no survival benefit from surgical therapy was demonstrated. Interestingly, the Mintz study was conducted by investigators based at cancer centers and, as a consequence, may have included a higher percentage of patients with active systemic disease. The patients entered in the trials reported by Patchell et al and Vecht et al were identified in neurologic centers. Differences in patient selection may have led to different conclusions about the value of surgical therapy for patients with a single brain metastasis. As it stands, patients with good performance status and limited systemic disease

Nguyen  
DeAngelis

P E E R V I E W P O I N T

will likely benefit from surgical therapy, whereas those with poor performance status and active systemic cancer are unlikely to benefit from surgical intervention.

Stereotactic radiosurgery employing a gamma knife or other technologies is being used increasingly to treat patients with metastatic brain tumors. This treatment is appropriate for patients who have one or, at most, a few metastatic brain tumors. Evidence from case series suggests that radiosurgery will replace craniotomy as the treatment of choice for patients with small metastatic lesions, but large randomized clinical trials will be necessary to prove that surgical removal and radiosurgery are equally effective therapies for brain metastases. Radiosurgery is said to be safer than craniotomy, but this advantage will only be realized when focused radiation does not cause necrotic lesions in the brain that require surgical drainage. It is much less clear, however, whether stereotactic radiosurgery can replace whole-brain radiation therapy. This important patient care issue is now the subject of a large randomized controlled clinical trial in North America.

One final point: randomized trials have contributed significantly to our understanding of

the management of patients with brain metastases [2–5]. Each has generated important data and improved patient care. The decision to undertake a randomized controlled clinical trial is daunting, but history suggests that the reward more than justifies the effort.

J. Gregory Cairncross, MD  
Professor and Head  
Department of Clinical Neurosciences  
University of Calgary  
Calgary, Alberta, Canada

REFERENCES

1. Cairncross JG, Kim JH, Posner JB. Radiation therapy for brain metastases. *Ann Neurol* 1980;7:529–541.
2. 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;322:494–500.
3. Veitch CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993;33:583–590.
4. 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 brain metastasis. *Cancer* 1996;78:1470–1476.
5. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998;280:1485–1489.

P E E R V I E W P O I N T

**The Controversy of Adjuvant Whole-Brain Radiation Therapy**

*Commentary by David G. Kirsch, MD, PhD,  
and Jay S. Loeffler, MD*

**B**rain metastases occur in a variety of different clinical settings, ranging from a single metastasis without extensive extracranial disease to multiple brain metastases with widespread systemic disease. In this thorough review, Drs. Nguyen and DeAngelis discuss the supportive medical therapies and definitive treatment options available to care for patients with brain metastases. Since patients with brain metastases are a heterogeneous group, therapy for brain metastases should be tailored to the specific clinical circumstances of each patient.

An area of controversy that is highlighted in this review is the role of adjuvant whole-brain radiation therapy (WBRT) after surgical resection or radiosurgery for a brain metastasis. Randomized trials have demonstrated that when used in combination with WBRT, surgery or radiosurgery improves survival for patients with a single brain metastasis compared with WBRT alone [1–3]. However, should patients who undergo radiosurgery or surgical resection of a brain metastasis also receive WBRT?

This question has been addressed in a randomized trial of patients with a single brain metastasis who were treated with surgery alone or surgery followed by WBRT [4]. The primary endpoint of this trial was recurrence of tumor in the brain. For patients who received WBRT following surgery, recurrence of tumor was significantly

## PEER VIEW POINT

Nguyen  
DeAngelis

less frequent than it was among patients who received surgery alone (18% vs 70%;  $P < 0.001$ ). Furthermore, patients who received WBRT were less likely to die of neurologic causes than were those who had surgery only. With this class 1 evidence in favor of WBRT, what fuels this controversy? As Drs. Nguyen and DeAngelis point out, the use of postoperative radiation therapy remains controversial because survival is unaffected by WBRT and because of a potential risk for neurotoxicity in long-term survivors.

However, adjuvant WBRT should not be abandoned because of the absence of a survival benefit. As with other therapies for patients with metastatic cancer, the potential risks and benefits must be assessed for each patient. Although patients will temporarily lose their hair, other short-term side effects, such as nausea, headache, and skin irritation, are uncommon and can usually be controlled with medications. What patients and many physicians fear most is significant neurologic decline from radiation therapy. Although cranial irradiation can have devastating effects on the developing nervous system in young children, prospective studies of WBRT in adults do not find significant cognitive deficits as a result of cranial irradiation with modern fractionation schemes and doses [5, 6]. Prophylactic cranial irradiation (PCI) improves survival in patients with small-cell lung cancer in complete remission. A prospective, randomized study of PCI in 300 patients did not show a significant difference in neuropsychological function at 2 years for patients who received WBRT (24 Gy in 3-Gy fractions) compared with patients who did not receive PCI [5].

In contrast, a frequently cited retrospective study from 1989 identified 12 patients with dementia that was attributed to cranial irradiation [7]. It is important to examine the details of how these patients were treated before extrapolating these findings to current WBRT practices. Of the 12 patients, 9 received daily doses of 5–6 Gy of WBRT. The other 3 patients received doses of 3 Gy/d to 30 or 36 Gy. Three of the patients also received potentially neurotoxic hormonal therapy or chemotherapy. Autopsies of two of these patients demonstrated coexistent processes (senile plaques and progressive multifocal leukoencephalopathy), which may have contributed to their dementia. An important conclusion of this report was that daily fractionation schedules of

large doses may predispose patients to delayed neurologic toxicity. However, studies of PCI using 2- to 3-Gy fractions have not shown an increased risk of radiation-induced dementia [5, 6, 8].

What are the risks of delaying WBRT until tumor recurrence? In a randomized study of postoperative WBRT or observation, patients who received WBRT immediately after surgery had a reduction in neurologic mortality compared with patients who received WBRT at recurrence [4]. Similarly, a retrospective review of 36 patients with brain metastases treated with radio-surgery alone noted a recurrence of tumor anywhere in the brain of 47%. Remarkably, 71% of these patients were symptomatic, and 59% had an associated neurologic deficit [9].

Since the risk of long-term neurotoxicity with WBRT at 2–2.5 Gy/d is small and because postoperative WBRT substantially decreases the risk of tumor recurrence in the brain (which can cause substantial neurologic symptoms), we advocate that most patients with brain metastases who are treated with surgery or radiosurgery should also receive WBRT.

Nonetheless, the role of adjuvant WBRT remains controversial. Randomized trials are currently open comparing radiosurgery alone and radiosurgery with WBRT in the Eastern Cooperative Oncology Group and the American College of Surgical Oncology Group. These trials deserve consideration by clinicians and patients, who remain unsure of the value of adjuvant WBRT.

David G. Kirsch, MD, PhD  
Jay S. Loeffler, MD  
Department of Radiation Oncology  
Massachusetts General Hospital  
Harvard Medical School  
Boston, Massachusetts

### REFERENCES

1. 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;322:494–500.
2. 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;29:711–717.
3. 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;363:1665–1672.
4. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998;280:1485–1489.

PEER VIEWPOINT

5. Arriagada R, LeChevalier T, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst* 1995;87:183–190.
6. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer* 1997;33:1752–1758.
7. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology* 1989;39:789–796.
8. Stuschke M, Eberhardt W, Pottgen C, et al. Prophylactic cranial irradiation in locally advanced non-small-cell lung cancer after multimodality treatment: long-term follow-up and investigations of late neuropsychologic effects. *J Clin Oncol* 1999;17:2700–2709.
9. Regine WF, Huhn JL, Patchell RA, et al. Risk of symptomatic brain tumor recurrence and neurologic deficit after radiosurgery alone in patients with newly diagnosed brain metastases: results and implications. *Int J Radiat Oncol Biol Phys* 2002;52:333–338.

PEER VIEWPOINT

*Commentary by Samuel T. Chao, MD,  
Steven A. Toms, MD, and John H. Suh, MD*

**D**rs. Nguyen and DeAngelis have written a clear, concise review of the treatment of brain metastases, which is the most common neurologic complication of cancer. Despite advances in imaging, surgery, irradiation, and chemotherapy, long-term survival from brain metastases is rare. Thus, active research is ongoing to improve quality of life and survival.

**PROGNOSTIC FACTORS**

Management options, as discussed in the article, include corticosteroids, whole-brain radiotherapy (WBRT), surgery, stereotactic radiosurgery (SRS), and chemotherapy. With the variety of treatment options available, optimal management is controversial and the subject of active research. Stratification of patients into prognostic groups using the Radiation Therapy Oncology Group's (RTOG) recursive partitioning analysis (RPA) class system has been useful in determining whether patients would benefit from

more aggressive therapies, such as surgery and SRS. The most important factors in determining prognosis are performance status, age, control of the primary tumor, and presence of extracranial disease (Table 1). Patients with favorable characteristics (RPA class I) have a median survival of 7.1 months, whereas patients with poor performance status have a median survival of 2.3 months [1]. In addition, patients with good neurological status before the start of treatment survive longer following treatment [2].

**STEREOTACTIC RADIOSURGERY**

RTOG 9508 studied the addition of SRS to WBRT for patients with one to three unresected brain metastases and found that there was a modest survival benefit for patients with a single brain metastasis, RPA class I, age younger than 50 years, and/or squamous cell or non-small-cell lung (NSCLC) primary tumor [3]. In patients with a single brain metastasis, survival improved from 4.9 months with WBRT alone to 6.5 months with the addition of SRS ( $P = 0.0393$ ). A local tumor control benefit and stable or improved Karnofsky

**Table 1**

**Prognostic Factors in Patients With Brain Metastases**

RPA CLASS	CHARACTERISTICS	MEDIAN SURVIVAL (mo)
I	KPS ≥ 70; controlled primary; age < 65 yr; no extracranial metastasis	7.1
II	KPS ≥ 70; uncontrolled primary; age ≥ 65 yr; and/or extracranial metastasis	4.2
III	KPS < 70	2.3

KPS = Karnofsky performance status; RPA = recursive partitioning analysis  
From Gaspar et al<sup>1</sup>

## PEER VIEW POINT

Nguyen  
DeAngelis

performance status were also associated with the addition of SRS. A phase III study of SRS versus SRS and WBRT in patients with one to three brain metastases is being conducted by the American College of Surgeons Oncology Group.

### SURGERY

As discussed in the article, resection plus WBRT improves survival in patients with a single brain metastasis, compared with WBRT alone [4]. Resection may also improve survival in selected patients with two to three metastases. Adjuvant WBRT improves local tumor control, prevents recurrence beyond the resection cavity, and prevents neurological death, compared with surgery alone [5]. In order to obtain the local tumor control benefit of WBRT following surgery for a single brain metastasis, GliSite® (Proxima Therapeutics, Inc., Alpharetta, Ga), a balloon brachytherapy system, is being investigated; the results from this study are pending. With this system, a balloon catheter is introduced in the resection cavity and loaded 1–3 weeks later with radioactive iodine (60 Gy at a depth of 1 cm).

### RADIATION SENSITIZERS

For the majority of patients with brain metastasis, WBRT is the mainstay of treatment and efforts to improve the outcome of WBRT continue. These efforts include radiation sensitizers such as efaproxiral, motexafin gadolinium, and temozolomide (Temodar).

Efaproxiral is an allosteric modifier of hemoglobin and enhances the diffusion of oxygen into tissues, thereby increasing the effects of radiation against hypoxic cells. In a matched-case analysis of RPA class II patients, survival improved from a median of 3.4 months to 7.3 months in patients receiving efaproxiral ( $P = 0.006$ ). Neurologic mortality was also lower in these patients [6]. In a subset analysis of a phase III trial, the improvement in survival was more pronounced in patients with breast cancer, who had a median survival of 8.67 months with efaproxiral versus 4.57 months without efaproxiral ( $P = 0.006$ ) [7]. The ENRICH (Enhancing Whole-Brain Radiation Therapy in Patients with Breast Cancer and Hypoxic Brain Metastases) trial is an ongoing phase III study of WBRT with or without efaproxiral in women with breast cancer.

Motexafin gadolinium is a redox modulator. Addition of this agent to WBRT did not improve overall survival, but did improve the median time

to neurologic disease progression in patients with NSCLC [2, 8]. The median time to neurologic disease progression in patients with NSCLC was 7.4 months without motexafin gadolinium and was not reached in patients who had been treated with motexafin gadolinium. Neurologic decline following WBRT was primarily due to progression of disease, rather than treatment toxicity [2]. Currently, this combination is under study in a phase III protocol for patients with NSCLC in the Study of Neurologic Progression with Motexafin Gadolinium and Radiation Therapy (SMART) trial.

A phase II randomized control trial studying WBRT versus WBRT with concurrent and post-radiation temozolomide was performed in Greece [9]. This study showed that the response rate in patients who received temozolomide was higher than those who received WBRT alone (96% vs 67%,  $P = 0.017$ ). Also, there was marked neurologic improvement in patients receiving temozolomide. The proportion of patients requiring corticosteroids at the end of 2 months was 67% for the temozolomide treatment arm versus 91% for the WBRT-alone arm. A phase III trial is under way in which NSCLC patients with brain metastases are randomized to receive treatment with WBRT plus temozolomide versus WBRT plus placebo.

### CONCLUSION

The management of brain metastasis is complicated in part by the variety of treatment modalities from which oncologists may choose, thus making reviews like this one necessary. By establishing prognostic factors, the role of each modality has been better defined. Attention has focused on radiation sensitizers, chemotherapy, and novel means of delivering radiation. Determining the precise roles of these newer modalities requires that patients be enrolled in clinical trials. With carefully designed trials and advancement in therapies, the quality of life and survival from brain metastasis will continue to improve.

Samuel T. Chao, MD  
Resident, Department of Radiation Oncology

Steven A. Toms, MD  
Director, Section of Metastatic Disease

John H. Suh, MD  
Director, Gamma Knife Center  
Brain Tumor Institute  
The Cleveland Clinic Foundation  
Cleveland, Ohio

**REFERENCES**

1. 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;37:745–751.
2. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol* 2004;22:157–165.
3. 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;363:1665–1672.
4. 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;322:494–500.
5. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998;280:1485–1489.
6. Shaw E, Scott C, Suh J, et al. RSR13 plus cranial radiation therapy in patients with brain metastases: comparison with the Radiation Therapy Oncology Group Recursive Partitioning Analysis Brain Metastases Database. *J Clin Oncol* 2003;21:2364–2371.
7. Suh JH, Stea BD, Kresl JJ, et al. A phase III, randomized, open-label, comparative study of standard whole brain radiation therapy (WBRT) with supplemental oxygen (O<sub>2</sub>), with or without RSR13, in patients with brain metastasis [abstract]. *Neuro-oncology* 2003;5:345–346.
8. Mehta MP, Rodrigus P, Terhaard CH, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *J Clin Oncol* 2003;21:2529–2536.
9. Antonadou D, Paraskevidis M, Sarris G, et al. Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. *J Clin Oncol* 2002;20:3644–3650.