

Physician

The Independent Medical Business Newspaper

Brain metastases (BM) are a common problem in clinical oncology today, occurring in an estimated 200,000 patients every year in the United States. This represents 15 percent of the 1.4 million patients diagnosed annually with cancer. The number of patients with BM may be increasing because of the aging of the U.S. population, better imaging, and better treatment for systemic disease. The risk of developing BM varies by tumor type. Almost half of lung cancer patients develop BM; 15 percent to 20 percent of breast cancer patients and 10 percent to 15 percent of melanoma patients develop BM.

Historically, the prognosis for BM is poor, with median survival of about one to two months for untreated patients. The median survival for patients treated with whole brain radiation therapy (WBRT) is approximately four to six months. Outcomes are improving with a modern interdisciplinary approach using a combination of treatments: surgery, stereotactic radiosurgery (SRS), and WBRT when appropriate. Though data on chemotherapy for BM are limited, new agents and clinical trials hold some hope for the future, and chemotherapy does play an important role in the control of systemic disease.

A new prognostic index has been published, based on a database of 1,960 patients from randomized trials of the Radiation Therapy Oncology Group (RTOG), a national clinical cooperative funded by the National Cancer Institute. The

Multidisciplinary treatment of brain metastases

Treatment options and general principles of management

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Graded Prognostic Assessment (GPA) index assigns a score of 0, 0.5, or 1.0 to each of four criteria: age, Karnofsky Performance Status (KPS), number of BM, and presence or absence of extracranial metastases (see Table 1). A patient with the best prognosis would have a GPA of 4.0, whereas a patient with the worst prognosis would have a GPA of 0. The median survival times for patients with a GPA of 0–1, 1.5–2.5, 3.0, and 3.5–4.0 were 2.6, 3.8, 6.9, and 11.0 months, respectively. These data make clear that not all patients have the same prognosis; some warrant aggressive, multimodality therapy while others may be best served by hospice.

This article summarizes the treatment options and general principles of management for patients with intracranial metastatic disease.

Medical management

The goals of medical management are palliative: Decrease the severity of symptoms, reverse or improve neurologic deficits and function, and control or prevent seizures. The emphasis is on minimizing potential side effects or complications of therapy.

The cornerstone of therapy

has been the use of **corticosteroids** to control brain edema. Corticosteroids have widespread effects on immune response, inflammation, glucose metabolism, endocrine function, and electrolyte and water homeostasis, and should be used only in patients presenting with symptoms of cerebral edema.

Although the mechanism of action is not fully elucidated, corticosteroids appear to decrease the brain's inflammatory response to the tumor, improve the integrity of the blood-brain barrier, and decrease the associated peritumoral vasogenic edema. The drug of choice has been dexamethasone because of its low mineralocorticoid activity and decreased level of pituitary/adrenal axis suppression, limiting some of the systemic side effects. Although the decrease in brain edema will improve the patient's symptoms, restoration of the blood-brain barrier will decrease the distribution of chemotherapeutic agents into the brain parenchyma, and immune suppression will limit the body's ability to mount a response to tumor antigens.

Complications of steroids include hyperglycemia, redistrib-

ution of body fat to the face and trunk, electrolyte and water imbalances (water and sodium retention and hypokalemia), hypertension, skeletal muscle wasting (steroid myopathy), alterations in mood and behavior, gastric ulceration, osteoporosis, aseptic bone necrosis, cataract formation, and immune suppression with resulting opportunistic infections.

Because of the many side effects of steroids, they should be used only when necessary to control symptoms and in the lowest dose that controls the symptoms.

The routine use of **anti-epileptic agents** is more controversial. While they are used by many practitioners for patients with lesions of the cerebral cortex, there are reasonable arguments to reserve this therapy for patients whose initial presentation is a seizure. Many of the antiepileptic drugs have significant side effects and potential complications, as well as significant drug-drug interactions and alterations of drug metabolism and clearance, which may have significant effects on any systemic chemotherapy regimen the patient is receiving. Although phenytoin and valproic acid have been the drugs of choice for many years, many physicians are changing over to newer agents, such as levetiracetam, which have a lower side-effect profile and have minimal effects on the metabolism and clearance of other drugs. The emerging standard of care is to use anti-convulsant therapy, usually levetiracetam, only when the patient presents with seizures.

Whole brain radiation therapy and stereotactic radiosurgery

Radiation therapy for BM is divided into two types: whole brain radiation therapy and stereotactic radiosurgery. WBRT is usually delivered Monday through Friday over two to four weeks. SRS is a one-day outpatient procedure during which a high dose of radiation is delivered to a small tumor in the brain. This treatment may be delivered with either a Gamma Knife or a modified linear accelerator (Fig. 1).

The Radiation Therapy Oncology Group has completed five prospective randomized clinical trials involving patients with BM, and another is ongoing. Two trials (RTOG 8528 and 9104) explored different fractionation schemes for WBRT and found no difference among the schemes studied. Two trials (RTOG 7916 and 8905) explored the possible role of radiosensitizers in conjunction with WBRT. No benefit was found.

The most recent completed study (RTOG 9508) was a randomized trial of WBRT alone versus WBRT + SRS. Results showed a survival benefit for patients with single BM treated with WBRT + SRS when compared to WBRT alone. Furthermore, there was significantly greater local control, less edema, and less steroid dependence in the WBRT + SRS group for patients with one to three BM. The ongoing trial (RTOG 0320) is a three-arm phase III trial comparing WBRT + SRS versus WBRT + SRS + Temozolamide versus WBRT + SRS + Erlotinib.

Despite the findings of these and other clinical trials, there is enduring debate about which patients should be treated with WBRT alone versus SRS alone versus WBRT + SRS. Results of ongoing trials are needed to better define optimal management of patients with BM.

Based on the results of RTOG 9508, the current standard of care for patients with one to three BM is WBRT + SRS.

Surgical resection

Because of the poor patient prognosis, palliative care with corticosteroids and WBRT has been the mainstay

TABLE 1. The Graded Prognostic Assessment (GPA).

SCORE	0	0.5	1.0
Age	> 60	50 – 59	< 50
KPS	< 70	70 – 80	90-100
Number of CNS metastases	> 3	2-3	1
Extracranial metastases	present	–	none

of patient management. Improvements in diagnostic imaging (high-resolution CT, MRI), operative image guidance, intraoperative imaging (ultrasound, CT, MRI), microscopic dissection technique, neuroanesthesia, and postoperative care with accompanying low perioperative morbidity and mortality have led to renewed interest in surgical resection of metastatic disease. Studies have demonstrated a significant benefit to surgical resection of single—and, potentially, multiple—metastatic lesions in select patients. A combination of surgical resection with WBRT compared to WBRT alone has demonstrated a significant improvement in median survival (40 weeks versus 15 weeks) and a longer median period of functional independence (38 weeks versus 8 weeks). Tumor recurrence and progression to neurologic death were also less likely in patients treated with a combination of surgery and WBRT.

Outcomes of surgery depend on careful patient selection based on age, functional status (KPS), tumor location and

size, amount of associated edema, tumor histology, and status and extent of extracranial disease. The Graded Prognostic Assessment, described above, is useful for patient selection.

In general, surgery should be considered in young patients with independent functionality (KPS \geq 70) and a solitary tumor that is well localized and is surgically accessible without significant perioperative risk. Consideration is also given to the need for immediate tumor debulking due to size (\geq 3 cm) or obstructive hydrocephalus, associated edema unresponsive to steroids or potentially complicating WBRT or other therapies, and the need for a histologic diagnosis in the absence of systemic disease (see Fig. 2).

Chemotherapy


Although chemotherapy may control systemic disease, its role in BM has been limited. Multiple factors can alter the efficacy of chemotherapy. First, the blood-brain barrier prevents many chemotherapy drugs from reaching the brain in significant concentrations. Second, many

tumors have widely varying chemo sensitivity based on their histology. Third, patients often have been heavily treated with multiple chemotherapy agents, conferring a degree of chemo resistance to the tumor. And last, many patients presenting with BM have life-limiting, uncontrolled systemic disease. Single-agent therapy has therefore shown limited efficacy, and those agents that have demonstrated some promise have failed due to systemic toxicity or the inability to significantly alter patient outcome.

Multimodality therapy may be a way to utilize chemotherapeutic agents in a more efficacious manner. In recent years, preliminary evidence has emerged suggesting that there may be a synergistic effect when WBRT is given with certain drugs, such as those being used in RTOG 0320 (Temozolamide and Erlotinib). Many other drugs have been studied without a documented improvement in survival, and further work is needed in this area.

Gaining new insights, knowledge

Brain metastases are a common problem, but we now understand this patient population is heterogeneous. With an interdisciplinary approach using modern imaging and the GPA prognostic index, clinicians now have the tools to distinguish which patients warrant aggressive treatment and which may be best served with less treatment or hospice.

Debate continues regarding optimal management, and the results of ongoing clinical trials are needed to better define which patients need which treatments. Participation in these clinical trials is strongly encouraged. For more information on these clinical trials, contact the authors. 

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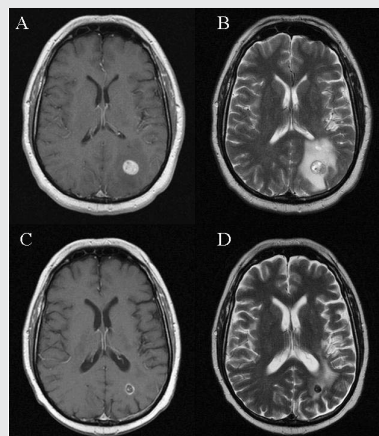


FIGURE 1. 46-year-old male with history of renal cell carcinoma diagnosed five years prior to presenting to the emergency department with a three-day history of hand clumsiness and difficulty with ambulation. MRI of the brain demonstrated three brain metastases, T1 weighted image with gadolinium contrast (A) and T2 weighted image (B) demonstrating the 2-cm left occipital homogeneously enhancing lesion with associated edema. MRI of brain one year and eight months after Gamma Knife stereotactic radiosurgery (C and D) showed marked decrease in tumor size and contrast enhancement with associated decrease in edema.

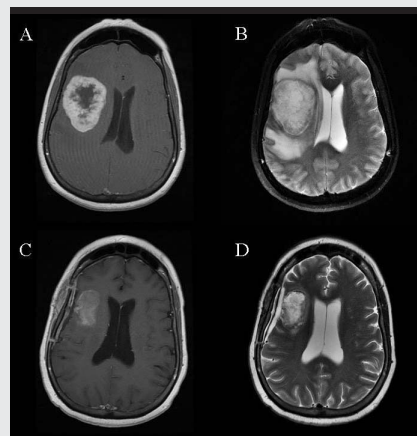


FIGURE 2. 55-year-old female presenting with generalized tonic clonic seizure and one-month history of left-sided weakness and severe headaches. MRI of the brain, T1 weighted image with gadolinium contrast (A) and T2 weighted image (B) demonstrated a 5-cm heterogeneously enhancing mass (metastatic adenocarcinoma of the colon primary) with significant peritumoral edema and mass effect. MRI of brain two months after surgical resection and completion of whole brain radiation therapy (C and D) showed resolution of edema and mass effect with a small amount of blood product within the resection cavity.