Brain metastases are a common complication of systemic cancer and a significant cause of morbidity. For patients whose brain metastases remain untreated, the prognosis is poor. The advent of contrast-enhanced magnetic

common complication of systemic cancer is the development of brain metastases—the predominant type of intracranial neoplasm found in adults. Brain metastases are a significant cause of morbidity, typically due to some combination of peritumoral edema, the effect of the tumor mass itself, or the presence of an obstructive hydrocephalus. Any of these conditions can cause an increase in intracranial pressure. Brain lesions may also directly compress adjacent neurons, resulting in focal irritation or neuron destruction.[1] Not surprisingly, they are an important contributing factor to patient mortality.[1-4] While statistical projections have put the number of patient deaths due to brain and other central nervous system neoplasms at approximately 2.4% (13,300 of 564,800) of all cancer deaths,[5] the actual number is likely to be higher because the death of patients with intracranial metastases is often attributed to underlying systemic disease.[1,2,6-8]

The incidence of brain metastases appears to be increasing,[1,6] possibly as a result of earlier and more accurate methods of detection. Other factors that may contribute to this increase are the success of aggressive treatment modalities that prolong survival, the increasing incidence of primary cancers with a propensity to metastasize to the brain (eg, lung and breast cancer), and the overall aging of the population.[1,8-10]

In 1998, it was projected that more than 1.2 million patients in the United States would be newly diagnosed with cancer.[5] Based on projections regarding the frequency of brain metastases stemming from various types of cancer, and using the high end of the projected ranges[48%, 32%, and 21% for patients with skin, lung, and breast cancer, respectively]we calculated that the yearly incidence of new brain metastases would reach more than 107,000 cases in 1998.[1]

The prognosis for untreated brain metastases is poor, with median survival projected to be 2 months or less.[3,11] While techniques for confirming diagnoses have improved substantially in the past decade or so, a review of the literature suggests that up to one-third of patients are asymptomatic, and consequently many of these metastases go undetected. Autopsy studies show that 24% to 31% of patients with cancer develop intracranial metastases,[9,12-14] and the results of several studies suggest that substantially higher percentages of patients have been diagnosed with intracranial metastases postmortem than during their lifetime. Hirsch et al reported that 21% of patients were clinically diagnosed based on signs and symptoms vs 50% at autopsy,[15] and Amer et al reported that 46% were diagnosed clinically vs 75% at autopsy.[16] Although clinical disease progression is expected to continue up to the time of death, making the development of more tumors likely, these findings still serve to underscore the challenge of diagnosing asymptomatic patients.

Once brain metastases have been successfully diagnosed, there are numerous treatment options to be considered, depending on the patient’s profile and underlying disease. Recent advances in technology and therapeutic techniques have expanded the possibilities for the management of brain metastases through the use of chemotherapy, radiation, surgery, and stereotactic radiosurgery, either alone or in combination.

This review addresses the array of considerations the clinician must weigh in the diagnosis and treatment of patients presenting with brain metastases. Emphasis is placed on the need to identify asymptomatic patients at greatest risk for developing brain metastases. In addition, an overview is provided of the advantages and disadvantages of the primary treatment options, with a focus on some of the current, prospective therapeutic approaches and the indications for their use.

Clinical Presentation

Presenting Signs and Symptoms
For cancer patients, the signs and symptoms of neurologic dysfunction are usually the initial indication that underlying disease has metastasized to the brain. Metastases are believed to be primarily disseminated hematogenously, particularly through the arteries.[1,17,18] Typically, tumoral microemboli are distributed in proportion to the relative blood flow to each area of the brain.[18-20] Consequently, 80% to 85% of metastatic tumors are located in the cerebral hemispheres, 10% to 15% in the cerebellum, and 3% to 5% in the brain stem.[14,19,21,22]. The clinical manifestations of intracranial lesions are generally dictated by the location of the metastases. Increased intracranial pressure and mental changes are symptomatic of a frontal metastatic lesion, visual field defects and cortical blindness are indicative of an occipital metastasis, motor weakness suggests a frontoparietal lesion, and a cerebellar metastasis may manifest itself as ataxia or symptoms related to hydrocephalus.[23]

Most neurologic symptoms can be ascribed to increased intracranial pressure (headache, nausea, vomiting, confusion, and lethargy), focal irritation, or destruction of adjacent brain tissue (aphasia, ataxia, visual field defects, hemiparesis, and focal seizures).[1,22,24] A review of six representative studies of patients with brain metastases secondary to a cross section of cancer types showed that the most common presenting symptoms were headache, focal weakness, mental and behavioral disturbances, seizure, ataxia, aphasia, visual field defect, and sensory change.[1]

Headache is the predominant presenting symptom, reported by approximately 50% of all patients with a single intracranial metastasis (40% reporting early morning headaches) and by a larger percentage of patients with multiple metastases.[17] Hemorrhage is also a serious complication, especially with metastases secondary to malignant melanoma, choriocarcinoma, and gestational and testicular cancers.[19] Patients have been reported to present with acute symptoms of stroke secondary to bleeding into a metastatic lesion, embolization of tumor cells, or tumor invasion or compression of an adjacent artery.[9,20]

Leptomeningeal Metastases—Leptomeningeal metastases are a somewhat unique subset of brain metastases. Between 30% and 50% of leptomeningeal metastases are secondary to leukemia, and 8% to 15% are secondary to solid tumors, primarily melanoma, lung cancer, and breast cancer. As with other brain metastases, leptomeningeal metastases typically develop following hematogenous dissemination involving the superficial arachnoid veins, but they may also result from the extension of intracranial metastases into the subarachnoid space or the ventricles. The primary symptoms of leptomeningeal metastases include headache, back pain, nausea/vomiting, paresthesias, and diplopia.[19]

Cancers Associated With Brain Metastases—The three types of cancers with the greatest predisposition for brain metastases are lung cancer (particularly adenocarcinoma and small-cell cancers), breast cancer, and melanoma.[1] Lung cancer is the leading cause of cancer death among men and women in the United States and is the primary site of cancer for 24% to 60% of all patients with metastases.[3,11,14,25-30] Breast cancer, the second most common cause of cancer death among US women and the leading cause of death for US women aged 15 to 54,[5] may be the site of primary disease for 10% to 30% of all brain metastases among women.[3,11,12,14,27,28] Melanoma is particularly prone to the formation of brain metastases and may account for between 5% and 21% of all patients with brain metastases.[3,11,25,26,31] Table 1 summarizes the most frequently reported symptoms of brain metastases from representative studies in patients with melanoma, lung cancer, and breast cancer.[13,15,16,32-35] The most commonly reported adverse events for this subset of patients are headache, cognitive dysfunction, seizure, motor symptoms, cranial nerve paralysis, cerebellar symptoms, and aphasia.

Treatment Considerations

Corticosteroids, notably dexamethasone and methylprednisolone, and anticonvulsants have become standard treatment for the control of peritumoral edema and seizures, respectively.[1,20,21,36] In particular, corticosteroids provide effective palliative therapy for acute symptoms of brain metastases, but they should only be used for symptomatic lesions. Patients should receive the lowest possible effective doses of corticosteroids and anticonvulsants to minimize toxicity, particularly corticosteroids, due to the severity and frequency of associated adverse events such as Cushing’s disease, hypertension, hyperglycemia, and peripheral myopathies.[1,20] Notably, response to acute corticosteroid therapy should be monitored carefully, because it is a useful indicator of a patient’s potential for neurologic recovery following surgical treatment of brain metastases.[37]

Good clinical practice dictates that any patient known to have cancer and presenting with one or more neurologic symptoms should be further evaluated for the presence of brain metastases. However, only about two-thirds of patients with brain metastases are thought to be symptomatic.
The majority of patients with no history of cancer and a single brain lesion are symptomatic,[21]; thus, most asymptomatic patients are likely to have underlying disease. Many of the newer antineoplastic agents approved for the treatment of melanoma, lung cancer, and breast neoplasms have much better safety profiles and show less neurotoxicity than some of their older counterparts, yet they are still associated with adverse events that could mask common signs and symptoms of brain metastases (Table 2).

For example, paclitaxel (Taxol) is associated with mild-to-moderate dysfunction of the peripheral nervous system in most patients treated on a weekly basis (severe reactions are reported for patients taking doses over 100 mg/m²). Symptoms of neuropathy usually begin 1 to 3 days after treatment and may last for 3 to 6 months.[38] Although routine diagnostic evaluation of all asymptomatic patients may not be feasible, magnetic resonance imaging (MRI) is being ordered more liberally for patients at risk of developing brain metastases. This at-risk group should include "asymptomatic" patients with primary melanoma, breast cancer, or lung cancer who are currently receiving or have recently been treated with chemotherapeutic agents that may mask the clinical signs and symptoms of brain metastases.

Contrast-Enhanced MRI
Once intracranial metastases are suspected, contrast-enhanced MRI is the best tool for determining whether a brain or leptomeningeal metastasis is present.[24] Compared with computed tomography (CT) and other radiographic techniques, contrast-enhanced MRI is associated with superior sensitivity and specificity in determining the presence of brain metastases and their location and number.[19,21,24] When used with T2-weighted spin-echo sequences, MRI is better equipped to detect even slight edema and to image regions of the brain such as the brain stem, temporal lobe, and cerebellum (which CT scans are unable to depict clearly).[24]

At present, single-dose gadolinium (gadolinium diethylenetriamine pentaacetic acid) is the most commonly used contrast agent,[1] although new agents (eg, gadolinium texaphyrin) and new techniques (eg, pulse sequence software, coil design, and postprocessing capabilities) are under investigation.[39] Despite the tremendous advantages of contrast-enhanced MRI, biopsy remains the most definitive test for differentiating brain metastases from cerebral abscess or a primary brain tumor.[1] It should also be noted that whereas contrast-enhanced MRI has great sensitivity, it does not have comparably high specificity in diagnosing leptomeningeal metastases. Consequently, definitive diagnosis of leptomeningeal metastases requires careful examination of the cerebrospinal fluid, collected ideally from one or more lumbar punctures.[19]

Age and Sex
Cancer patients between the ages of 50 and 70 years account for more than 60% of all patients with brain metastases. The rate of intracranial metastasis formation subsequently tends to decrease as age increases above 70, regardless of the location of the primary tumor.[14,40] However, the relationship between age and the risk of developing intracranial metastases can vary depending on the type of primary tumor. The underlying reason for this finding is that patients with melanoma and sarcoma die at a younger age. The mortality rate for patients with leukemia and lymphoma peaks once during childhood and again in late adulthood, which would also influence the relationship between age and risk of metastasis formation.[14]

Although conflicting results are presented in the literature,[41] age has proven to be a significant factor in determining survival rates. In a prospective randomized trial, Patchell et al found that, among patients with single intracranial metastases, increasing age was associated with a decrease in survival ($P < .01$, multivariate analysis) and quality of life ($P < .02$, multivariate analysis).[7] In another study, patients more than 60 years old with a single metastasis had a significantly greater risk of death than their younger counterparts.[42,43]

Among patients with nonrecurrent brain metastases secondary to breast cancer who had undergone extirpation of the brain lesions, Pieper et al found that the risk of death increased as patient age increased ($P$ of .012 or less, Cox regression multivariate analyses).[44] Increasing age was also found to be a prognostic factor for patients who underwent resection of recurrent brain metastases, with an age of 40 years or more being associated with a shorter survival time ($P = .055$, multivariate analysis).[45]

With a few notable exceptions, the patient’s gender does not appear to be a significant prognostic factor in determining the risk of brain metastasis. Amer et al reported that patients with melanoma primaries located on the head, neck, or trunk are at particular risk for developing intracranial lesions.[16] That said, the incidence of melanoma is higher among men than women, with men frequently developing tumors of the head, neck, or trunk. It has been hypothesized that this difference stems from greater occupational exposure to the sun by men relative to women.[1]

In addition, lung cancer is the leading cause of cancer among men and accounts for the majority of
Considerations in the Diagnosis and Management of Brain Metastases

Published on Diagnostic Imaging (http://www.diagnosticimaging.com)

brain metastases in the male population. Breast cancer, with its associated propensity to metastasize to the brain, has historically been the leading cause of cancer among women. Because of the greater incidence of lung cancer, there is an apparent increased risk for men to develop brain metastases.[14] However, this difference may disappear, as the incidence of lung cancer among women has increased rapidly and may surpass breast cancer as the leading cause of cancer in this population.[5]

**Neurologic Status**

Evaluation of a patient’s neurologic status is extremely valuable in determining patient prognosis and how best to manage treatment. The results of various studies show that more favorable baseline Karnofsky Performance Scale (KPS) scores (often defined as KPS scores > 70) are significant predictors of longer survival.[44,46] Consequently, patients who are neurologically normal or who have relatively minor deficits are typically good candidates for more aggressive treatments such as surgical therapy, because they survive resection of their metastases significantly longer than do those with moderate-to-profound presurgical impairment.[26,47]

In a study of 21 patients who underwent surgical excision of intraparenchymal brain metastases secondary to sarcoma, KPS scores of > 70 before surgery were associated with a longer survival time (15.7 months) than were preoperative KPS scores of 70 or less (6.6 months).[48] A review of 63 patients with brain metastases secondary to breast carcinoma indicated that higher presurgery KPS scores were associated with a reduced risk of mortality ($P = .011$, multivariate Cox regression).[44] Also, a KPS score of 70 or less significantly increased the risk of death ($P < .01$, multivariate analysis) among patients with recurrent metastases who had undergone a second surgery.[45]

Even among patients with pronounced neurologic deficits, however, surgery frequently results in considerable improvement in neurologic function by enhancing blood flow and reducing intracranial pressure and pressure on adjacent neurons, as long as the neurons have not been destroyed. A more accurate indicator of a patient’s potential for responding to surgery is the patient’s response to corticosteroid treatment before surgery. Patients whose neurologic function improves in response to corticosteroid therapy are more likely to recover after surgery.[37]

**General Health**

The general health of a patient is obviously profoundly affected by the status of the underlying cancer, but concurrent medical conditions must also be evaluated. Patients with potentially life-threatening cardiac or respiratory conditions are at increased risk for complications from anesthesia, making them poor candidates for surgery.[37] On the other hand, patients presenting with acute neurologic distress (eg, cerebral hemorrhage or herniation) should be treated on an emergency basis, which may entail surgical removal of the lesion.[1]

**Disease Status**

**Assessments**

Despite advances in techniques for the diagnosis and management of brain metastases, the goal of therapy remains prolongation and enhancement of quality of life. Consequently, the needs of each patient must be evaluated individually. The pragmatic approach has been to establish a projected duration of survival for each patient based on a comprehensive patient work-up. A thorough clinical history and physical examination are essential, as are high-quality chest x-rays. For patients with a known primary cancer, the work-up typically includes CT scans of the pelvis, abdomen, and chest; clinical laboratory evaluation for tumor markers; bone scans if appropriate; and an evaluation of the lesion for sensitivity to irradiation or chemotherapy.[1,37]

For patients suspected of having a brain metastasis secondary to an unknown primary tumor, a biopsy is indicated in order to make an accurate histologic diagnosis of the lesion and to determine the appropriate treatment strategy.

**Status of Primary Disease**

One of the most crucial factors in determining the projected duration of survival for patients with single brain metastases is the status of the primary cancer. In the presence of systemic disease, the duration of survival is shorter.[7,26,44,45,49] The management of lesions in patients with widely disseminated and uncontrolled systemic disease or with life-threatening cardiac or respiratory conditions has traditionally been limited to noninvasive modalities such as whole-brain radiotherapy (WBRT) and high-dose corticosteroids intended to minimize the discomfort of acute symptoms. In contrast, patients whose primary disease is deemed absent, under control, or limited in nature typically have a much more favorable prognosis. In general, such patients are strong candidates for surgical extraction of the neoplasm, provided their lesions can be resected or that excision will
increase life expectancy or quality of life. However, individual surgeons may have differing views as to which patients with controlled or limited disease are better candidates for surgery, because the designation of controlled or limited cancer does not reflect how well the primary disease is responding to therapy or whether any extracranial metastases are present. These patients, however, are in the minority. Over 50% of all patients with intracranial metastases have uncontrollable systemic cancer.[50]

For patients presenting with suspected brain metastases but with no known primary disease, histologic confirmation of a diagnosis (usually by open or stereotactic surgery) is indicated. However, initial evaluations should focus on lung cancer or melanoma as the likely site of primary disease due to their high rate of metastasis.[1,20] Despite the high propensity of breast cancer to metastasize to the brain, a patient rarely presents with a precocious metastasis secondary to breast cancer, presumably because the primary disease is detected earlier.[20]

**Metastases: Number, Location, and Type**
The presence of multiple metastases is often considered a negative prognostic factor for long-term survival.[44,47] Autopsy studies have reported that 60% to 85% of patients with intracranial metastasis who died of cancer have more than one lesion.[14,16,51,31] In a review of CT scans of 288 living patients with brain metastases, Delattre et al found that 51% had multiple metastases.[18] As noted previously, contrast-enhanced MRI is more effective than CT scans in detecting multiple lesions, so the percentage of living patients with multiple lesions may be closer to the rates reported from autopsy studies. However, it is also possible that living patients are less likely to present with more than one lesion compared with patients at autopsy because brain metastases often develop during the later stages of the primary disease.[1]

The location of brain metastases is an important factor in selecting appropriate management strategies. Although, historically, surgery was only considered appropriate for the removal of solitary tumors in the silent regions of the brain,[19] the advent of computer-guided stereotaxy, ultrasonography, cortical mapping, etc, means that most tumors can now be accessed surgically.[37,52] Nonetheless, resection of lesions located within eloquent (ie, functionally important) regions or deep within the brain poses a greater risk of morbidity, which may outweigh any benefit for a patient with limited expectations for survival. Metastases located in the brainstem, thalamus, and basal ganglia pose a particularly high risk of morbidity and are usually a contraindication for surgery.[37]

Histologically, not all metastases respond to irradiation and chemotherapy in the same manner. Metastases secondary to lymphoma, germ cell tumors, and small-cell lung cancer are more sensitive to irradiation and chemotherapy than are those secondary to melanoma, renal cell carcinoma, and many kinds of sarcomas. Thus, a careful histologic assessment of the primary tumor is essential in determining whether these modalities would be preferable to surgery or should be used in conjunction with other management options.[53]

**Interval Between Diagnosis of Primary and Brain Metastases**
Different types of cancer are disseminated at different rates in the course of their natural history. For instance, the median interval between diagnosis of the primary tumor and diagnosis of brain metastasis is 2 to 3 years for melanoma, breast cancer, and colon cancer, 1 year for renal cancer, and 6 to 9 months for lung cancer.[1] A major deviation in the median interval between initial diagnosis of cancer and subsequent diagnosis of brain metastases may be an indicator of the extent of systemic disease and whether metastases are likely to be present in other, extracranial locations.[24] A shorter interval between diagnosis of the primary tumor and diagnosis of a brain metastasis has been associated with a shorter survival time.[7,45]

**Recurrent Metastases**
Although there are many similarities in the management of new and recurrent metastases, there are also important differences. First, the signs and symptoms of radiation-induced necrosis and its appearance on CT scans and MRI studies can be mistaken for recurrent lesions.[1,54,55] Thus, patients previously treated with WBRT or radiosurgery who are suspected of having a recurrence should undergo a biopsy or, alternatively, positron-emission tomography (PET) or dynamic MRI to confirm the diagnosis.

Second, patients previously treated with WBRT may not be eligible for further irradiation because it may exceed the maximum tolerated dose.[52] Moreover, if the patients were initially treated with WBRT rather than by craniotomy, they may be more likely to have a poor prognosis as defined by having more negative prognostic indicators (eg, presence of systemic disease, KPS score of 70 or less, age of 40 years or more), and recurrent lesions are typically not treated in such patients.[1,45,52]
Patients who have previously undergone craniotomy or radiosurgery are the strongest candidates for treatment of recurrent metastases. Between 31% and 48% of patients who undergo surgical resection of an intracranial metastasis may develop a recurrence. The number of patients at risk for recurrent brain metastases is increasing because patients undergoing craniotomy are living longer.

Lastly, metastases that recur at the same site as previous lesions must be carefully evaluated to determine whether they can still be resected. Those that cannot be surgically resected due to their proximity to eloquent regions of the brain or major blood vessels may require radiosurgery.

Treatment Options

Conventions for Tumor Management
The primary tools for the management of intracranial metastases include corticosteroids and chemotherapeutic agents, irradiation, surgery, and stereotactic radiosurgery. Conventionally, radiotherapy (particularly WBRT) has been the preferred treatment for control of brain metastases. In the early and mid-1990s, the results of several randomized, prospective studies supported the use of surgery plus WBRT in selected patients with a single brain metastasis, and stereotactic radiosurgery is well suited for the management of small and surgically inaccessible intracranial metastases.

However, the success of more effective therapy in prolonging life has highlighted the potential for long-term morbidity associated with radiation therapy. Although only about 25% of patients with intracranial metastases may benefit from surgical resection, the finding that surgery and radiosurgery may be effective management options has triggered a search for the appropriate populations and circumstances for their use. Thus, considerable effort has been directed toward finding a balance between the use of these various treatment options, and tailoring them to the unique needs of the patient.

More prospective, randomized studies are needed before an informed consensus can emerge regarding the optimal means for managing brain metastases. Here, we provide an overview of the potential advantages and disadvantages of some of the therapeutic approaches currently under investigation (see Table 3 for summary).

Pharmacologic Therapy
Chemotherapy has not typically played a key role in the management of intracranial metastases and is rarely used as such. This is the case, in part, because the types of cancer most likely to metastasize to the brain are considered relatively insensitive to chemotherapeutic agents. However, the results of various uncontrolled studies suggest that chemotherapy may be effective treatment for some metastases, particularly those secondary to germ cell tumors, and perhaps to a lesser degree, those secondary to small-cell lung cancer and breast cancer. Until its role in the management of brain metastases has been more definitively delineated, chemotherapy may best be reserved for lesions known to be chemosensitive.

In contrast to chemotherapy, most symptomatic patients with brain metastasis benefit from treatment with corticosteroids. According to some reports, corticosteroid therapy alone may prolong the median survival of patients with brain metastases to 2 months, but the primary benefit is in terms of immediate palliation of symptoms. Clinical improvements in symptoms can be detected 6 to 24 hours after administration of the first dose. As patients live longer, the deleterious effects of long-term corticosteroid use may become of greater concern, but the short-term benefits typically outweigh these disadvantages.

Whole-Brain Radiotherapy
Whole-brain radiotherapy is the preferred treatment for control of brain metastases, especially for patients with advanced systemic disease, because it is noninvasive, palliative, and increases the median survival time by 3 to 6 months, depending on extenuating factors such as the extent of primary disease and the neurologic functioning status of the patient. The primary therapeutic objective of WBRT is palliation of the symptoms of neurologic dysfunction associated with brain metastases.

Response rates to WBRT vary but tend to range from 50% to 70%, although radiation is less effective in the treatment of large lesions. Irradiation is particularly effective for the treatment of radiosensitive lesions such as germ cell lesions or tumors secondary to small-cell lung cancer or lymphomas. However, lesions secondary to melanoma, many types of sarcoma, and renal cell carcinoma are all relatively radioresistant.

One approach aimed at enhancing the palliative effects of radiation has been to employ
dose-fractionation regimens that differ from the standard schedule of 30 Gy administered in 10 fractions. The intent is to elicit a strong initial response, decrease hospital stays, extend the duration of response, and reduce the complications associated with radiation.[1]

The Radiation Therapy Oncology Group has conducted several investigations since 1980 testing various fractionation schedules.[59-61] Despite some encouraging early findings, the results of a randomized phase III study detected no difference in the median survival of the group treated with the standard fractionation radiotherapy regimen, compared with the group treated using the accelerated hyperfractionation regimen.[62] Consequently, standard radiotherapy treatment schedules are still used by most cancer centers.

**Prophylactic Cranial Irradiation** Another approach aimed at improving patient outcome has been to irradiate the brain of patients prophylactically (prophylactic cranial irradiation) immediately after lung cancer is diagnosed, in an attempt to destroy micrometastatic seeds not detected by CT or MRI scans. Rosenstein et al found that prophylactic cranial irradiation significantly increased the life span of treated patients,[63] although no other study has demonstrated any significant advantage. On the other hand, several investigators have reported that prophylactic cranial irradiation is associated with significant neurotoxicity.[64-66] Given the fact that patients with cancer are living longer, there is also concern that at least 50% of those who are treated with prophylactic cranial irradiation may never develop intracranial metastases and should not be subjected unnecessarily to any of the risks of radiation-induced morbidity.[67]

**Complications of WBRT** Despite the indisputable therapeutic value of WBRT, it is also associated with morbid complications that can occur immediately after treatment and last for up to several months, as well as more serious complications that occur much later. Acute effects include alopecia, nausea, headaches, dermatitis, cerebral edema, otitis media, and lethargy.[1,42] Late effects include brain atrophy, neurocognitive deterioration, and dementia (in patients who received WBRT in fractions of 3 Gy or more); radiation necrosis; cognitive, gait, and bladder dysfunction; leukoencephalopathy; and hypothyroidism or other neuroendocrine dysfunction.[1,9,20,26,57,68]. As patients live longer due to improvements in disease management, the incidence of these deleterious late effects can be expected to increase.

**Surgery** The primary objectives of surgery are to obtain immediate symptom relief, gain greater local control of the lesion, and allow for confirmed histologic diagnosis of the disease.[20] Improvements in stereotactic techniques, cortical mapping, and use of ultrasonography have made most lesions surgically accessible.[52] Several studies have shown that surgery, which is usually followed by WBRT, can considerably prolong life and improve neurologic functioning or stabilize deficits among selected patients with single brain metastases and minimal or controlled systemic disease.[7,26,42,43]

Conventionally, the perception has been that prolonged survival was only possible for patients with single lesions and controlled systemic disease. This perception is supported by the results of the retrospective study by Hazuka et al, who compared the surgical outcome of 18 patients with multiple metastases and 28 patients with single metastases and found that the median survival for patients with a single metastasis was considerably better than that of patients with multiple metastases (12 vs 5 months, respectively). Notably, in this study, patients with multiple metastases did not have all metastatic brain tumors resected.[69] In contrast, various studies have shown that patients with select multiple and recurrent metastases can also benefit from surgery.

**Complete Surgical Extirpation** Two retrospective reviews at The University of Texas M. D. Anderson Cancer Center in Houston provided statistical evidence that complete surgical extirpation of multiple metastases may be as effective as resection of a single metastasis, providing the lesions can be completely removed.[8,48] In one review, the cases of 56 patients who underwent resection for multiple brain metastases were examined. Of these, 30 patients (group A) had at least one lesion remaining after resection, compared with 26 patients (group B) who had all lesions removed. For comparative purposes, a third group of patients was selected that matched group B in most respects but that had undergone resection of only a single metastasis. The median duration of survival for groups B and C was 14 months, which was significantly longer than that of group A (6 months, P of .012 or less).[8]

In the second review, investigators considered the cases of 21 patients with intraparenchymal brain metastasis secondary to sarcoma, 6 of whom had multiple metastases. Overall, the median survival of the 17 patients who had all lesions resected was 14 months, compared with 6.2 months for the 4 patients in whom some of the lesions remained.[48] Consequently, the policy at M. D. Anderson is to surgically remove up to four metastases in selected patients, provided the lesions are otherwise
Repeat Craniotomy

Although radiosurgery is frequently used for the management of recurrent metastases (see section on Stereotactic Radiosurgery),[1] repeat craniotomy has also been found to alleviate symptoms and prolong life.

In a study of 48 patients who underwent repeat craniotomy for recurrent metastases, Bindal et al found that repeat craniotomy was associated with prolonged survival and improved quality of life.[45] Results of multivariate analyses indicated that patients with the most favorable prognosis (1) were less than 40 years old, (2) did not have systemic disease, (3) had a KPS score > 70 before resection, (4) had a primary carcinoma other than melanoma or breast carcinoma, and (5) had a time to recurrence of 4 months or more. The median survival time of these patients was 11.5 months. Furthermore, patients who underwent reoperation following a second recurrence survived significantly longer (median: 8.6 additional months) than did patients who did not undergo further surgical intervention (median: 2.8 months; \( P < .0001 \)).[45]

Similarly, Sundaresan et al reported that among 21 patients, surgical excision of recurrent metastasis was associated with an improvement in neurologic function in 66%, and with a median survival time of 9 months following the second surgery.[70]

In a retrospective analysis of 109 patients with recurrent intracranial metastases secondary to non-small-cell lung cancer, Arbit et al found that repeat craniotomy could significantly prolong median survival if the lesion was completely resected.[71] The median survival from the time of initial surgery was 15 months for the 32 patients who underwent additional surgery, compared with 10 months for the 77 patients who had no further surgery \( (P < .001) \).

In addition, this study found that patients with adenocarcinoma as the primary lesion were significantly more likely to have a longer survival time than were patients with squamous cell or large cell carcinoma \( (P < .03) \), and that women and patients who underwent complete resection had a tendency toward increased survival. However, the effect of WBRT on these patients was inconclusive in that the duration of survival did not appear to differ among patients irradiated before or after the first surgery, compared with patients who did not receive WBRT until after they had undergone a second surgery.[71]

Surgery Plus WBRT vs Surgery Alone

Currently, standard practice is to use WBRT as adjuvant therapy following surgery or radiosurgery. Various studies have shown that surgery plus radiotherapy is associated with a longer survival. Patients with single brain metastases and inactive extracranial disease who were treated with surgery plus radiotherapy have been shown to retain a higher neurologic functional status and to survive longer (median survival: 12 months), compared with patients treated with radiotherapy alone (median survival: 7 months).[42,43] In a prospective, randomized study, Patchell et al found that among patients with a single brain metastasis, surgery followed by radiotherapy was associated with a longer survival, a longer period of functional independence, and fewer recurrences at the original site, compared with radiotherapy alone.[7]

Subsequently, Patchell et al compared the outcome of patients with a single metastasis treated with surgery plus postoperative WBRT with those treated using surgery alone.[72] Patients treated with combination therapy had a lower rate of recurrence anywhere in the brain \( (P < .001) \) and were less likely to die of a neurologic cause \( (P = .003) \), compared with patients treated with surgery alone. Treatment with surgery plus radiotherapy was not associated with a longer survival or functional independence compared with surgery alone, but these findings were attributed to a failure to control the underlying systemic cancer rather than failure of the postoperative radiotherapy.

These investigators concluded that routine use of postoperative WBRT was justified in order to prevent deaths due to neurologic causes.[72] In addition, Skibber et al conducted a retrospective review of patients with brain metastases secondary to melanoma who had no systemic cancer. The results indicated that patients treated with surgery plus WBRT had a significantly longer survival \( (P = .002) \) than patients treated with surgery alone.[73]

Stereotactic Radiosurgery

With stereotactic radiosurgery, a lethal dose of radiation can be accurately and noninvasively administered in a single fraction to an intracranial metastasis. Because the radiation is applied by convergence of multiple, highly collimated beams of radiation with a sharp drop-off in dose at the beam edge, it is associated with minimal collateral damage to surrounding tissue.[1,52]

Radiosurgery is frequently used to manage tumors that may otherwise be unreachable or lesions that recur at the same site as a previous lesion but may no longer be resectable.[1] Because radiosurgery is noninvasive and requires no anesthesia, it is the preferred treatment for patients with medical conditions that render them intolerant of anesthesia. In addition, it may be less
expensive than surgery because it may require a shorter in-patient hospital stay.\[52\]
A retrospective study was conducted at Brigham and Women’s Hospital in 248 consecutive patients treated with radiosurgery between May 1986 and May 1993. To be eligible for the study, patients had to have a KPS score of 70 or more, a lesion with a maximum diameter of 4 cm or less, and no evidence of acute neurologic deterioration. Among patients in the study, 76% had recurrent disease and 69% had one metastasis. The median survival time of patients treated with radiosurgery was 9.4 months; the rate of local disease control was 85% at 1 year after treatment and 66% at 2 years. These results indicated that radiosurgery is effective therapy for patients with multiple lesions and recurrent metastases.\[74\] According to a review by Wen and Loeffler, radiosurgery is associated with local lesion control rates ranging from 73% to 94%.\[20\]
The efficacy of radiosurgery stems from focused application of radiation beams directed at the tumor target. Because the dose of radiation is inversely proportional to the volume of the target lesion, it is most effective in small tumors; with large tumors, radiosurgery is more like radiotherapy. The limitations of radiosurgery include the inability to provide histologic confirmation of the diagnosis, delayed effects, and, as a consequence of delayed effects, the possible need for higher doses of corticosteroids for longer periods of time than are required for surgery.\[1,52\]

**Stereotactic Radiosurgery vs Surgery**
The results of retrospective trials comparing radiosurgery with surgery are mixed. In a retrospective study involving four institutions that was conducted by Auchter et al,\[46\] the results of radiosurgery plus WBRT in 122 patients with single, intracranial metastasis who had no previous history of cranial surgery or WBRT were compared with the results of surgical resection plus WBRT or WBRT alone in a series of matching patients from randomized studies conducted by Patchell et al\[7\] and Noordijk et al.\[43\] Patients treated with radiosurgery plus WBRT had a median survival of 56 weeks, and the duration of functional independence was 44 weeks (n = 122). In contrast, in patients treated with surgery plus WBRT, Patchell reported a median survival of 40 weeks and a duration of functional independence of 38 weeks (n = 25); Noordijk et al reported a median survival of 43 weeks and a duration of functional independence of 33 weeks (n = 32). For patients treated with WBRT alone, Patchell et al reported a median survival of 15 weeks and a period of functional independence of 8 weeks (n = 23); Noordijk et al reported a median survival of 26 weeks and a 15-week period of functional independence (n = 31).\[43\]
Bindal et al also compared the outcome of radiosurgery vs surgery among patients retrospectively matched in terms of age, sex, primary tumor characteristics, preoperative KPS score, number of brain lesions, and time to metastasis. In this study, the median survival time of patients treated surgically was 16.4 months, which was significantly longer than the 7.5-month median survival of patients treated with radiosurgery (P £ .005 for both univariate and multivariate analyses).\[2\]
Additional prospective, randomized studies comparing surgery with radiosurgery are needed to accurately determine the degree to which stereotactic radiosurgery may be effective in the management of brain metastases.

**Conclusions**
Recent technologic and surgical advances have provided more options for managing brain metastases. Clearly, for optimal management, treatment must be tailored to the unique needs of each patient. This often requires a balance between the use of corticosteroids, WBRT, surgery, and radiosurgery.

**References:**


64. Fleck JF, Einhorn LH, Lauer RC, et al: Is prophylactic cranial irradiation indicated in small-cell lung


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