Management of Brain Metastases

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Brain metastases are the most common type of brain tumor in adults and are an increasingly important cause of morbidity and mortality in cancer patients. In recent years, important advances have been made in the diagnosis

Introduction

Brain metastases are a common complication in cancer patients and an important cause of morbidity and mortality. They develop in approximately 10% to 30% of adults and 6% to 10% of children with cancer.[1-6] Each year in the United States, an estimated 97,800 to 170,000 new cases of brain metastasis are diagnosed.[1,2,6] This number may be increasing as a result of the increased ability of magnetic resonance imaging (MRI) to detect small metastases and improvements in systemic therapy, leading to longer patient survival.[1,6-9]

In adults, the primary tumors most often responsible for brain metastases are lung cancer (50%), breast cancer (15% to 20%), unknown primary tumor (10% to 15%), melanoma (10%), and colon cancer (5%).[1-3,10] In children, the most common sources of brain metastases are sarcomas, neuroblastoma, and germ cell tumors.[1,4,11] Studies using MRI suggest that the proportion of single metastases is lower than was previously believed, accounting for only one-third to one-fourth of patients with cerebral metastases.[7,12] Metastases from breast, colon, and renal cell carcinomas are often single, while melanoma and lung cancer have a greater tendency to produce multiple metastases.[1,13]

Method of Spread and Distribution

The most common mechanism of metastasis to the brain is by hematogenous spread.[1] These metastases are usually located directly beneath the junction of the gray and white matter.[13] Brain metastases tend to occur at this site because the blood vessels decrease in size at this point and act as a trap for clumps of tumor cells. Brain metastases also tend to be more common at the terminal “watershed areas” of arterial circulation.[1,13] The distribution of brain metastases roughly follows the relative weight of (and blood flow to) each area. Approximately 80% of brain metastases are located in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem.[13] For unclear reasons, pelvic (prostate and uterus) and gastrointestinal tumors have a predilection to metastasize to the posterior fossa.[13]

Clinical Manifestations

It is estimated that more than two-thirds of patients with cerebral metastases experience neurologic symptoms during the course of their illness.[7] The clinical features of brain metastases are extremely variable, and the presence of brain metastases should be suspected in any cancer patient who develops new neurologic symptoms. The majority of patients with brain metastases present with progressive neurologic dysfunction resulting from a gradually expanding tumor mass and the associated edema, or, rarely, from the development of obstructive hydrocephalus. Approximately 10% to 20% of patients present acutely with seizures, while another 5% to 10% present acutely as a result of strokes caused by embolization of tumor cells, invasion or compression of an artery by tumor, or hemorrhage into a metastasis.[8,14,15] Melanoma, choriocarcinoma, and thyroid and renal carcinomas have a particular propensity to bleed.[8] The clinical presentation of brain metastases is similar to that of other brain tumors and includes headaches, focal neurologic dysfunction, cognitive dysfunction, and seizures. Headaches occur in approximately 40% to 50% of patients with brain metastases. These are usually dull, nonthrobbing, and often indistinguishable from tension headaches.[16] The headaches are usually on the same
side as the tumor, although they can be diffuse. Headaches characteristic of increased intracranial pressure, such as early morning headaches, or headaches exacerbated by coughing, bending, and straining, are present in less than half of patients with brain metastases. The headaches may be associated with nausea, vomiting, and transient visual obscurations. Patients with multiple metastases and posterior fossa metastases have a higher frequency of headaches.[1] Papilledema is observed in fewer than 10% of patients at the time of presentation.

Focal neurologic dysfunction is the presenting symptom in 20% to 40% of patients. Hemiparesis is the most common complaint, but the precise symptom varies depending on the location of the metastases.[1] Cognitive dysfunction, including memory problems and mood or personality changes, are the presenting symptoms in one-third of patients, while seizures are the presenting symptom in another 10% to 20%.[17-20]

**Diagnosis**

Brain metastases must be distinguished from primary brain tumors, abscesses, demyelination, cerebral infarctions or hemorrhages, progressive multifocal leukoencephalopathy, and the effects of treatment, including radiation necrosis. In a study by Patchell et al, 11% of patients who were initially felt to have a single brain metastasis eventually were found to have a different diagnosis after the lesion was biopsied.[21] Half of the nonmetastatic lesions were primary brain tumors, while the other half were infections. The false-positive rate for diagnosis of multiple metastases undoubtedly is significantly lower than the 11% rate for single metastases. Nonetheless, in any patient in whom the diagnosis of brain metastases is in doubt, a biopsy should be performed since this is the only reliable method of establishing the diagnosis.

Breast cancer patients with a single dural-based lesion pose a particular diagnostic dilemma. Since the incidence of meningiomas is increased in patients with breast cancer, it is important to differentiate a dural-based metastasis from a meningioma.[22,23] Frequently, imaging studies are inconclusive, and a biopsy or surgical resection of the lesion is needed.

In addition to diagnosing brain metastases, it is also important to differentiate patients with a single or solitary metastasis from those with multiple brain metastases since their subsequent treatment differs. The term “single brain metastasis” refers to a single cerebral lesion, with no implication made regarding the extent of extracranial disease. “Solitary brain metastasis” describes the relatively rare occurrence of a single brain metastasis that is the only known site of metastatic cancer in the body.[1]

Although computed tomographic (CT) scans detect the majority of brain metastases, the best diagnostic test for brain metastases is contrast-enhanced MRI.[12,24,25] This test is more sensitive than enhanced CT scanning or nonenhanced MRI in detecting lesions in patients suspected of having cerebral metastases, and in differentiating these metastases from other central nervous system (CNS) lesions.[24,25] Radiographic features that help differentiate brain metastases from other CNS lesions include the presence of multiple lesions (which helps distinguish metastases from gliomas or other primary tumors), localization of the lesion at the gray-white matter junction, more circumscribed margins, and relatively large amounts of vasogenic edema compared to the size of the lesion.[7]

In the majority (80%) of patients, brain metastases develop after the diagnosis of systemic cancer (metachronous presentation).[1,2] However, in some patients, brain metastases may be diagnosed before the primary tumor is found (precocious presentation) or at the same time as the primary is detected (synchronous presentation).

For patients who present with brain metastases without a known primary tumor, the lung should be the focus of the evaluation. Over 60% of these patients will have a lung primary or pulmonary metastases from a primary tumor located elsewhere.[1,26,27] If the chest radiograph is nondiagnostic, a chest CT scan should be performed, as this significantly increases the likelihood of detecting a lung tumor.[26] These patients also should have a CT scan of the abdomen and pelvis and a bone scan to determine the extent of metastatic disease. Breast cancer is an uncommon cause of brain metastases without a known primary tumor, possibly due to its earlier detection on physical examination, and its tendency to produce brain metastases in the setting of widely disseminated disease. [27]

**Management Goals**

The management of patients with brain metastases can be divided into symptomatic and definitive therapy. Symptomatic therapy includes the use of corticosteroids for the treatment of peritumoral
edema, anticonvulsants for control of seizures, and anticoagulants or inferior vena cava filters for the management of venous thromboembolic disease.[8] Definitive therapy includes treatments directed at eradicating the tumor itself, such as surgery, radiotherapy, and chemotherapy.

Symptomatic Therapy

Corticosteroids
Corticosteroids were first used for treating peritumoral edema by Kofman et al in 1957 in patients with breast cancer.[28] Galicich et al introduced the use of dexamethasone in 1961,[29] and this has remained the standard treatment for peritumoral edema ever since. Corticosteroids produce their antiedema effect by reducing the permeability of tumor capillaries, [30] and are indicated in any patient with symptomatic edema.

Most patients are started on dexamethasone, which, compared with other corticosteroids, has relatively little mineralocorticoid activity, thus reducing the potential for fluid retention. In addition, dexamethasone may be associated with a lower risk of infection and cognitive impairment.[30] Dexamethasone therapy is usually started as a 10-mg loading dose, followed by 4 mg four times a day; however, there is some evidence that lower doses may be as effective.[31] Although most patients improve symptomatically within 24 to 72 hours, neuroimaging studies may not show a decrease in the amount of edema for up to 1 week.[32] In general, headaches tend to respond better than do focal deficits. If 16 mg of dexamethasone is insufficient, the dose may be increased up to 100 mg/d. Steroid dose is usually tapered following irradiation, although the tapering process may begin earlier in patients with minimal peritumoral edema.

Adverse Effects—Despite their usefulness, corticosteroids are associated with a large number of well-known side effects, including myopathy, weight gain, fluid retention, hyperglycemia, insomnia, gastritis, acne, and immunosuppression.[33] The frequency of these complications can be reduced by using the lowest possible dose.

There is increasing evidence that brain tumor patients who receive corticosteroids are at increased risk of developing Pneumocystis carinii pneumonia.[34] This complication can be prevented by treating patients who are on prolonged courses of a corticosteroid, especially those over the age of 50 years, with trimethoprim/sulfamethoxazole prophylaxis.[7]

Anticonvulsants
As mentioned previously, seizures are the presenting symptom in approximately 10% to 20% of patients with brain metastases, and occur at some stage of the illness in another 10% to 20% of patients.[17-20] Patients with brain metastases who present with seizures should be treated with standard anticonvulsants. In order to minimize toxicity, the lowest effective anticonvulsant dose should be used and polytherapy should be avoided whenever possible. Electroencephalography may be useful if the diagnosis of seizures is in doubt but is not routinely needed for patients who give a clear history of seizures or, conversely, do not have symptoms suggestive of seizures.

Adverse Effects and Drug Interactions—In addition to the usual complications of anticonvulsants, brain tumor patients experience an increased incidence of particular side effects, especially drug rashes. Approximately 20% of brain tumor patients treated with phenytoin and undergoing cranial irradiation develop a morbilliform rash and a small percentage develop Stevens-Johnson syndrome.[35,36] Stevens-Johnson syndrome also has been described in brain tumor patients receiving carbamazepine,[37] while patients receiving phenobarbital have an increased incidence of shoulder-hand syndrome.[38]

In addition to producing adverse effects, anticonvulsants also have clinically significant interactions with other drugs commonly used in patients with brain metastases. Phenytoin induces the hepatic metabolism of dexamethasone and significantly reduces its half-life and bioavailability.[39]

Conversely, dexamethasone may also reduce phenytoin levels.[40]

A number of chemotherapeutic agents commonly used in cancer patients interact with phenytoin, causing serum drug levels to fall and potentially leading to breakthrough seizures.[41] Also, hepatic enzyme–inducing anticonvulsants, such as phenobarbital and phenytoin, may interfere with chemotherapeutic agents, such as paclitaxel (Taxol).[42]

Role in Patients With Supratentorial Metastases—Because the risk of seizures in patients with infratentorial metastases is very low, anticonvulsant therapy usually is not indicated. The role of anticonvulsant therapy in patients with supratentorial brain metastases who have not had a seizure is controversial.

Cohen et al retrospectively reviewed 160 patients with brain metastases who had not suffered a seizure. They found that patients receiving prophylactic phenytoin had the same frequency of late
seizures (10%) as did patients receiving no antiseizure prophylaxis.[18] Glantz et al conducted a prospective, placebo-controlled, randomized study evaluating the efficacy of valproic acid in protecting 74 patients with newly diagnosed brain metastases from seizures.[19] There was no significant difference in the incidence of seizures between patients receiving valproic acid (35%) or placebo (24%), suggesting that prophylactic anticonvulsants were not effective in these patients.

Weaver et al conducted a prospective, randomized study of prophylactic anticonvulsants in 100 brain tumor patients who had not had seizures, including 60 with metastases.[20] Overall, 26% of patients had seizures during the study. There was no difference in the seizure rate between patients who did and did not receive anticonvulsants.

Recently, Glantz et al performed a meta-analysis of the randomized clinical trials addressing this issue. They concluded that there is no statistical evidence showing a significant benefit of prophylactic anticonvulsants.[43]

Recommendations—Because of the increased incidence of allergic reactions in patients with brain metastases receiving anticonvulsant therapy, and the lack of clear evidence that anticonvulsant therapy reduces the incidence of seizures, routine anticonvulsant therapy is probably unnecessary in patients with brain metastases who have not experienced a seizure. Possible exceptions to this are patients with brain metastases in areas of high epileptogenicity (eg, the motor cortex), patients with multiple metastases from melanoma,[44] and patients with both brain metastases and leptomeningeal metastases.[8] These patients have a higher incidence of seizures and may benefit from prophylactic anticonvulsant therapy.

Treatment of Venous Thromboembolic Disease

Venous thromboembolic disease is common in patients with brain metastases, occurring in approximately 20% of patients.[45] The optimal therapy is unknown. These patients are often perceived to be at increased risk of intracranial hemorrhage when treated with anticoagulants because of the vascularity of the tumors and anecdotal case reports of hemorrhage. As a result, the majority of brain metastases patients with venous thromboembolic disease are managed with inferior vena cava filtration devices rather than anticoagulation. However, Levin et al found that complications occur in up to 60% of brain tumor patients with venous thromboembolic disease who are treated with inferior vena cava filters.[46]

Moreover, several retrospective studies have suggested that the risk of intracranial hemorrhage may not be significantly increased in patients with primary brain tumors who are anticoagulated after the immediate postoperative period.[47] More recently, Schiff and DeAngelis reviewed the Memorial Sloan-Kettering experience with anticoagulation in patients with brain metastases who developed venous thromboembolic disease.[48] Of the 42 patients who received anticoagulation at some stage of their treatment, only 3 (7%) experienced cerebral hemorrhage, 2 in the setting of overanticoagulation.

These studies suggest that anticoagulation may be more effective than inferior vena cava filter placement, and is aceptably safe when the prothrombin time is maintained within the normal range, especially in patients with brain metastases that generally do not hemorrhage, such as breast cancer.

Definitive Treatment

The definitive management of brain metastases is directed at relieving neurologic symptoms and achieving long-term tumor control. The therapeutic modalities available include surgery, radiotherapy, radiosurgery, chemotherapy, and hormonal therapy. The optimal combination of therapies for each patient depends on a careful evaluation of numerous factors, including the location, size, and number of brain metastases; the patient’s age, general condition, and neurologic status; and the extent of the systemic cancer, as well as its response to past therapy and its potential response to future treatments.[7]

Surgery

The goals of surgery in patients with brain metastases are: to provide immediate relief of symptoms resulting from the mass effect of the tumor; to establish a histologic diagnosis; and to improve local control of the tumor. Recent advances in neuroanesthesia and neurosurgery, including the use of computer-assisted stereotaxy, intraoperative functional mapping, intraoperative ultrasound, and functional and intraoperative MRI, have significantly improved the safety of surgical resection of brain metastases.[7,49,50]

For patients who are candidates for surgery, the most important factor to consider is the extent of
extracranial disease (Figure 1a, Figure 1b, Figure 1c and Figure 1d). Patients with extensive systemic disease generally have a very limited prognosis and only rarely benefit from surgery. Other important factors influencing the decision concerning surgery include the presence of single or multiple metastases, the location of the tumor, the neurologic status of the patient, and the interval between diagnosis of the primary neoplasm and the brain metastasis.[7,51-53]

**Single Brain Metastasis**—Until relatively recently, the optimal therapy for patients with a single brain metastasis was controversial. A number of uncontrolled, retrospective studies had suggested that patients with a single brain metastasis who underwent surgical resection in addition to radiotherapy generally had better outcomes than patients who were treated with radiotherapy alone. However, these studies were limited by the inevitable selection bias resulting from the inclusion in surg-ical series of patients in better condition.[10,51-57] Three randomized, prospective studies have now evaluated the role of surgery as an adjunct to whole-brain radiation therapy (WBRT) in patients who have a single brain metastasis.[21,58-60] Patchell et al[21] were the first to address this issue in a prospective, randomized study. They randomly assigned 54 patients with or without active systemic cancer and a single brain metastasis to receive either biopsy of the metastasis followed by whole-brain radiation (36 Gy in 12 fractions) or surgical resection followed by radiotherapy. Of the 54 original patients, 6 (11%) did not have a metastasis and were excluded from the study, leaving 48 patients.

The patients treated with surgery and whole-brain radiation had fewer local recurrences than did those who received whole-brain radiation alone (20% vs 52%), as well as improved survival (40 vs 15 weeks) and a better quality of life, as measured by Karnofsky performance status. The median time to recurrence for patients receiving surgery and radiotherapy was > 59 weeks, as compared with 21 weeks for patients receiving whole-brain radiotherapy alone. Multivariate analysis showed that the factors that correlated significantly with increased survival were surgical treatment of the metastasis, the absence of extracranial disease, longer time to the development of the brain metastasis, and younger age.

A second, prospective, randomized trial evaluating the role of surgery in patients with a single brain metastasis was conducted by Vecht et al.[58,59] In this study, 63 patients with a single brain metastasis (documented by CT scanning) were randomized to receive either surgery and whole-brain radiation or whole-brain radiation alone. The radiotherapy dose was an unconventional scheme of two fractions per day of 2 Gy each, for a total of 40 Gy given over 2 weeks. Unlike the study of Patchell et al, patients in this study who were randomized to radiotherapy alone did not undergo a stereotactic biopsy to confirm the diagnosis of metastasis, and MRI was not performed to exclude multiple small metastases that may have been missed by CT imaging.

The overall survival of patients treated with surgery and radiotherapy was significantly longer than that of patients treated with radiotherapy alone (10 vs 6 months; P = .04). In addition, combined-modality treatment also resulted in significantly increased functionally independent survival (7.5 vs 3.5 months; P = .06). The greatest benefit of surgery plus whole-brain radiation was seen in patients with stable extracranial disease (median survival, 12 vs 7 months; median functionally independent survival, 9 vs 4 months). Patients with active extracranial disease had a median survival of only 5 months and a functionally independent survival of 2.5 months and did not appear to benefit from the addition of surgery. This is consistent with the concept that the extent of systemic disease largely determines patient survival and overrides any potential advantage that the addition of surgery may provide in controlling the brain metastasis.[6,7]

Patients over 60 years old had decreased survival rates compared to younger patients (hazard ratio of dying, 2.74; P = .001). This finding is consistent with the general importance of age as an adverse prognostic factor in patients with brain tumors.

In contrast to these two studies, a more recent, multicenter, randomized study conducted by Mintz et al failed to detect a difference in survival or quality of life between patients who underwent surgery plus radiotherapy and those who had radiotherapy alone.[60] In this study, the 43 patients randomized to radiotherapy alone had a median survival of 6.3 months, as compared with a median survival of only 5.6 months in the 41 patients randomized to surgery plus radiotherapy. The failure of this study to demonstrate that the addition of surgery to radiotherapy improved patient outcome may be due to the fact that it included patients with a lower baseline median Karnofsky performance score and a higher proportion of patients with extracranial disease.[60,61]

A fourth study, conducted by the Radiation Therapy Oncology Group (RTOG) and the Southwest Oncology Group (SWOG), was initially intended to be a randomized comparison of surgery plus
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radiotherapy vs radiotherapy alone.[62] However, because of poor patient accrual, the study’s design was changed to a prospective physician preference trial. Ultimately, 80 of the 97 registered patients were evaluable. After correction for other prognostic factors, patients treated with surgery and radiotherapy showed greater neurologic improvement than did patients receiving whole-brain radiation alone (79% vs 59%), as well as decreased recurrence (22% vs 45%) and improved survival.[62]

Overall, these studies provide support for the use of surgery in addition to whole-brain radiation in patients with a single brain metastasis and stable extracranial disease.

**Multiple Brain Metastases**—The role of surgery in patients with multiple brain metastases is usually limited to: resection of a large, symptomatic, or life-threatening lesion; obtaining tissue for diagnosis in patients without a known primary tumor; or differentiating a brain metastasis from other cerebral lesions such as a meningioma.[7] However, as surgical techniques have improved, the feasibility of resecting multiple lesions has increased.

In one study, Bindal et al evaluated the efficacy of surgery in 56 patients with multiple brain metastases.[63] These patients were divided into those who had one or more lesions remaining after surgery (group A; N = 30) and those who had all lesions removed (group B; N = 26). Also, the patients in group B were matched (by tumor type, presence or absence of extracranial disease, and time from diagnosis of primary tumor to diagnosis of brain metastases) to patients undergoing surgery for a single metastasis (group C; N = 26).

The median survival durations for patients in groups A, B, and C were 6, 14, and 14 months, respectively. These results suggest that if all lesions can be removed surgically in patients with multiple brain metastases, the outcome is significantly improved, and is comparable to the outcome of patients who undergo surgery for a single lesion.

However, in contrast to this study, Hazuka et al[64] found that surgery was of little benefit in patients with multiple brain metastases. They described a series of 28 patients with a single metastasis and 18 patients with multiple metastases. The patients with multiple metastases who underwent surgery and radiation therapy had a median survival of only 5 months, compared to a 12-month median survival for patients with single brain metastases.

In the studies of both Bindal et al and Hazuka et al, surgical morbidity and mortality for patients with multiple brain metastases were low and were comparable to morbidity and mortality reported for patients with a single metastasis undergoing surgery. However, the conflicting results of the two studies make it difficult to draw firm conclusions regarding the value of surgical resection in patients who have multiple brain metastases.

**Recurrent Metastatic Brain Tumors**—Surgery may have a role in patients who develop recurrent disease after standard treatment for brain metastases, especially in those with a single, symptomatic lesion. In an early study, Sundaresan et al reported the results of reoperation in 21 patients with brain metastasis.[65] Two-thirds of the patients experienced neurologic improvement after the second surgery; this improvement lasted a median of 6 months. No patient died, and only one patient experienced a worsening of neurologic deficits after surgery.

Bindal et al reviewed 48 patients who underwent reoperation for recurrent brain metastasis at M. D. Anderson Cancer Center.[66] The median interval between the first craniotomy and the diagnosis of recurrence was 6.7 months, and the median survival time after reoperation was 11.5 months. Following surgery, symptoms improved in 75% of patients and deteriorated in 10.4% of patients. There was no operative mortality.

Multivariate analysis revealed that survival was negatively affected by the presence of systemic disease (P = .008), Karnofsky performance status < 70 (P = .008), time to recurrence < 4 months (P = .008), age > 40 years (P = .051), and primary tumor type of breast or melanoma (P = .028).

Arbit et al reported on 109 patients with recurrent brain metastases from non-small-cell lung cancer who were treated at Memorial Sloan-Kettering Cancer Center.[67] Of these patients, 32 (30%) underwent a reoperation. The median interval between the first and second operation was 5 months. The median survival duration following the second operation was 10 months. Patients who underwent reoperation survived significantly longer than the 77 patients who did not undergo a second procedure (median survival from the time of the first operation, 15 vs 10 months; P < .001). These results provide support for surgical resection of recurrent brain metastases in selected patients with symptomatic lesions. Factors that should be considered when deciding whether surgery is advisable include: the length of time since the initial operation, the location of the recurrent tumor, the age and performance status of the patient, the extent of extracranial disease, and the radiosensitivity of the tumor.[6,68] In general, the sooner the metastasis recurs after the initial resection, the less likely it is that a second operation will provide a significant period of
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Radiation Therapy

Radiation therapy has been the mainstay of treatment for patients with brain metastases for nearly 40 years. Overall, conventional whole-brain radiation therapy increases median survival to 3 to 6 months.[1,10] Radiation is effective in the palliation of neurologic symptoms and also significantly decreases the likelihood of death due to neurologic causes. Unfortunately, for most patients, overall survival is more likely to be determined by the activity and extent of extracranial disease than by success or failure of radiation therapy or surgery in controlling brain metastases.

The main goal of radiation therapy is to improve neurologic deficits caused by the tumor deposit. The published overall response rate is symptom-dependent, but ranges from 64% to 85%.[17,69,70] In one study, 74% of patients had improvement of neurologic symptoms, such as headaches, with radiation therapy, and 65% maintained this improvement for the duration of their lives or for at least 9 months.[71] Cranial nerve deficits improve in approximately 40% of patients. However, the potential for improvement is directly related to the time from diagnosis to radiation therapy.[7] Early treatment is generally associated with a better outcome. The majority of patients with significant neurologic dysfunction improve with the use of steroids and radiotherapy, while less than 50% of patients with moderate neurologic dysfunction will improve following therapy.[70]

Optimal Dose-Fractionation Schedule—The optimal dose-fractionation schedules for patients with brain metastases have been evaluated in randomized trials conducted by the RTOG.[72,73] Two RTOG trials of several dose-fraction schedules were subsequently reported together.[70] In the first trial, patients were randomized to 40 Gy in 4 weeks, 40 Gy in 3 weeks, 30 Gy in 3 weeks, or 30 Gy in 2 weeks. The second trial randomized patients to 40 Gy in 3 weeks, 30 Gy in 2 weeks, or 20 Gy in 1 week.

The overall response and median survival rates were equivalent in all arms of these studies. Median survival was 18 weeks in the first trial and 15 weeks in the second. Brain metastasis was the cause of death in 40% of patients in both trials. Patients treated in the shortest time and with larger fractions responded more quickly, but the duration of the clinical response and the time to progression were similar in each treatment arm. Symptoms were palliated in 75% to 80% of the patients in all treatment arms of these protocols.[73] In order to explore the efficacy and toxicity of ultrarapid treatment schedules, the RTOG treated 26 patients with 10 Gy in one fraction and 36 patients with 12 Gy in two fractions.[74] The promptness of response, percentage of patients demonstrating neurologic improvement, and overall survival with this schedule were similar to the results obtained with more protracted schedules described above. However, the median duration of improvement with ultrarapid treatment was only 4 weeks, compared to 10 weeks in the protracted radiotherapy trials.

While these RTOG studies failed to identify the best dose and fractionation schedule for the treatment of brain metastasis, they enabled the identification of clinical factors associated with better survival.[75,76] Patients with breast cancer and no soft-tissue metastases, ambulatory lung cancer patients with no extracranial disease, and other ambulatory patients with no extracranial metastases had a median survival of 28 weeks, as compared with 11 weeks for the remaining patients. There was no survival advantage to any fractionation scheme even among this select group of patients.

In order to examine the role of radiation dose escalation in this prognostically favorable subset of patients with brain metastases, the RTOG randomized 309 of these patients to either 30 Gy in 10 fractions or 50 Gy in 20 fractions.[77] The median survival of patients in the 30-Gy arm was 18 weeks and that of patients in the 50-Gy arm was 17 weeks, suggesting that there was no therapeutic benefit to dose escalation.

Accelerated fractionation is another approach that has been explored to improve the results of whole-brain radiation in patients with brain metastases. This technique uses multiple daily fractions of radiotherapy, with the goals of decreasing overall treatment time and reducing the risk of tumor cell repopulation. The RTOG performed a phase I/II trial of accelerated fractionation in patients with single or multiple brain metastases with controlled, stable or absent primary disease, or those with uncontrolled primary disease but no evidence of extracranial metastases. [78] The entire brain was treated twice daily with 1.6-Gy fractions to a total dose of 32 Gy; subsequently, a boost was administered twice daily to encompass all of the disease. The boost dose was increased in successive groups from 16 Gy to 22.4 Gy to 32 Gy to 42.4 Gy. Median survival increased from 4.2 months at a total dose of 48 Gy to 5.3 months at 54.4 Gy to 4.8 months at 60 Gy to 6.4 months at 70.4 Gy.
Based on these encouraging results, the RTOG conducted a randomized, phase III study comparing accelerated hyperfractionated radiotherapy (1.6 Gy twice daily, to a total dose of 54.4 Gy) vs standard therapy (30 Gy in 10 daily fractions) in patients with unresected brain metastases, limited systemic disease, and good Karnofsky performance status (≥ 70). There were 429 evaluable patients, two-thirds of whom had lung primaries. Unfortunately, the median survival in both groups was 4.5 months, suggesting that accelerated hyperfractionation provided no benefit over conventional therapy. [79]

**Radiation Sensitizers**—The use of biochemical modification of radiation effect (radiation sensitizers) has also been explored in patients with brain metastases. However, the results to date have generally been disappointing. Studies using radiosensitizers, such as misonidazole[80] and bromodeoxyuridine,[81] failed to show any additional benefit over radiation therapy alone. Nonetheless, there continues to be interest in radiation sensitizers, and newer agents, such as gadolinium texaphyrin, are currently being evaluated in clinical trials.

**Recommendations**—There is currently no consensus on the optimal radiation schedule for patients with brain metastases. Standard treatment regimens for brain metastasis include all of the dose ranges evaluated in the early RTOG studies[70] and depend on such issues as the severity of CNS symptoms, extent of systemic disease, and physician preference. Typical radiation treatment schedules consist of total doses of 30 to 50 Gy in 1.5- to 4-Gy daily fractions. The most commonly employed treatment schedule is 30 Gy in 10 fractions over 2 weeks. For patients with a good prognosis who are likely to survive more than 1 year, more prolonged fractionation (eg, 40 Gy in 2-Gy fractions) may reduce long-term morbidity from radiation.

**Postoperative Radiation Therapy**
The goal of postoperative whole-brain radiation in patients with solitary brain metastasis is to destroy microscopic residual cancer cells at the site of resection and at other locations within the brain. Theoretically, this should reduce the recurrence rate and prolong survival. Although it is standard practice for patients to receive postoperative radiotherapy as an adjuvant to surgery, until recently, the value of this approach was based solely on the results of retrospective studies (Table 1).[82-87] Some of these studies demonstrated that adjuvant whole-brain radiation reduced the recurrence rate, [83,84,87] and two studies demonstrated a prolongation of survival.[83,87] Recently, Patchell et al published the results of a randomized trial that examined the role of postoperative whole-brain radiation in patients with a single metastasis.[88] In this study, 95 patients underwent surgical resection of the metastasis and were then randomly assigned to treatment with whole-brain radiation (50.4 Gy in 28 fractions) or no further treatment. Patients who received radiation were significantly less likely to suffer a treatment failure in the brain than those who were not irradiated (18% vs 70%; P < .001), and this was true at both the original site of disease (10% vs 46%; P < .001) and other areas of the brain (14% vs 37%; P < .01). Treated patients also were less likely to die of neurologic causes than untreated patients (14% vs 44%; P = .003), but there was no difference in overall survival (48 vs 43 weeks; P = .39) or duration of functional independence (37 vs 35 weeks; P = .61) between the treated and untreated groups. The results of this study suggested that postoperative whole-brain radiation significantly reduces the incidence of neurologic death in patients with a resected solitary metastasis but has little impact on overall survival, which depends mainly on the extent of systemic disease. The authors concluded that the reduction of neurologic death justifies the routine use of postoperative radiotherapy. However, it remains unclear whether there are certain groups of patients, such as those with radioresistant tumors (eg, melanoma or renal cell cancer), for whom whole-brain radiation may not be useful after complete surgical resection of the metastases. Also, the long-term neurocognitive complications of postoperative radiation therapy have not been fully evaluated.

**Late Radiation Toxicity**
An important benefit of aggressive treatment for brain metastases is the likelihood that some patients will become long-term survivors. In these patients, late complications of whole-brain radiation can be debilitating. These complications include leukoencephalopathy and brain atrophy, leading to neurocognitive deterioration and dementia; brain necrosis, resulting in more specific neurologic sequelae (depending on the site of necrosis); and communicating hydrocephalus, causing cognitive, gait, and bladder dysfunction.[8,33,89] Neuroendocrine dysfunction, such as hypothyroidism, may also occur.[33]

The risk of late complications from whole-brain radiation is related to total dose, fraction size, patient age, extent of disease, and neurologic impairment at presentation.[90] Prior or concurrent chemotherapy may also affect the occurrence of late CNS toxicity.

If whole-brain radiation is to be given, a dose-fraction schedule should be utilized that takes into
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account the patient’s overall clinical status while maximizing the palliation of symptoms and, if appropriate, minimizing the risk of long-term complications. In a retrospective review by DeAngelis et al of 70 patients treated with postoperative radiation therapy using ≥ 300-cGy fractions, 11% showed evidence of dementia.[89] Therefore, patients with a good prognosis, such as those with a single brain metastasis and no or controlled systemic disease, are best treated with daily fractions of ≤ 200 cGy (eg, 40 to 45 Gy in 1.8- to 2.0-Gy daily fractions) to decrease the likelihood of long-term CNS toxicity.

Reirradiation
Occasionally, patients are reirradiated with whole- or partial-brain radiotherapy at the time of brain recurrence. The percentage of patients who undergo reirradiation is quite small, since most patients whose disease recurs within the CNS also have progressive extracranial disease and are treated with supportive measures only. However, there are times when recurrence of brain metastasis develops in a patient with controlled systemic disease.

Patients with a solitary or a few (≤ 3) metastases are candidates for treatment with radiosurgery (see discussion below), as this modality will have less toxicity than repeat whole-brain radiation and is more likely to be effective than systemic therapy. Other patients should be considered for treatment with systemic chemotherapy or hormonal therapy.

For patients who are not eligible for radiosurgery or systemic therapy, treatment with whole- or partial-brain reirradiation may be indicated. Several retrospective studies have addressed this issue.[91-94] Overall clinical response rates range from 42% to 75%, and median survival from the time of reirradiation varies from 3.5 to 5 months.

The published techniques of reirradiation include doses from 8 Gy in 2 weeks to 30.6 Gy in 3 weeks (median, ~ 20 Gy in 2 weeks). However, there is no consensus as to which dose-fractionation schedule is most appropriate or the optimal interval between the initial course of radiation and reirradiation.[94] Some investigators have argued that reirradiation should be considered for patients who remain in good general condition but experience neurologic deterioration 4 or more months after a satisfactory response to the initial course of whole-brain radiation. [94] The tolerance of the brain is more than likely to be exceeded by reirradiation, but with the limited survival of these patients, there are inadequate data to evaluate the consequences of this treatment.

Stereotactic Radiosurgery
Stereotactic radiosurgery is a technique of external irradiation that utilizes multiple convergent beams to deliver a high single dose of radiation to a radiographically discrete treatment volume. [7,95] Radiosurgery can be performed with high-energy x-rays produced by linear accelerators, with gamma rays from the gamma knife, and, less frequently, with charged particles, such as protons, produced by cyclotrons.[95]

All of the stereotactic radiation techniques result in a rapid fall-off of dose at the edge of the target volume, resulting in a clinically insignificant radiation dose to normal, nontarget tissue. Metastases are usually small (< 3 cm), radiographically discrete lesions that are noninvasive, making them ideal targets for radiosurgery.

An increasing number of uncontrolled studies have confirmed the effectiveness of stereotactic radiosurgery in treating brain metastases (Table 2). Radiosurgery produces local control rates of 73% to 94% and is associated with a 5% to 10% risk of radiation necrosis.[7,96-106]

In a multi-institution trial involving 116 patients treated with radiosurgery (mean dose, of 17.5 Gy) for a single brain metastasis, local tumor control was obtained in 99 patients (85%).[98] The 2-year actuarial tumor control rate for the whole group was 67% ± 8%, with a plateau in the curve at 18 months. Multivariate analysis showed that better local control was obtained in patients who received whole-brain radiation in addition to radiosurgery and in patients with “radioresistant” histologies (melanoma and renal cell carcinoma).

In the largest series reported to date, Alexander et al reported on the results of radiosurgery using a linear accelerator in 248 patients with 421 metastatic lesions.[96] At the time of radiosurgery, 77 patients had no evidence of systemic disease while 171 had stable systemic disease. Of the lesions treated, 126 were classified as “radioresistant” (melanoma, renal cell carcinoma, and sarcoma), with the remaining 295 lesions representing all other histologies.

With a median observation period of 26 months, 48 (11%) of 421 lesions progressed within the radiosurgery volume. The actuarial 1-, 2-, and 3-year local control rates were 85%, 65%, and 65%, respectively. Control rates for radioresistant histologies were statistically equivalent to rates for other lesions.

The median survival time for the whole group, measured from the radiosurgery treatment, was 9.4 months. In a multivariate analysis, factors associated with improved survival included the absence of
systemic disease (relative risk [RR], 4.4; P = .0001) and age < 60 years (RR, 1.6; P = .002). The development of symptomatic radiation necrosis requiring reoperation for increasing mass effect and steroid dependency occurred in 7% of patients in this series.

**Radiosurgery vs Conventional Surgery**—The studies by Patchell et al [21] and Vecht et al [58,59] indicate a survival advantage for patients with a single brain metastasis who are treated with surgery and radiotherapy, compared to patients treated with radiotherapy alone (Table 3). Many clinical investigators believe that radiosurgery can serve as an alternative to surgical resection [97-99,103,106].

Moreover, radiosurgery has several potential advantages over surgery. It can be used to treat metastases in surgically inaccessible areas of the brain, such as the brainstem. Since radiosurgery is a noninvasive procedure that can be performed on an outpatient basis, it is associated with less morbidity than surgery. In addition, there is increasing evidence that radiosurgery may also be more cost-effective than surgery [106,107]. In a study by Mehta et al, the average cost per week of survival was $310 for radiotherapy, $524 for resection plus radiation, and $270 for radiosurgery plus radiation [107].

While there are no completed randomized trials comparing radiosurgery to surgery, Auchter et al [99] identified 122 patients who met the selection criteria used by Patchell et al [21] and were treated with whole-brain radiation (median dose, 37.5 Gy) followed by a radiosurgery boost (median, 17 Gy). The overall local control rate was 86%, with an actuarial median survival of 56 weeks and a median duration of functional independence (Karnofsky performance status > 70) of 44 weeks. These results are comparable to the results of the surgery and radiation therapy arms of the studies of Patchell et al [21] and Vecht et al [58,59] studies and are better than the results of the whole-brain radiation-alone arms.

In contrast, Bindal et al retrospectively compared 34 consecutive patients treated with radiosurgery with 62 clinically matched patients treated with conventional surgery [108]. The median survival for patients treated surgically was 16.4 months, compared to 7.5 months for those treated with radiosurgery (P = .0009). Based on these results, the authors concluded that surgery was superior to radiosurgery for the treatment of a single brain metastasis. However, the low local control rate in the radiosurgically treated patients (61%) and differences in the extent of systemic disease between the surgery and radiosurgery groups may have accounted for the poor results of radiosurgery.

Brandt et al also compared surgery and radiosurgery in a series of 56 patients [109]. In this study, the median survival of the radiosurgically treated patients was 11.4 months, comparable to the 10.4-month median survival for the surgically treated patients.

Ideally, a prospective, randomized study comparing surgery to radiosurgery for the treatment of single brain metastases would resolve the issue of the relative efficacy of these two therapies. However, attempts to conduct such a study have been unsuccessful so far due to poor patient accrual resulting from patient and/or physician preference for either surgery or radiosurgery.

**Whole-Brain Radiation Plus Radiosurgery**—The role of whole-brain radiation in patients treated with radiosurgery is controversial, especially in patients with relatively radioresistant tumors, such as melanoma [103,106]. In a recent study by Patchell et al [88], 37% of patients treated with radiosurgery suffered a failure in other sites within the brain if they did not also receive whole-brain radiation. Although some studies have shown improved local control in patients who received whole-brain radiation in addition to radiosurgery [98], most such studies have shown no increase in overall patient survival [96,105,106].

Currently, most centers treat patients with brain metastases with both radiosurgery and whole-brain radiation, and limit the use of up-front radiosurgery alone to cases for which there are no alternatives, such as patients who have had prior high-dose radiation to the head and neck area or those who refuse to undergo whole-brain radiation. However, further studies are needed to clarify this issue.

**Recommendations**—The introduction of radiosurgery over the past decade represents one of the major advances in the treatment of brain metastases. Young patients with good performance status, limited extracranial disease, and one or two small lesions are particularly suited to this form of treatment [96,106]. Adverse prognostic factors include poor performance status (< 70), progressive systemic disease, large tumor size, infratentorial location [101], and multiplicity of metastases (two or more lesions) [104].

For patients with a single, small, asymptomatic or mildly symptomatic lesion, radiosurgery probably can be used as a substitute for surgery with comparable outcomes [99,109]. Radiosurgery also has an important role in patients who experience a recurrence of brain metastasis following whole-brain radiation (Figure 1a, Figure 1b, Figure 1c, and Figure 1d).
Interstitial Brachytherapy
Interstitial brachytherapy involves the implantation of radionuclides into the wall of the surgical cavity, with the objective of delivering an additional dose of radiation to the residual tumor while limiting the amount of radiation to the surrounding brain. The relatively sharp border between metastases and the surrounding brain makes them ideal lesions for brachytherapy. Brachytherapy for brain metastases has been evaluated in several small uncontrolled studies using iodine-125 sources; median survival durations have ranged from 9 to 18.3 months.[110-112]
Although brachytherapy is rarely used to treat small lesions suitable for radiosurgery, it may have a limited role in treating metastases that are too large for radiosurgery.
A more recent brachytherapy strategy involves the use of a photon radiosurgery system. This is a battery-powered, miniature x-ray generator with an attached probe that can be placed stereotactically into metastases at the time of craniotomy to deliver a single fraction of high-dose radiation (12.5 Gy) in less than 1 hour. [112,113] Preliminary results suggest that this procedure is well tolerated and produces effective local tumor control. [112,113]

Chemotherapy
The role of chemotherapy in the treatment of patients with brain metastases has not been clearly defined. At present, chemotherapy is rarely used as part of overall management of these metastases. Traditionally, it has been assumed that the blood-brain barrier prevented chemotherapeutic agents from entering the CNS. [114] However, there is evidence that the blood-brain barrier is, in fact, partially disrupted within brain tumors.[114] This suggests that other factors also contribute to the generally disappointing results of chemotherapy for brain metastases. These may include the intrinsic resistance to chemotherapy of many tumors that metastasize to the brain, the use of chemotherapeutic agents designed to penetrate the blood-brain barrier rather than agents known to be most effective against the primary malignancy, and the tendency for brain metastases to develop following the failure of primary chemotherapeutic agents to control systemic disease.[114,115]
Although, the results of chemotherapy for brain metastases have generally been disappointing, a number of uncontrolled studies have demonstrated favorable response rates of brain metastases from chemosensitive tumors such as breast cancer, small-cell lung cancer, and germ cell tumors.[1,114]

Brain Metastases From Breast Cancer—Patients with metastatic breast cancer have been treated with chemotherapy since 1970. In the largest series to date, Rosner et al.[116] treated 100 consecutive breast cancer patients with brain metastases with several chemotherapy regimens, including CFP (cyclophosphamide, fluorouracil, and prednisone) and CFPMV (CFP, methotrexate, and vincristine). Of note, these patients had not received prior chemotherapy for their systemic disease. Overall, 50% of patients had an objective response (10% had a complete response and 40%, a partial response). In addition, disease stabilized in 9% of patients. The median duration of remission was 10 months for complete responders and 7 months for partial responders.
Rosner et al subsequently treated an additional 26 patients with progressive brain metastases from breast cancer with one of four chemotherapeutic regimens: (1) CFP, (2) CFPMV, (3) cyclophosphamide and doxorubicin, or (4) mitomycin (Mutamycin) and vinblastine.[117] Objective responses were seen in 61% of patients, while another 15% had stable disease. The median survival for responders was 12 months, as compared with 2.4 months for nonresponders. Interestingly, prior systemic chemotherapy did not affect the response of the brain metastases, arguing against the concept of the brain as a pharmacologic sanctuary.
Boogerd et al[118] treated 20 patients with brain metastases from breast cancer with CMF (cyclophosphamide, methotrexate, and fluorouracil) or CAF (cyclophosphamide, Adriamycin, and vincristine). Seven patients had developed recurrent disease after whole-brain radiation. Objective tumor regression occurred in 76% of patients after two cycles of chemotherapy. The median duration of neurologic remission was 30 weeks, and the median survival was 25 weeks. When the results of these chemotherapy patients were compared to 29 historical controls treated with whole-brain radiation, the neurologic response rate, duration of response, and median survival were better in the patients treated with chemotherapy.
Several other small series have reported responses to a variety of regimens, including cisplatin (Platinol) plus etoposide[119]; and the TPDC-FuHu regimen, which combines lomustine (CCNU [CeeNu]) with various drugs designed to improve its efficacy, including thioguanine, procarbazine (Matulane), dibromodulcitol, fluorouracil, and hydroxyurea (Hydrea). [120]

Brain Metastases From Small-Cell Lung Cancer—There have also been many studies evaluating the response of brain metastases from small-cell lung cancer to chemotherapy.[114,121] Kristensen
et al reviewed 12 patient series with a total of 116 patients published between 1981 and 1990. [121]
Of the 12 studies, 11 used an epipodophyllotoxin and in 5 it was combined with either cisplatin or carboplatin (Paraplatin).
The overall response rate to chemotherapy without irradiation in patients with intracranial metastases at diagnosis was 76%, while the response rate at relapse was 43%. These results suggest that intracranial metastases from small-cell lung cancer respond to chemotherapy as readily as do other metastatic locations of small-cell lung cancer.

**Brain Metastases From Other Tumors**—Favorable responses to chemotherapy have also been seen in patients who have metastases arising from choriocarcinoma, germ cell tumors, and ovarian cancer. [114, 122,123] The results of chemotherapy for brain metastases from less chemosensitive tumors, such as non-small-cell lung cancer and melanoma, have been generally disappointing. However, newer regimens, such as TPDC-FuHu[120] and carboplatin plus etoposide[124] for non-small-cell lung cancer and temozolomide (Temodal) for melanoma, have produced slightly higher response rates. Overall, these studies suggest that chemotherapy has some activity against brain metastases, especially those from chemosensitive tumors, such as breast cancer, small-cell lung cancer, and choriocarcinoma. In these patients, chemotherapy may have a role as palliative therapy for disease recurring after radiotherapy or, possibly, as initial treatment in patients who have small, asymptomatic tumors. As newer drugs are introduced, the effectiveness of chemotherapy for brain metastases may improve.

**Hormonal Therapy**
In patients with hormone-responsive tumors, such as breast cancer, there are anecdotal reports of patients responding to hormonal agents, such as tamoxifen (Nolvadex)[125] and megestrol acetate.[126]

**Prognosis**
The median survival of patients with untreated brain metastases is approximately 1 month.[127] The addition of steroids increases survival to 2 months,[13,69] while whole-brain radiation further improves survival to 3 to 6 months.[10,69,70,76] Patients with a single brain metastasis and limited extracranial disease who are treated with surgery and whole-brain irradiation have a median survival of approximately 10 to 16 months.[21,56,58,59] Favorable prognostic factors include the absence of systemic disease, young age (< 60 years old), good performance status (Karnofsky performance status \( \geq 70 \)), long time to the development of metastasis, surgical resection, and fewer than three lesions.[1,56,70,76,128-130]

Recently, Gaspar et al performed a recursive partitioning analysis of prognostic factors from three RTOG brain metastases trials and identified three prognostic classes. [129] Class 1 patients had a Karnofsky performance status of 70 or higher, were < 65 years of age, and had a controlled primary and no extracranial metastases; these patients had a median survival of 7.1 months. Class 3 patients consisted of those with a Karnofsky performance status of < 70; their median survival time was 2.3 months. Class 2 patients included all of the remaining patients; these patients had a median survival of 4.2 months. Use of this classification potentially allows new therapies to be evaluated in homogeneous patient groups.[129,130]

**Summary**
Brain metastases represent an increasingly important problem in cancer patients. In recent years, important advances have been made in the diagnosis and management of this condition. As a result, most patients receive effective palliation, and the majority do not die from their brain metastases. However, further studies are needed to define the optimal role of conventional treatments and to develop more effective novel therapies. Until such studies are conducted, treatment algorithms, such as those developed by the National Comprehensive Cancer Network (NCCN; see Figure 2,) can help guide clinical management.

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