# Guidelines for the Initial Management of Metastatic Brain Tumors: Role of Surgery, Radiosurgery, and Radiation Therapy CME

Matthew G. Ewend, MD David E. Morris, MD Lisa A. Carey, MD Alim M. Ladha, MD Steven Brem, MD

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## Abstract and Introduction

Abstract Brain metastases are an increasingly important determinant of survival and quality of life in patients with cancer. Current approaches to the management of brain metastases are driven by prognostic factors, including the Karnofsky Performance Status, tumor histology, number of metastases, patient age, and status of systemic disease. Most brain metastases are treated with radiosurgery, computer-assisted surgery, or whole brain radiation therapy. Remarkable advances in computer-assisted neuronavigation have made neurosurgical removal of metastases safer, even in eloquent areas of the brain. Computerization also enhances the efficacy and safety of conformal radiosurgery planning using various modern stereotactic radiosurgery (SRS) technologies, including newer frameless-based systems. Controversial issues include whether to defer whole brain radiotherapy (WBRT) in patients undergoing SRS or image-guided surgery and when to use SRS “boost” in a patient undergoing WBRT. The determination of how best to apply these treatments for individual patients cannot be standardized to a single paradigm, but data from well-controlled studies help physicians make informed decisions about the benefits and risks of each approach.

Introduction The diagnosis of brain metastasis is increasingly common and partly results from improvements in systemic therapy of cancers, particularly cancers of the lung and breast. The number of Americans with brain metastases is estimated to be greater than 150,000 per year, making brain metastasis the most common brain tumor. Furthermore, poor penetration of systemic chemotherapy into the central nervous system (CNS) provides tumors with a “pharmacological sanctuary,” leaving the metastasis undertreated compared with the primary site.

For example, the monoclonal antibody trastuzumab treats HER2-positive breast cancer systemically but is far less effective for brain metastases. In addition, improved neuroimaging (MR scan, PET scanning) has led to increased detection of brain metastases.

Although CNS metastasis can arise from any malignancy, most brain metastases arise from 5 organ sites: lung, breast, kidney, colorectal, and cutaneous (melanoma). In addition, brain metastases without a known primary are seen in as many as 15% of patients with brain metastasis.[1] Non-small cell lung cancer has a predilection for the brain and is the

most common type of brain metastasis, accounting for approximately 50% of all cases.[2-4] Melanoma has a higher predilection for the brain, but because of its lower overall incidence, is a less common source for brain metastases.

Significant advances have been made in the treatment of brain metastases, resulting in longer survival and enhanced quality of life (QOL). Unfortunately, long-term survival after development of brain metastases is rare. Brain lesions left untreated may cause neurologic death.

The natural history of untreated cerebral metastases is dismal, with median survival reported as less than 2 months.[5] Although the use of surgery, radiosurgery, and whole brain radiation therapy (WBRT) improves survival, the goal of 2-year survival is still rarely achieved. Nevertheless, the advent of image-guided neurosurgical procedures and computer-assisted radiosurgery has made neurologic death rare in these patients, with overall survival more a function of the pace of the underlying cancer. This article reviews the factors that guide management decisions, focusing on selection and timing of surgery, radiosurgery, and radiation therapy.

## Initial Medical Stabilization: Control of Seizures and Cerebral Edema

Initial management of patients with brain metastasis has the goal of stabilizing CNS symptoms, preventing neurologic deterioration, and defining the extent of CNS and systemic involvement. For rare patients presenting with significant midline brain shift, compression of the ventricular system with obstructive hydrocephalus, intratumoral or intracerebral hemorrhage, or massive brain edema, surgical decompression may be the first emergent priority to prevent brain herniation syndromes and irreversible neurologic injury.

For patients with a known diagnosis of cancer and unexplained neurologic symptoms, evaluating the brain with imaging should have a low threshold. Patients generally present with headache, mild neurologic impairment, or seizure. Patients presenting with seizures or those undergoing surgery are placed on anticonvulsant medication.

Among patients with brain metastases, 15% to 20% present with seizures.[6] Phenytoin, carbamazepine, levetiracetam, and valproic acid are frequently used as first-line agents, along with newer agents. The American Academy of Neurology now recommends that anticonvulsants be administered only to patients at risk for seizure, and use should be minimized to single therapy at the lowest effective dose.[7] Their meta-analysis concluded that prophylactic anticonvulsants did not reduce the risk for a first seizure.

Similarly, the European Federation of Neurological Sciences (EFNS)[6] recommended that prophylactic anticonvulsants be withheld for patients with no history of seizures. When anticonvulsants were needed, EFNS further recommended that non-enzyme-inducing agents be used whenever

possible to avoid impacting metabolism of chemotherapy and steroids. Therefore, for those patients with no history of seizures who are not undergoing surgery, antiepilepsy medication may be omitted. If anticonvulsants are started in preparation for surgery, discontinuation can be strongly considered after the perioperative period.

For most patients, the perilesional vasogenic edema common with brain metastases responds to oral glucocorticoid steroids. The cerebral edema is best visualized on T2-weighted or fluid-attenuated inversion recovery MR images. Recommended dosages of dexamethasone vary significantly; EFNS recommended starting dosages between 4 and 8 mg/d,[6] whereas the authors previously recommended a starting dosage of 16 mg/d in 4 doses.[8] For patients with more acute neurologic issues, dosages approaching 100 mg/d in divided doses can be considered.

Ideally, steroid dose should be tapered as quickly as the clinical situation allows because of the toxicity associated with long-term (> 3 weeks) use, including personality changes, suppressed immunity, metabolic derangements, insomnia, and impaired wound healing.

For patients with incidentally discovered brain metastasis without significant mass effect or edema, withholding steroids and antiepilepsy medication may be appropriate.

Diagnostic Workup of Suspected Brain Metastases

Once patients are stabilized medically, definitive staging assesses the extent of disease systemically and in the CNS. Within the CNS, determining the number of lesions is a key first step. MRI is the gold standard because of its high resolution and sensitivity (Figure 1); it can identify multiple lesions when a prior CT identifies only a single tumor.[9,10] Single brain metastases likely occurs in one fourth to one third of patients as determined by MRI.[10]

Figure 1. (click image to zoom) A 64-year-old woman presented with a single brain metastasis 9 months after diagnosis of non-small cell lung cancer. Her systemic metastatic disease was under good control. The cerebellar lesion (A) was treated with frameless robotic radiosurgery, and whole brain radiotherapy was deferred. The tumor responded to stereotactic radiosurgery (B). After 6 months, the patient developed a second intracranial lesion (C) and was treated with radiosurgery and subsequent WBRT (300 cGy × 10 fractions). This case raises the issues of whether WBRT should be given up-front in high-functioning patients or used as salvage therapy.

Determination of oligometastases (usually defined as 2 or 3 tumors) can influence management decisions. Between 4 and 8 lesions constitutes diffuse multifocal disease, and 9 or more tumors can be considered to be miliary disease, normally treated with WBRT or systemic chemotherapy. The exact break point between oligo- and diffuse metastatic disease is arbitrary, reflecting that tumor number detected on MRI is a biologic continuum. Surgery, if indicated, should not be delayed for concurrent

staging of the systemic disease burden. In general, however, CT scan of the chest and abdomen or fluorodeoxyglucose (FDG)-PET scan in selected primary tumor settings usually provides information for systemic therapy. Determining whether systemic disease progression is present or the progression is isolated to CNS is valuable.

## Initial Determination of Factors Affecting Prognosis and Treatment Pathway

Optimal treatment for a patient with brain metastases must be individualized based on prognostic factors, patient preference, status of systemic disease, and expertise available at the treating center.

Based on an analysis of 1200 patients with brain metastases treated with different protocols, the Radiation Therapy Oncology Group (RTOG) defines a recursive partitioning analysis (RPA) classification system (Table 1).[11] The group with the best prognosis (RPA class I) had favorable characteristics, including Karnofsky Performance Status (KPS) of 70% or greater (able to care for self); controlled systemic disease; age younger than 65 years; and metastases to the brain only. Their median survival was 7.1 months. Patients in RPA class III had the poorest median survival (2.3 months), with a KPS of less than 70% (requires at least some assistance). Median survival was 4.2 months for patients in RPA class II. Patients with a single brain metastasis treated with aggressive therapy have shown survivals ranging from 10 to 12 months.[2,3,12]

Another variable often considered is time from initial diagnosis to development of brain metastasis. Synchronous presentation carries a worse prognosis. For example, Thomas et al.[13] reported median survival of only 3 months in patients diagnosed with a synchronous presentation of brain and systemic cancer. However, exceptions exists, such as patients presenting with a single brain and peripheral lung lesion that are both completely resectable. These patients can do surprisingly well; complete resection of the lung lesion with no nodal positivity is the key determinant of survival.[14]

Occasionally, tumors such as germ cell tumors can spread to the CNS and still be cured with systemic therapy. Finally, the histology of the primary cancer and availability of unused treatment options greatly influence decision making for CNS lesions. For example, it may be appropriate for patients with chemosensitive breast cancer (e.g., estrogen and progesterone receptor-positive tumor in a chemo-naïve patient) to undergo aggressive CNS treatment, in contrast to a patient with melanoma on third-line therapy. Taking into account these prognostic factors, patients and treating physicians must then decide how best to approach the CNS disease. In end-stage disease, hospice can be considered an appropriate option.

## Surgical Therapy

The objectives of surgical therapy for brain metastasis include tissue diagnosis, removal of mass effect, resolution of edema, definitive therapy for the local lesions with improved QOL, and improved overall survival when combined with radiation therapy compared with radiation therapy alone. In most cases, surgery is performed for a single brain lesion, but can be applied to multiple lesions if each of the lesions is treated with surgery or radiosurgery.[15] With the advent of radiosurgery as an equivalent or alternative treatment for single brain lesions, surgery is usually indicated for a subset of single brain lesions (Table 2).

The most common criterion for choosing surgery over radiosurgery is tumor size; lesions larger than 3 cm are less favorable for radiosurgery, and surgery is usually preferable. Lesion location is also clearly an important consideration. Lesions near speech or motor centers benefit from careful intraoperative monitoring. Intra-axial metastases deep in the brainstem and basal ganglia are rarely approached with surgery, unless they are exophytic laterally into the surrounding cisterns or temporal lobe and are surgically accessible with a reasonable degree of safety.

Lesions in the posterior fossa, even when smaller than 3 cm, may be better treated with open surgery if combined size and edema is significant and incipient brainstem or fourth ventricular compression is present. Resecting these lesions will resolve mass effect more rapidly than radiosurgery. Because of the proximity to cerebrospinal fluid, caution is required in the posterior fossa to avoid meningeal seeding of tumor cells.[16]

Another strong indication for surgery is the need for pathologic confirmation of tissue diagnosis. This can occur in the following settings: 1) no prior diagnosis of cancer (synchronous presentation), 2) first site of failure with no other extracranial sites of disease, or 3) when the imaging or clinical presentation is peculiar for brain metastases. When the lesion is large, or when other sites are not easily biopsied, resection can provide both tissue diagnosis and definitive treatment of the brain lesion simultaneously.

Less commonly, surgery is undertaken for patients with oligometastases in the brain. The group at M. D. Anderson Cancer Center[16] reported that in patients with 2 to 3 brain metastasis, complete resection of all lesions resulted in equivalent outcomes compared with patients undergoing resection for single lesions. However, when surgery did not remove all of the lesions, little benefit was seen in overall survival.

Occasionally a single dominant lesion will cause significant morbidity because of size and mass effect. In these patients, it is reasonable to resect the dominant tumor and then treat the remaining tumors with a combination of radiosurgery or external beam radiation therapy.

Surgical resection of brain metastases can be achieved with low morbidity, mortality, and discomfort for patients. With the introduction

of computer-assisted, stereotactic image guidance, and modern neuronavigation, metastatic tumors can be resected with minimally invasive techniques, such as small incisions, circumscribed small bone flaps, and trans-sulcal approaches that spare neurologic function and reduce blood loss, operating times, and hospital stays. Postoperative hospital stays of between 1 and 3 days for surgical resection of brain metastases are now common.

Because metastatic tumors usually appear at the grey-white junction, they are usually easily accessible and are distinct from surrounding brain in color and texture, making complete excision (gross total removal) expected and common. Because surgical wounds must heal before radiation therapy or systemic chemotherapy is started, usually taking from 10 days to 3 weeks, the delay can be a reason for treating the tumor with stereotactic radiosurgery (SRS) rather than surgery. This problem of wound healing is becoming increasingly important with the introduction of antiangiogenesis agents, such as bevacizumab, because these agents may interfere with the reparative neovascularization required for wound healing.

Two randomized trials have established the efficacy of surgical therapy,[3,12] which showed that the combination of surgical resection and radiotherapy was superior to radiation alone in preventing tumor recurrence and prolonging survival. The addition of surgery to radiation therapy reduced local recurrence rate from 52% to 20% and increased survival from 15 to 40 weeks.[3] A third randomized clinical trial failed to show a benefit to surgery.[17] This trial seemed to have a larger proportion of patients with systemically active disease, and the lack of a benefit for surgery implies that patients must be well enough and live long enough to experience a benefit.

Direct surgical access to tumors allows a unique opportunity to add local therapy at the resection site to decrease the rate of recurrence. The most commonly used techniques for this are either local radiation, delivered with seed-based or liquid-filled balloons, or local chemotherapy. The rationale is that small nests of residual tumor cells infiltrated into the brain can serve as sites of local recurrence. Phase II studies of local radiation therapy suggest that local radiation can slow tumor recurrence, although with the added risk for radiation necrosis.[18] Likewise, local chemotherapy, particularly using biodegradable carmustine-polymer wafers, has shown promising results, with low local recurrence rates and minimal added morbidity.[4]

### Radiosurgery

Using ionizing radiation to kill tumor cells requires the radiation to be administered so that the tumor is destroyed without causing unacceptable damage to the surrounding brain. Two strategies are commonly used: 1) fractionating the treatment, which exploits the relative difference in the ability of normal tissue and tumor tissue to repair radiation damage between treatments (the rationale for

fractionated external beam radiotherapy), and 2) to deliver much of the radiation into the tumor, with a smaller dose reaching the surrounding normal tissue (the rationale for radiosurgery).

SRS is defined as the delivery of multiple intersecting radiation beams designed to deliver a high dose of radiation to a selected target with very rapid decline in radiation dose outside the target volume. This is achieved through the use of high-precision stereotactically based treatment systems that deliver the beams with accuracy on the level of 1 mm.[19] Usually this is delivered in a single fraction although multiple fractions are possible (hypofractionation, usually 3-5 fractions), especially with systems that use either removable head frames or real-time imaging instead of traditional head frames that require pin fixation to the skull.

Various equipment can deliver radiosurgery using linear accelerators, gamma radiation sources, or proton beams. Although each of these systems has its proponents, no system has been found to be superior to the others in the treatment of brain metastases; in general, local control rates as high as 75% to 95% can be achieved. When operated by a skilled multidisciplinary team, most brain metastases can be well treated by any commercially available systems.

Brain metastases are an ideal target for radiosurgery, because they are often spherical, have distinct borders, and do not contain normal brain within the radiographically defined limits. In addition, they are easy to define on contrasted MRI, the main imaging modality used to target for radiosurgery.

SRS can be used to treat brain metastases either as the sole initial therapy or in conjunction with fractionated radiotherapy or surgery. The American Society for Therapeutic Radiology and Oncology performed an evidence-based review of the role for radiosurgery in treating brain metastases.[20]

To address whether adding radiosurgery to WBRT improves local control of brain metastases, RTOG 9508 randomized 320 patients with brain metastases to either WBRT alone or WBRT plus SRS. Results showed that the combination of SRS with WBRT resulted in a better response rate at 3 months and better local control rate at 1 year (82% vs. 71%).

In a small single-institution trial, Kondziolka et al.[21] found an even larger difference in local control rate (92% for SRS/WBRT vs. 0% for WBRT alone). Neither study showed a significant difference in survival across the entire group. Patients with 2 to 4 lesions showed survival times of 11 months in the SRS/WBRT arm and 7.5 months in the WBRT-alone arm (P = .22).[21]

In RTOG 9508, survival was 6.5 months in the WBRT group versus 5.7 months in the SRS/WBRT group (P = .014). Univariate analysis of the RTOG 9508 showed an improvement in survival for patients with single lesions (6.5 vs. 4.9 months), but this did not extend to those with multiple

lesions. Multivariate analyses showed a survival advantage for patients in RPA class I and those with favorable histology (squamous cell carcinoma or non-small cell lung cancer).

Many studies show that even radiation-resistant tumors, defined by a lack of response to fractionated therapy, respond well to single-fraction radiosurgery.[22,23] Finally, patients in RTOG 9508 treated with SRS/WBRT were more likely to maintain or improve KPS at 6 months and decrease steroid use. Added toxicity from SRS was low in both trials. Therefore, radiosurgery, when added to WBRT, seems to result in superior local control, maintenance of KPS, and steroid-dependence. Because of the multifactorial cause of death in these patients, superior local control does not necessarily translate into a survival advantage.

A second question about radiosurgery is whether it can be used without WBRT as the initial treatment for brain metastases. A single randomized trial from a large Japanese consortium evaluated patients with 1 to 4 brain metastases randomized to either SRS alone or SRS with WBRT.[24] No survival difference was seen between the groups (8.0 vs. 7.5 months for SRS alone and SRS/WBRT, respectively). The 12-month CNS recurrence rate was 47% in the SRS/WBRT group versus 76% in the SRS-alone group, and the use of salvage therapy was significantly more common in the SRS group. In long-term survivors, no difference occurred in mini-mental status scores, implying that SRS alone followed by salvage therapy after recurrence does not negatively impact survival compared with combined SRS/WBRT up-front.

However, a tradeoff exists between a higher CNS recurrence rate and use of salvage therapy instead of initial WBRT. Interestingly, improved control occurred at the site of the radiosurgery treatment when whole brain radiation was added.[24] The decision to treat with radiosurgery alone or in conjunction with whole brain radiation is variable without a single absolute algorithm.

Whole Brain Radiotherapy

WBRT can treat the macroscopic tumor visualized on MRI and the small microscopic deposits that may be present at diagnosis but are radiographically invisible. Several studies convincingly show that WBRT decreases the rate of CNS recurrence. Aoyama et al.[24] showed that adding WBRT to SRS decreased development of new, peripheral brain metastases from 76% for SRS alone to 47%. Furthermore, Patchell et al.[2] showed that recurrence anywhere in the brain occurred in 70% of patients undergoing surgery alone and that the addition of a relatively long course of radiation (5040 cGy in 28 fractions) decreased the recurrence rate to 18%. Survival between the groups was not significantly different (48 vs. 43 weeks for surgery/WBRT and surgery alone, respectively). Many patients who underwent surgery alone received WBRT at CNS progression.[25]

Based on these studies, WBRT seems to reduce the rate of CNS tumor progression when used in conjunction with local therapy for single or

oligometastasis disease. External beam radiotherapy is accepted as standard care for multiple brain (≥ 4) metastases.[26] However, significant controversy remains about the use of WBRT for oligometastatic disease when the tumors (usually 2-3) are treated with surgery or radiosurgery (Table 3).

The rationale to withhold WBRT after treatment of oligometastatic disease is based on the premise that many patients will not develop distant recurrence, and WBRT confers a risk for long-term cognitive impairment. Furthermore, WBRT takes considerable time to perform in patients with a limited lifespan and those undergoing systemic chemotherapy. Furthermore, it may still be effective if treatment is deferred until recurrence rather than using it prophylactically. CNS recurrence rates of 70% to 76% have been reported in the SRS and surgical randomized trials that withhold WBRT.[2,24] In the Japanese trial, 29 of 65 patients in the SRS group required salvage therapy.[24] This implies that 36 of 65 (56%) patients never required whole brain treatment, sparing the cost, time, and risk of cognitive decline. Older studies show that patients undergoing WBRT, particularly in larger fractions and in conjunction with chemotherapy, can develop radiation-induced dementia.[27]

The argument for giving WBRT up-front is based on the view that tumor progression is a larger threat to cognitive function than radiation effect from WBRT. A study of a radiation sensitizer, motexafin-gadolinium (MGd), which randomized patients to either WBRT alone or WBRT with administration of MGd did not show a benefit to the MGd across the study population, but yielded interesting data about neurocognitive outcomes in patients with brain metastasis.

First, patients with brain metastases present with neurocognitive deficits. The baseline testing showed that 90% of patients had at least 1 abnormal test, and 42% were abnormal in 4 or more of the 8 tests. Neurocognitive decline correlated closely with tumor recurrence. In another study comparing SRS with or without WBRT, tumor control was the most important variable in stabilizing Mini-Mental State Examination scores.[28]

Chemotherapy and Biologic Therapy

Experience with chemotherapy has been primarily through small series with relatively low success rates. Whether this is because of drug resistance of the CNS tumor, difficulty in drug delivery across the blood-brain barrier, or a combination of both is unclear. Although many newer and exciting targeted therapies do not easily enter the CNS, use of future chemotherapies and targeted therapies is a particularly fertile area for achieving long-term survival of patients with brain metastases.

The response of patients with multiple brain metastases to WBRT is lower than would be desired; improved chemotherapy and biologic therapy are most likely to improve outcomes in this group. For example, patients treated with trastuzumab for HER2+ breast cancer often developed brain

metastases.[29] However, the HER1/2 kinase inhibitor lapatinib has shown clinical activity in CNS metastases from HER2+ breast cancer that progressed after locoregional therapy.[30]

## Conclusions

The incidence of brain metastases is increasing, likely because of increased detection and longer survival of patients with cancer. As systemic therapy improves, disease control in the pharmacologic sanctuary of the CNS is likely to be an increasingly important determinant of survival and QOL. Effective treatment exists for CNS disease using combined surgery, radiosurgery, and radiation therapy. General guidelines exist for treating patients with a single CNS metastasis and those with a small number of or widespread metastases (see NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers; in this issue; to view the most recent version, visit the NCCN Web site at www.nccn.org).

High-quality randomized studies are increasing and have elucidated when to use 1 or combinations of these 3 treatments. However, these data provide general guidelines, often grouping together all patients with brain metastasis, although those with breast cancer versus melanoma versus lung cancer often have dissimilar clinical outcomes. For example, the decision to perform WBRT in a woman with 3 metastatic brain tumors resulting from breast cancer after only a 6-month progression-free interval with active systemic disease differs from that for a patient with an isolated CNS metastasis caused by renal cell carcinoma without signs of systemic disease and a 3-year interval since the primary tumor was detected.

Although many treatments are sufficient to prevent neurologic death during the lifespan (3-24 months) after CNS metastasis, neuro-oncology will face several future challenges. For instance, when systemic therapies advance further, will these systemic therapies offer protection from CNS disease? Will current brain-based therapies continue to prevent CNS recurrence over longer periods? Finally, will increasing neurocognitive side effects be seen as patients live longer?

Reprint Address Matthew G. Ewend, MD, Division of Neurological Surgery, Burnett-Womack 3013, University of North Carolina, Chapel Hill, NC 27599. E-mail: ewend@med.unc.edu

Tables Table 1. Radiation Therapy Oncology Group Classification: Recursive Partitioning Analysis

Table 2. Surgery Versus Sterotactic Radiosurgery: Factors Influencing Decision in Patients With 1 to 4 Brain Metastases

Table 3. Whole Brain Radiotherapy: Factors Influencing Recommendation After Radiosurgery or Open Surgery for Local Treatment of 1 to 3 Brain Metastases

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